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A Review Article on Alzheimer's disease (AD): Current Landscape in Treatment Research for Alzheimer's disease

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ABSTRACT:

Alzheimer's disease (AD) is a progressive Neurodegenerative disorder characterized by cognitive decline, memory loss and functional impairment. AD is a complex multifactorial disorder, influenced by both genetic and environmental factors. It is the most common cause of dementia globally and is clinically characterized by a progression from episodic memory problems to a slow general decline of cognitive function, our current understanding of AD pathologies involves various hypotheses such as cholinergic, amyloid, tau protein, Inflammatory, oxidative stress, metal ion, glutamate ecotoxicity, microbiota-gut-brain axis, and abnormal autophagy and detailed information on signalling pathways linked to AD pathogenesis. This review mainly highlights the aetiology, clinical features, diagnosis and treatment (pharmacological & non-pharmacological therapies) of people with Alzheimer's disease and also focussed on current Landscape in treatment Research for AD, Alzheimer's Deng Development pipeline 2024.

Key words:
Alzheimer's disease, Dementia, Neurodegenerative, cognitive function, signalling pathways, Landscape, Genetic and Environmental.

Introduction:

Alzheimer's disease (AD) was originally described by Alois Alzheimer in 1906 and was renamed by Emil Kraepelin. AD is the most common cause of dementia and is clinically characterized by a progression from episodic memory problems to a slow general decline of cognitive function. The disease first targets the hippocampus, the area of the brain critical for memory formation, and gradually spreads to other regions, worsening cognitive impairment. Although AD does not directly cause death, its progression makes individuals more vulnerable to various complications, which can ultimately be fatal.[1]

During 2015, the global prevalence of AD has been estimated to be 48 million people. In a vital statistical report, during 2013 the mortality rate of AD was 26.6 death, and it was ranked as the sixth cause of death in United State.[2]

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AD is a complex, multifactorial disorder influenced by both genetic and environmental factors. Key environmental risks include aging, diabetes, obesity, smoking, sedentary habits, and depression, while genetic susceptibility is strongly linked to the apolipoprotein E ε4 allele. Early symptoms are often subtle, leading to delayed diagnosis and advanced cognitive decline by the time of detection. Diagnosis involves a combination of clinical assessment, reports from patients or caregivers, cognitive tests like the Mini-Mental State Exam (MMSE), and imaging techniques such as MRI to evaluate brain changes. Early detection remains crucial for better management of the condition.[3]

The disease is associated with the destruction of more than 100 billion neurons and their associated 100 trillion connections. There is a progressive loss of cortical neurons and formation of amyloid plaques, intraneuronal neurofibrillary tangles, and accumulation of a beta-amyloid in the arterial walls of cerebral blood vessels (amyloid angiopathy). Beta-amyloid is the major component of the plaques, whereas hyperphosphorylated *tau* protein is the major constituent of the neurofibrillary tangles. The pathological process of atrophy begins in the hippocampus and spreads to diffuse areas of the temporal, parietal, and frontal lobes of the cerebral cortex. There is a symmetric enlargement of the third and fourth ventricles. The loss of neurons, especially in the nucleus basalis causes a relative deficiency of acetylcholine resulting in different clinical manifestations. The neurotransmitter, acetylcholine is necessary for clear thinking. It gets destroyed by the enzyme acetylcholinesterase (ChE). Since acetylcholine deficiency has been observed in AD, ChE inhibitors have been used to block the action of ChE to increase the cerebral concentration of acetylcholine essential for synaptic transmission. Donepezil, rivastigmine, and galantamine (ChE inhibitors) facilitate an increase in the level of acetylcholine.[4]

These agents show improvement in global function and reduce cognitive disturbances. There is a reduction in behavioural disturbances and temporary stabilization of activities of daily living.[5]

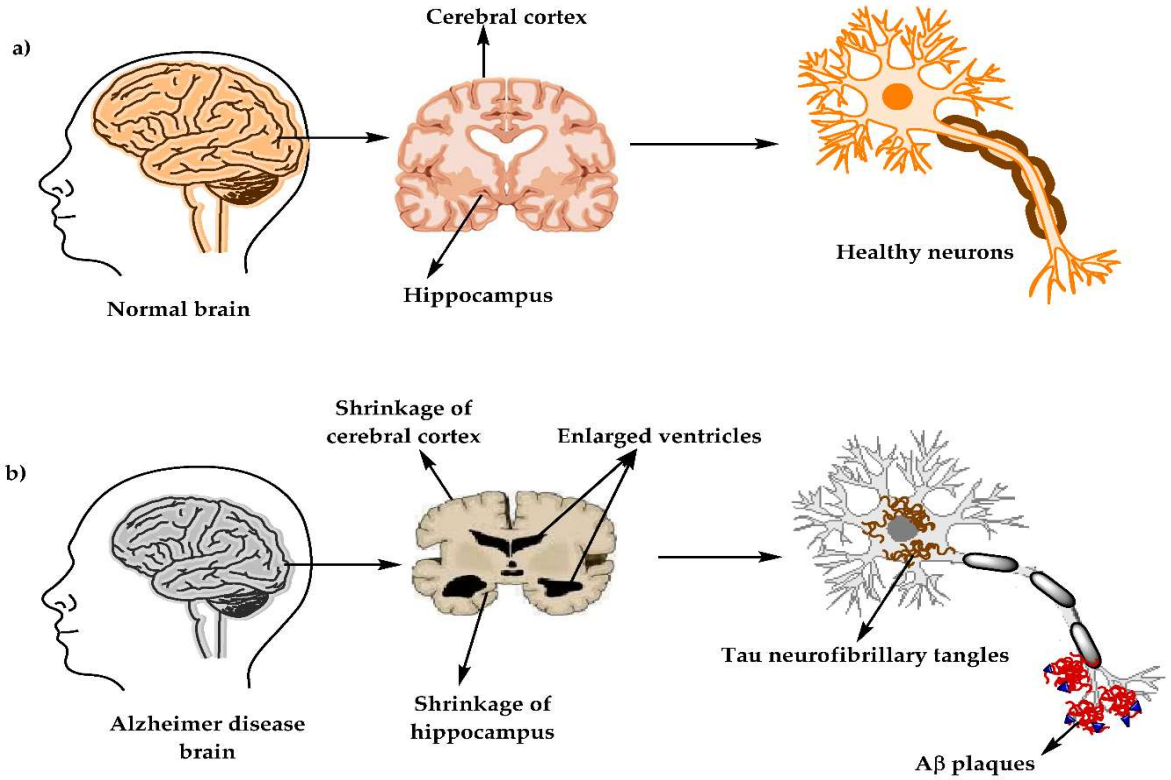


Figure 1: The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's disease (AD) brain.

EPIDEMIOLOGY:

- Worldwide, Alzheimer's disease is regarded as major health burden estimating approximately 57.4 million people affected by it.
- As per Global Burden of Disease Study (GBDS) 2019 by the year 2050, the number of dementia cases will get a steep increase by 166% approximately impacting life of 152.8 million individuals.
- As per this study, India was fourth largest contributor of dementia and by the year 2050, India is expected to surpass Japan and USA to secure second position worldwide whereas china remains first. [6]

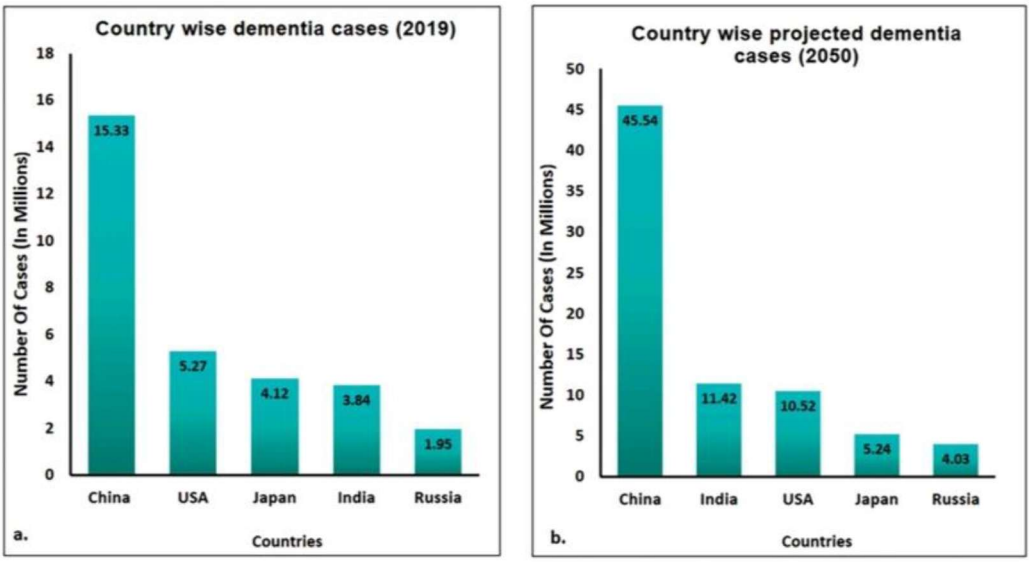


Figure 2: Top five contributors to the world-wide dementia case load [7] (source - singh et al)

- In the year 2019, India had approximately 3.69 million active cases of Alzheimer's disease and other dementia.
- Prevalence rate in India was about 4.3%.
- Out of all the states, Kerala, Goa, Andhra Pradesh, Tamil Nadu, Himachal Pradesh ranked top five states for high number of cases. [8]

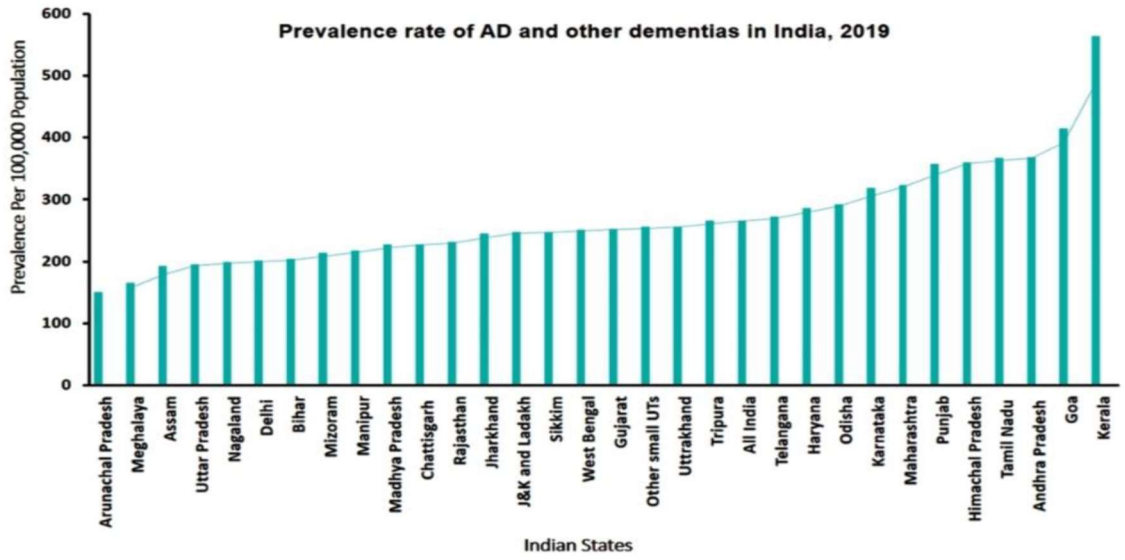


Figure 03: Prevalence rate of Alzheimer's disease and other dementias in India, 2019 [8] (source - Nicholas et al, 2022)

These results are positively correlated with the geriatric population of particular states

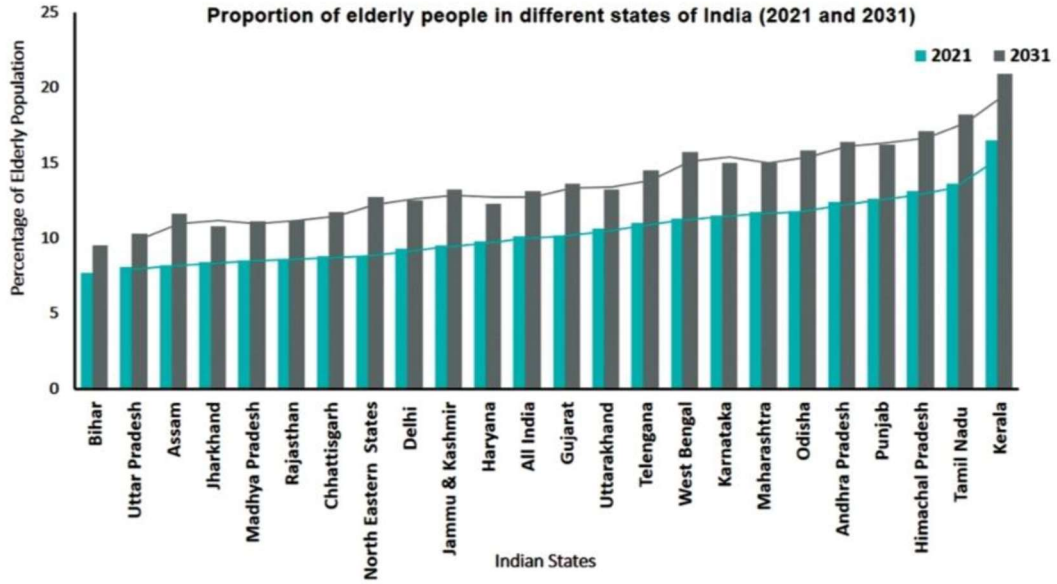


Figure 04: Estimated percentage of elderly people constituting population of different states in the year 2021 and 2023 [9] (source - Elderly in India 2021- MOSPI)

- Proportion of disease burden was observed to be higher in females than male populations.
- Number of deaths accounting from 1990-2019 were approximately 0.13 million

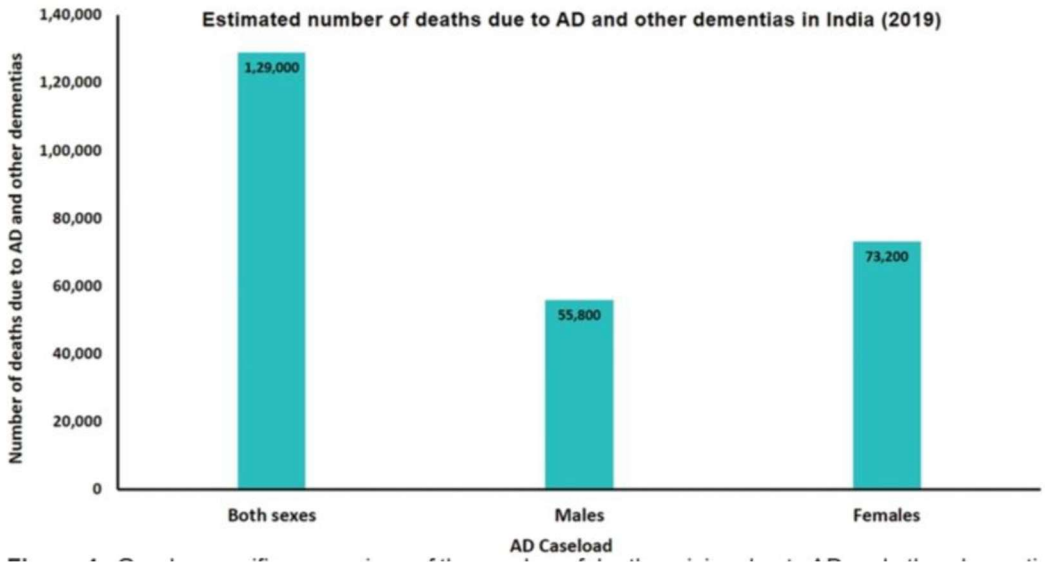


Figure 05: Estimated number of deaths due to Alzheimer's disease and dementia in India (2019) (source - singh et al - 2021)

Prevalence of Alzheimer's disease in India is increasing with respect to increase in age. It is one of leading cause of dementia with prevalence of 7.4% among 60 year and older patients accounting approximately 8.8 million affected individuals. Dementia is one of the top causes of death and disability in the older adults affecting quality of life.[10]

Whereas globally over 55 million people are living with dementia and Alzheimer's disease. Approximately 10 million new cases of dementia and Alzheimer's disease are diagnosed every year worldwide. In terms of mortality, dementia and Alzheimer's disease are 7th leading cause of death worldwide.[11]

AETIOLOGY

Both genetic and environmental risk factors play a role in the manifestation of AD. The greatest risk factor is age. At age 65, the likelihood of having AD is about 3%, rising to over 30% by age 85. The incidence of AD under the age of 65 is less certain, but estimates suggest that this age group accounts for around 3% of AD cases[9]. AD can be classified by when the disease manifests, and whether it is inherited. Early-onset Alzheimer's disease (EOAD) occurs before age 65, whereas late-onset Alzheimer's disease (LOAD) accounts for over 95% of cases and manifests beyond age 65. Familial AD shows Mendelian (usually dominant) inheritance, while sporadic AD shows no simple familial link. Nearly all EOAD are familial as these cases are due to mutations in APP, PSEN1 or PSEN2, and a vast majority of LOAD are sporadic. Genome wide association studies (GWAS) and sequencing have now provided more than 20 risk loci in total that contribute to sporadic cases, but often there is no identifiable genetic cause.[12]

Histopathological studies revealed relevant multifactorial disorders from which different hypotheses originated to shed light on the likely mechanisms and effective targets of the disease. The emerged hypotheses include the following: (a) cholinergic hypothesis, (b) amyloid cascade hypothesis, (c) tau hypothesis, (d) mitochondrial cascade hypothesis, (e) oxidative stress hypothesis (f) excitotoxicity hypothesis, (g) neuroinammatory hypothesis, and (h) others (like genetic factors, environmental factors, etc.)[13]

Table I: Hypotheses of Alzheimer's Disease and Their Descriptions.[14]

HYPOTHESIS OF ALZHEIMER DISEASE	DESCRIPTION
I. Cholinergic hypothesis.	**1. Cholinergic System Degeneration:** Although AD affects the entire central neurotransmitter system, the cholinergic system is disproportionately damaged, strongly correlating with the severity of cognitive impairment. **2. Role of Acetylcholine (ACh):** ACh is crucial for cognitive processes, and thus, efforts have focused on increasing ACh levels to help maintain cognitive function. **3. Acetylcholinesterase Inhibitors (AChEIs):** These drugs were developed to boost ACh by inhibiting the enzyme that breaks it down, thus increasing its availability in the brain. **4. Symptomatic Treatment:** AChEIs primarily alleviate symptoms without repairing neuronal damage or halting disease progression, acting as symptomatic rather than curative treatments. **5. Exploring New Therapeutic Targets:** Given the limitations of AChEIs, research is now focusing on alternative mechanisms and targets for better disease management and potential disease-modifying effects.
II. Amyloid cascade hypothesis.	**1. Senile Plaques as a Hallmark**: Extracellular senile plaques are a key pathological feature in AD, contributing to neuronal damage and disease progression. **2. Role of Amyloid Beta (Aβ)**: Amyloid β protein (Aβ) is the main component of these plaques, existing in three forms—soluble monomers, soluble oligomers, and insoluble fibrils—that are typically degraded and cleared under normal conditions. **3. Amyloid Precursor Protein (APP) and Enzymatic Cleavage**: APP, crucial for neuronal membrane function, is abnormally cleaved in AD by two enzymes—β-secretase (BACE1) and γ-secretase—leading to the overproduction of insoluble Aβ. **4. Formation of Aβ42 Peptides**: Due to mutations, AD brains overproduce the hydrophobic Aβ42 peptide, which readily aggregates into amyloid plaques, in contrast to Aβ40. **5. Elevated BACE1 in AD**: Increased levels of BACE1 in sporadic AD brains accelerate the initial cleavage of APP, enhancing the buildup of Aβ and contributing to plaque formation.
III. Tau hypothesis.	**1. Tau and Microtubule Stability:** Tau is a microtubule-associated protein that helps stabilize tubulin assemblies, which are essential for intracellular transport in neurons. **2. Hyperphosphorylation of Tau:** In AD, tau undergoes pathological hyperphosphorylation, leading to the formation of neurofibrillary tangles (NFTs) within neurons, which are toxic and disrupt cellular functions. **3. Impact on Cell Transport and Mitochondria:** Hyperphosphorylated tau inhibits tubulin assembly, impairs

	intracellular transport, and damages mitochondrial integrity, causing mitochondrial dysfunction and cell toxicity. **4. Enzymatic Dysregulation:** Dysfunction of glycogen synthase kinase-3 beta (GSK-3β) and protein phosphatase 2A (PP2A) is linked to abnormal tau phosphorylation in AD. **5. Intracellular Tangles vs. Extracellular Plaques:** Unlike amyloid plaques, which accumulate extracellularly, tau tangles form inside neurons and are thought to play an earlier and possibly more central role in sporadic AD than amyloid aggregation.
IV. Mitochondrial hypothesis	**1. Mitochondrial Dysfunction and Oxidative Stress:** Genetic and environmental factors cause mitochondrial dysfunction over time, with oxidative stress playing a key role in disrupting mitochondrial function and leading to mitochondrial fragmentation in AD. **2.Impact on Amyloid Cascade**: In sporadic, late-onset AD, mitochondrial changes are proposed to influence amyloid precursor protein (APP) expression and amyloid accumulation, triggering the amyloid cascade associated with AD pathogenesis. **3.Interplay with Amyloid and Tau Pathology:** There are significant correlations between mitochondrial dysfunction, Aβ amyloidosis, and tau hyperphosphorylation, suggesting a complex interaction among these factors in AD progression.
V. Oxidative stress hypothesis.	**1.Oxidative Stress and Protein Metabolism:** In sporadic AD, oxidative stress arises from abnormal metabolic reactions in the CNS, with amyloid β (Aβ) generating free radicals and contributing to oxidative damage, leading to hallmark features like amyloid plaques and neurofibrillary tangles. **2. Evidence of Increased Oxidative Stress:** Elevated levels of metals (Fe, Al, Hg), increased lipid peroxidation, decreased polyunsaturated fatty acids, and higher levels of protein and DNA oxidation all indicate heightened oxidative stress in AD brains. **3.Energy Metabolism Impairment:** AD brains show reduced cytochrome c oxidase activity and diminished energy metabolism, alongside persistent reactive oxygen and nitrogen species (ROS/RNS)-mediated damage.
VI. Excitotoxicity hypothesis	**1. NMDA Receptor Overstimulation:** Excessive activation of NMDA receptors by glutamate leads to excitotoxicity, causing neuronal damage in acute injuries and, with sustained mild activation, contributes to chronic neurodegeneration in conditions like AD. **2. Challenges in Progressive AD:** AD's progressive nature requires stage-specific treatments, as drugs effective in early stages may not work in later stages, highlighting the need for varied approaches at each disease phase. **3. Long-term Safety in Chronic Treatment:** Since AD requires long-term management, drug safety for chronic use is essential, and recent advancements in anti-AD drugs have

	aimed at targeting a broader range of pathological mechanisms.
VII. Neuroinflammation hypothesis.	**1. Neuroinflammation and Proinflammatory Cytokines:** AD brains show elevated levels of proinflammatory cytokines, such as TNF-α and IL-6, indicating a link between neuroinflammation and disease progression. **2. Activated Microglia and Astrocytes:** Microglial activation in response to amyloid plaques releases proinflammatory mediators, causing neurotoxicity, neuronal damage, and reduced Aβ clearance. **3. Early Inflammatory Response:** Neuroinflammation, including the overexpression of cyclooxygenase-2 in neurons, appears as an early pathological feature in AD, potentially contributing to the disease's progression.

SIGNS AND SYMPTOMS

Table II. Signs and symptoms of AD with a clinical description[15-16]

Stages	Mild	Moderate	Advanced
Activities of Daily Living	- Can perform basic daily activities, such as hygiene & dressing. - May struggle with tasks like taking public transport, managing money, or cooking.	-Requires assistance with daily activities, including dressing and hygiene. - High risk of falling	- Cannot manage daily activities, including feeding, bathing, and using the toilet. - May be bed-bound and have significant mobility issues.
Behaviour	- Shows apathy, with less interest in previous activities. - Rapid mood changes.	- Tends to wander, repeat questions, or show sleep pattern reversal. - Can be easily agitated, depressed, or suspicious	- Exhibits vocalizations like shouting or crying as a means to communicate. - Often refuses care due to confusion.

Cognitive Decline	- Short-term memory loss and reduced judgment. - Difficulty following conversations, abstract thinking, and finding the right words. - Misplaces items frequently	- Long-term memory becomes vague, and recognizing family may be difficult. - Challenges in communication due to repetitive speech or inability to follow contexts - Forgets personal details, like address or phone number.	- Cannot identify common objects. - Loss of ability to recognize familiar faces, including self. -Cannot understand language and may not respond.
Disorientation	-Occasionally disoriented but able to find familiar locations.	- Confusion with time and place concepts, and gets lost in familiar places.	- Complete loss of orientation, unable to differentiate day from night

RISK FACTORS[17]

Age

Age is the single most significant factor. The likelihood of developing Alzheimer's disease doubles every 5 years after you reach 65. But it's not just older people who are at risk of developing Alzheimer's disease. Around 1 in 20 people with the condition are under 65. This is called early- or young-onset Alzheimer's disease and it can affect people from around the age of 40.

Family history

The genes you inherit from your parents can contribute to your risk of developing Alzheimer's disease, although the actual increase in risk is small. But in a few families, Alzheimer's disease is caused by the inheritance of a single gene and the risks of the condition being passed on are much higher. If several of your family members have developed dementia over the generations, and particularly at a young age, you may want to seek genetic counselling for information and advice about your chances of developing Alzheimer's disease when you're older. The Alzheimer's Society website has more information about the genetics of dementia.

Down's syndrome

People with Down's syndrome are at a higher risk of developing Alzheimer's disease. This is because the genetic changes that cause Down's syndrome can also cause amyloid plaques to build up in the brain over time, which can lead to Alzheimer's disease in some people.

Head injuries

People who have had a severe head injury may be at higher risk of developing Alzheimer's disease, but much research is still needed in this area.

Cardiovascular disease

Research shows that several lifestyle factors and conditions associated with cardiovascular disease can increase the risk of Alzheimer's disease.
These include:

- Smoking
- Obesity
- Diabetes
- High blood pressure
- High cholesterol

Genetic factor of AD

In familial AD, genetic mutations in APP, presenilin 1, and presenilin 2 have been recognized. γ-Secretase, an enzyme linked to overproduction of insoluble Aβ, is encoded by presenilin 1 and presenilin2. In sporadic AD, polymorphism in multiple genes has been identified. Among them is polymorphism in the ε4 and ε2 variants of the apolipoprotein E (APOE) gene. So, APOE is considered one of the most fundamental risk factors of sporadic AD. Some studies revealed that the genetic factor accounts for about 80% of AD**.**

Environmental factors

Air pollutions, tobacco smoke, pesticides, Exposure to electromagnetic fields, Solvents and aluminium could elevate the risks of AD.

Other risk factors

In addition, the latest research suggests that other factors are also important, although this does not mean these factors are directly responsible for causing dementia.

These include:

- Hearing loss
- Untreated depression (though depression can also be one of the symptoms of Alzheimer's disease)
- Loneliness or social isolation
- Sedentary lifestyle

Pathophysiology of Alzheimer's disease (AD):

❖ Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also with subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus.[18]

Several mechanisms have been proposed to explain changes in the brain that result in symptoms of AD, including misfolding of proteins (Aß aggregation and deposition leading to the formation of plaques and hyperphosphorylation of tau protein leading to NFT development); synaptic failure and depletion of neurotrophins and neurotransmitters; and mitochondrial dysfunction (oxidative stress, impaired insulin signalling in the brain, vascular injury, inflammatory processes, loss of calcium regulation, and defects in cholesterol

metabolism).[19]

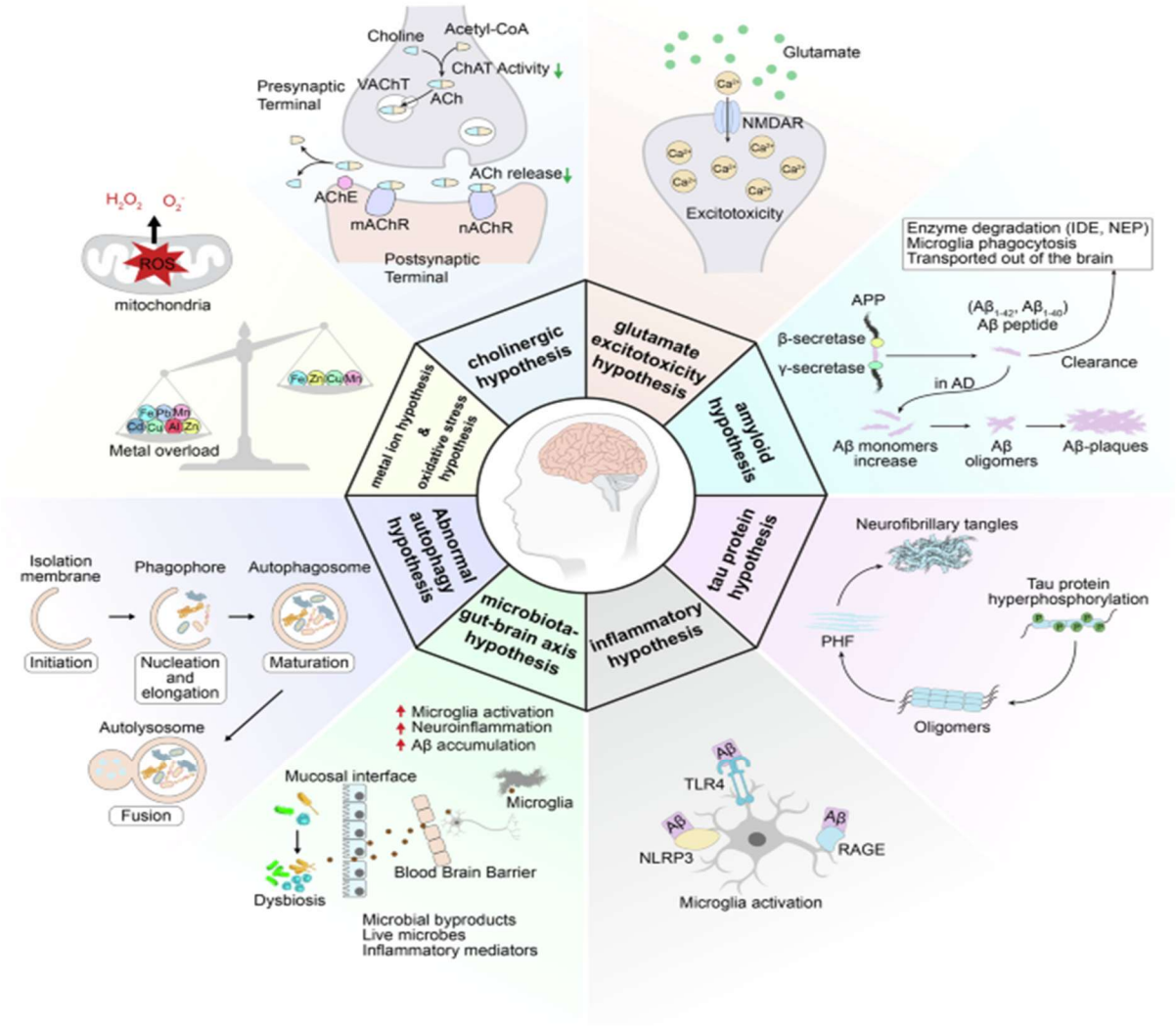


FIGURE NO 6: Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies.

Diagram for the pathogenesis of AD, including the cholinergic hypothesis, the glutamatergic hypothesis, the amyloid hypothesis, the tau protein hypothesis, the inflammatory hypothesis, the microbiota-gut-brain axis hypothesis, the oxidative stress hypothesis, the metal ion hypothesis, and the abnormal autophagy hypothesis.[20]

Signalling pathways linked to AD pathogenesis

a) Neuroinflammatory signalling:

Several pathological factors in AD, such as Aβ, pro-inflammatory cytokines, and oxidative stress, activate microglia and initiate downstream signalling pathways such as MAPK, NF-κB, and PI3K/Akt. The activation of these pathways further promotes the activation of microglia and the production of inflammatory mediators, exacerbating neurotoxicity.

b) Lysosomal dysfunction:

Lysosomes rely on a rich array of acidic hydrolases to selectively degrade and recycle both intracellular and extracellular materials, playing a crucial role in maintaining cellular homeostasis. Lysosomal dysfunction is considered a critical factor in the development of many

diseases, which may manifest as impaired acidification, abnormal expression of lysosomal enzymes, lysosomal membrane stability issues, transport defects, and defects in autophagosome/endosome-lysosome fusion.

c) Cholesterol metabolism:

Cholesterol is abundant in the brain, serving as a critical component of the myelin sheath and the membranes of neural cells, including neurons and glial cells. The balance between cholesterol synthesis, transport, metabolism, and clearance is crucial for neuronal growth, synaptic plasticity, and learning and memory functions. In AD, cholesterol biosynthesis and catabolism are impaired, contributing to the progression of AD through mediation of Aβ, tau, inflammation, and other pathological changes.

d) Mitochondrial dysfunction:

Mitochondria are the primary source of cellular energy and mediate a multitude of biological processes including biosynthesis, redox balance, calcium signalling, and apoptosis, serving as the core drivers of vital activities. Observations in AD-afflicted brains of regionally reduced glucose metabolism and alterations in several mitochondrial enzyme activities suggest mitochondrial dysfunction. This is primarily manifested by defects in energy metabolism, increased oxidative stress, calcium ion imbalance, and abnormal mitochondrial dynamics, all potentially leading to neuronal dysfunction and even apoptosis, exacerbating the neurodegenerative changes in AD.

e) Calcium signalling:

Intracellular calcium could originate from the opening of plasma membrane calcium channels, such as voltage-gated and ligand-gated calcium channels, and the release of organelles like the ER and mitochondria. Calcium plays a multifaceted role in regulating gene expression, neurotransmitter release, membrane excitability, and inducing synaptic plasticity. Additionally, plasma membrane calcium ATPases (PMCA), the sarco/ER calcium ATPase (SERCA), the sodium-calcium exchangers (NCX), and Ca^{2+}-binding proteins also regulate cytosolic calcium concentration. Maintaining this calcium homeostasis is fundamental to calcium signalling, and disruption in cytosolic calcium concentration gradients, as well as abnormalities in calcium signalling pathways, may lead to neurodegenerative diseases such as AD and Parkinson's disease (PD), cardiovascular diseases, and metabolic disorders.

f) Insulin signalling:

Insulin regulates glucose metabolism, neuronal growth and survival, synaptic plasticity, and cognition, functions closely linked to two main insulin signaling pathways: phosphatidylinositol 3-kinase (PI3K)-Akt and Ras/Raf-MAPK. The PI3K-Akt pathway is a crucial component of insulin signaling, and in AD brains, there is observed a decrease in IRS-associated PI3K activity and reduced phosphorylation of Akt kinase. Lower levels of Akt activation weaken the inhibition of glycogen synthase kinase-3 (GSK-3), which in turn positively affects the phosphorylation of tau protein and the production of Aβ. mTORC1, a downstream molecule of Akt, also serves as a critical nexus linking insulin signaling with the autophagy system. Its role in the inhibitory phosphorylation of IRS1, synaptic protein synthesis, synaptic plasticity, and autophagy regulation is significantly correlated with the accumulation of pathological protein aggregates and impaired learning and memory functions in AD.

g) Dysregulated neurotrophic signalling pathway:

Neurotrophic factors not only promote the survival, growth, and differentiation of neurons but are also crucial for maintaining synaptic plasticity and neuronal signalling functions. In AD, key neurotrophic factors include NGF and brain-derived neurotrophic factor (BDNF), which exert their effects through specific receptors such as tropomyosin-related kinase (Trk) and $p75^{NTR}$ ($Protein^{75kDa}$ neutrophil receptor), further promoting the degeneration of basal forebrain cholinergic neurons.

h) BBB dysfunction:

The BBB is formed by components such as endothelial cells, astrocytes, and pericytes, along with the basement membrane, and together with other cells like microglia and neurons, they constitute the neurovascular unit (NVU). The BBB not only allows highly selective permeability of substances entering and exiting through specialized structures (seal off adjacent BECs) but also dynamically regulates cerebral blood flow through the process of neurovascular coupling, maintaining homeostasis and neuronal function in the CNS.

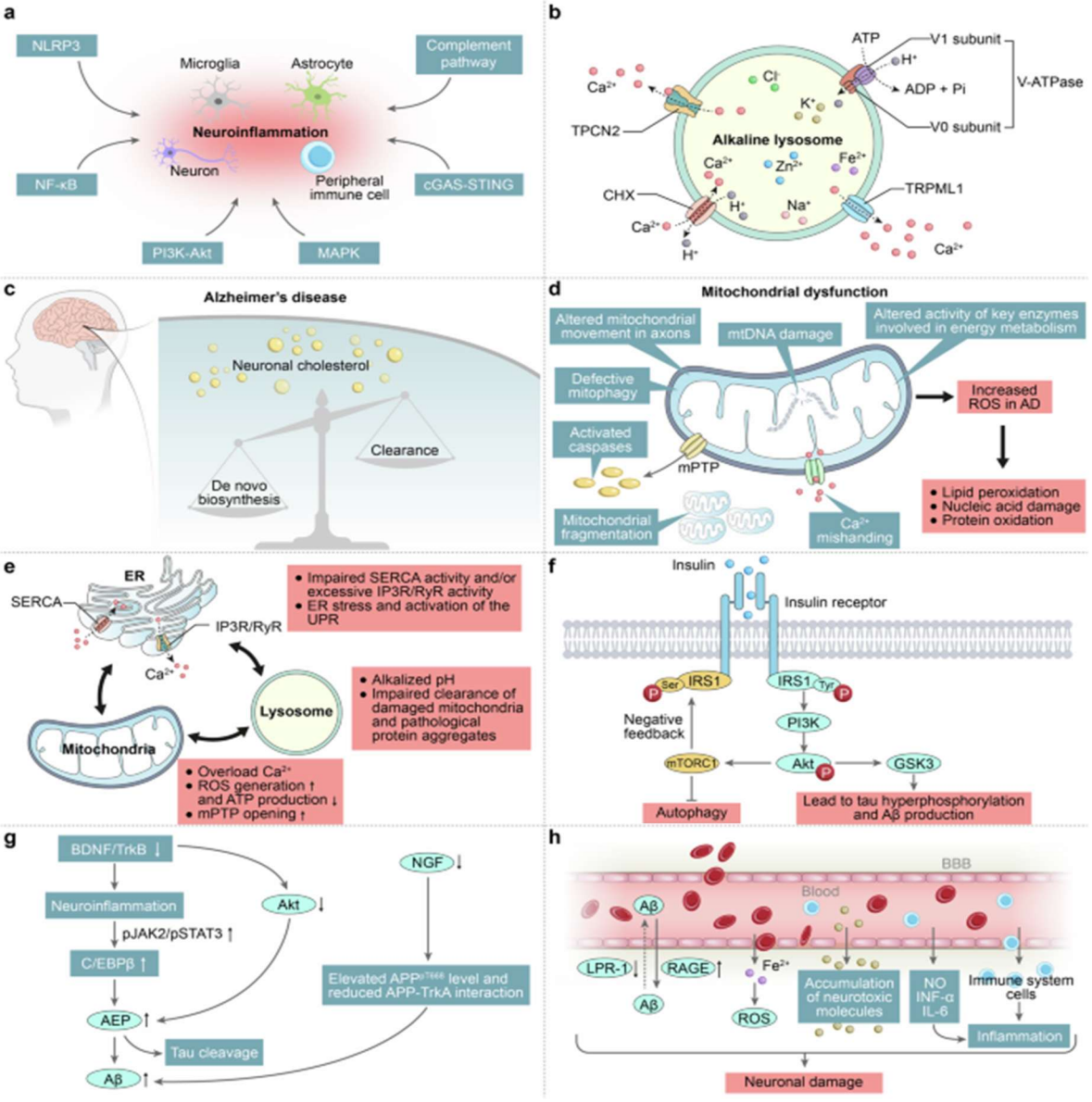


FIGURE NO 7: Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies

a) Neuroinflammatory signalling
b) Lysosomal dysfunction
c) Cholesterol metabolism
d) Mitochondrial dysfunction
e) Calcium signalling
f) Insulin signalling
g) Dysregulated neurotrophic signalling pathway
h) BBB dysfunction

DIAGNOSTIC TESTS FOR ALZHEIMERS DISEASE

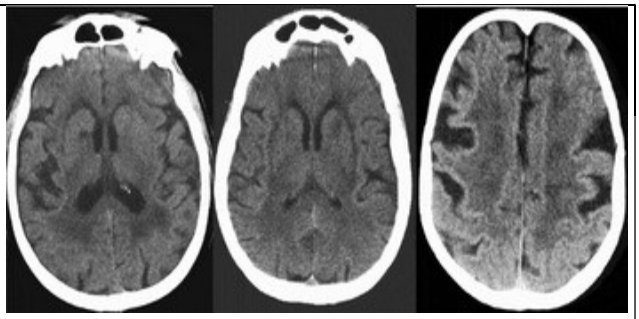
Diagnosis of AD involves a combination of assessments to evaluate cognitive function, brain health and other biomarkers. Here is an overview of common diagnostic tests for Alzheimer's:

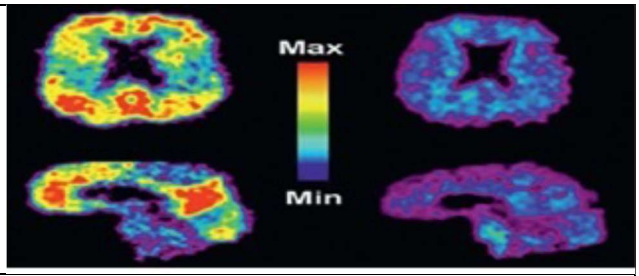
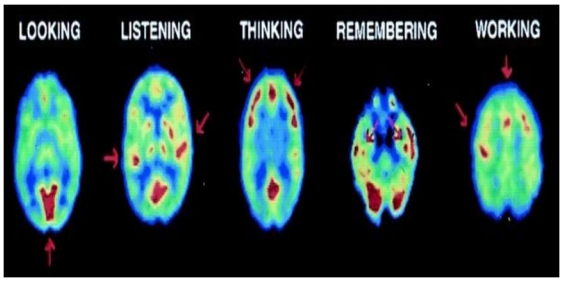
1. **MEDICAL HISTORY AND PHYSICAL EXAMINATION:**
   - **Medical history** - including gathering information about symptoms, family history of dementia, medications and any medical condition which may affect cognition.
   - **Physical examination** - include assessing sensory functions, movement, reflexes etc which may contribute to cognitive performance [21]

2. **COGNITIVE TESTING:**
   - **Mini - Mental State Examination and Montreal Cognitive Assessment** -are common cognitive screening tools used to evaluate memory, problem solving skills etc
   - **Neuropsychological tests:** helps identifying specific pattern of cognitive decline. [22]

3. **CEREBROSPINAL FLUID ANALYSIS:**
   - Lumbar puncture can measure levels of amyloid-beta, tau and phosphorylated tau proteins in CSF, abnormal levels of which is associated with Alzheimer's Pathophysiology. [23]

4. **BRAIN IMAGING TECHNIQUES:**
   These are also used a imaging biomarkers for diagnosis of AD

COMPUTED TOMOGRAPHY SCAN (CT-SCAN)	
It can rule out conditions like brain tumours, stroke or haemorrhages that may cause symptoms similar to Alzheimer's	
MAGNETIC RESONANCE IMAGING (MRI)	

Identifies structural brain changes like atrophy, particularly in the hippocampus and other regions associated with Alzheimer's	
POSITRON EMISSION TOMOGRAPHY (PET SCAN) Specialised PET scan can measure brain metabolism (FDG-PET) or amyloid beta plaques and tau tangles associated with Alzheimer's	

- **Functional MRI**: It reflects neural activity by measuring glucose metabolic rate in the brain, which is usually impaired before structural anatomic brain changes become detectable
- **Structural MRI**: most widely used neuro imaging techniques to support the diagnosis of AD is structural magnetic resonance imaging (MRI), the most commonly used sequence being T1-weighted showing good contrast between gray and white matter
- **Single-Photon Emission Computed Tomography (SPECT)** is more economical than the other techniques, but it is particularly delicate for the initial examination of changes in cerebral blood flow. It is particularly used when analysing the cerebral functions.[24]

5. **EMERGING BIOMARKER TEST** :
   - **Blood biomarker test** - There are advancements in development of blood tests that detects Alzheimer related proteins which includes beta amyloid and tau which is less invasive and easily accessible tool
     - **Amyloid beta** - production and deposition of these cells is root cause for development of Alzheimer's diseases.
     - **Tau** - Elevated levels of tau proteins in csf is key characteristics of AD
     - **Neuro filament light** - can predict progression of cognitive decline, brain atrophy in people with AD
     - **Phosphorylated tau** - Here the tau protein gets abnormally phosphorylated present in AD
   - **Genomic testing** - there are some advanced genomic profiling to identify genetic variants associated with Alzheimer's but it is not widely used in routine diagnostics.[25]

6. **NEUROPSYCHOLOGICAL TESTING**
   - **Electroencephalogram (EEG)** - is useful for detecting abnormalities in brain wave patterns associated with decline in cognitive functions
   - **Electromyogram (EMG)** - is useful in differentiating AD from other neurological related disorders which involves motor dysfunctions.[26]

NON-PHARMACOLOGICAL STRATEGIES TO SLOW DISEASE PROGRESSION: [27-28]

Non pharmacological therapies have become more important over the last number of years, as evidence of the role of certain protective factors against the progression of dementia have become available, e.g. physical activity, life style factors and educational stimuli. since there is no current cure for AD - a degenerative disease that negatively affects the quality of life of patient as well as of the family or career - non- pharmacological treatment interventions should be considered.

Strategy	Role in slowing disease progression
Blood pressure	• Blood pressure monitoring may have direct benefit on patients physical and cognitive health. • Anti-hypertensive medications which manipulate the RAS may be neuroprotective.
Diet	• Adherence to a healthy diet should be advised and supported. • Lower rate of mortality in those who follow a Mediterranean diet. • Personalised supplementation to address specific dietary deficiencies, e.g. vit D, VIT B12 and folate, may be useful. • Sunlight exposure for improving vit D intake
Exercise	• Almost any physical activity maintained by AD patients may have a role in slowing the progression of cognitive and functional symptoms. • Exercise helps to protect from consequences of frailty.
Cognitive stimulation therapy	• Improvements in MMSE. • Improvement in quality of life. • See table II
Social networks	• Maintaining social networks help maintain independence and quality of life. • Social engagement can reduce agitation-encourage ways to improve social interaction.
Behavioural and psychological symptoms of Dementia(BPSD)	• Medicines used for behavioural and psychological symptoms have limited effect in AD population. Non-pharmacological interventions for symptoms of agitation, depression and psychosis need to be investigated further. • Social engagement and steps taken to improve quality of life via diet, physical activity and pain management to protect from distressing symptoms.

Category	Approach	Benefits
Reality orientation (RO)	• *Informal RO :* Care staff should continuously convey basic information about who the patients is, where he/she is and what time it is. • *Formal/class RO :* Patients meet daily, for 30-40min sessions in a classroom; perform specific tasks, e.g. rehearsal of spatial and temporal information,	• Temporally and spatially reorient patients. • Beneficial effects on cognition for mild to moderate AD. • Enhance the conventional pharmacological treatment.

	discussion of current social events/episodes of their personal stories with supportive material, such as a whiteboard or newspapers.	
Cognitive stimulation therapy (CST)	• *5-week programme*: Visual imagery, word association and categorization tasks. • *14-session programme*: Physical games, sounds, childhood, food, current affairs, scenes, word association, being creative, categorising objects, orientation, using money, number games, word games and team quiz; session + 45minutes long; starts with warm-up activity and song, choosing a group name; themed sessions that incorporate a RO board, reminiscence, multisensory stimulation and implicit learning.	• Beneficial effects for mild to moderate AD patients, stable on cholinesterase inhibitor treatment. • Significant cognitive effects and slow down decline. • Preserve implicit memory. • Reduce neuropsychiatric disturbances, particularly depression/dysphoria, apathy.
Reminiscence	Two types of individual and group sessions: • Guided by an individual's free call 1.Group meeting at least once a week 2.Patients encouraged to about past experiences, activities, and events. • Using a life review procedure 1.Patients actively search for autobiographical memories and rebuilding their life story. 2.Construction of a life book with personal materials to serve as a memory aid, e.g. photographs, music	• Improve global cognition. • Reduced depressive symptoms.
Spaced retrieval	• Association of names with faces, or names with objects. • Patients are trained to recall information over progressively longer intervals of time.	• Increased retention span. • Recall of meaningful items. • Maintenance effects of spaced retrieval training.
Music therapy	• Benefits of use of sounds: Socialization, communication, coordination and expression. • Music sessions usually consist of listening to songs of different styles in a passive or participative manner.	• Benefits up to advanced stage of AD. • Reduction in frequency and extent of neuropsychiatric symptoms especially anxiety and depression. • Stimulates memory.

	• Helps the recovery of memories by evoking autobiographical events together with a sense of personal dignity and self-awareness. • Stimulates communication skills, impaired due to AD, leading to isolation because of inability to speak.	• Improved and communication and personal autonomy.
Bright light therapy	• Reduce circadian rhythm deregulation and likelihood of night time disturbances and sun syndrome, i.e. confusion/agitation in late afternoon/early evening. • Bright light consists of a set of fluorescent bulbs installed in a box; patients should sit close to the light box, with their eyes open. but not looking directly at light.	• Indication of changes in: agitation/aggression; depression/dysphoria; aberrant motor behaviour; appetite/eating disorders[1]
Visual art therapy	• It is based on painting, sculpting or colouring • Patients with cognitive difficulties gradually loss their ability to verbalize their thinking and feelings, basic visual and motor skills remain for a longer time	• Helps patients to express their feelings and share their stories • It is suitable for all dementia phases[2]

Basic principles of care for the patient with AD:[29]

• Help family members, friends and others understand the disease.

• Find the optimal level of autonomy and adjust expectations for patient performance over time.

• Changes in communication skills

- ✓ Consider vision, hearing, or other sensory impairments to adapt.

• Changes in personality and behaviour

- ✓ Avoid confrontation.
- ✓ Remain calm, firm, and supportive, if the patient becomes upset.
- ✓ Keep the person with AD safe: In the home, when going out and when driving.
- ✓ Reduce choices, keep requests and demands of the patient simple, and avoid complex tasks that lead to frustration.
- ✓ Identify the symptom and causative factors, and adapt the caregiving environment to remedy the situation.
- ✓ Personal discomfort may trigger behaviours: Monitor for pain, hunger, thirst, constipation, full bladder, fatigue, infections, skin irritation, comfortable temperature, fears, and frustrations.
- ✓ Environmental triggers: Noise, glare, an insecure space, and too much background distraction, including television.

• Changes in activities of daily living

- ✓ Provide everyday care: Activity and exercise, healthy diet, personal hygiene, dressing and grooming.
- ✓ Adapt daily activities: Daily household chores, going out, music, eating out, travel, spiritual activities, holidays, visitors.
- ✓ Provide frequent reminders, explanations, and orientation cues.
- ✓ Employ guiding, demonstration, and reinforcement.
- ✓ Maintain a consistent, structured environment with stimulation level appropriate to the individual patient.
- ✓ Interventions should redirect the patient's attention rather than be confrontational and should specifically address known triggers. Creating a calm environment and removing stressors and triggers is key.

• Attend to medical problems

- ✓ Commonly include falls, incontinence, constipation, flu, pneumonia, dehydration.
- ✓ Bring sudden declines in function and the emergence of new symptoms to professional attention.

• Changes in intimacy and sexuality

- ✓ Address or adapt to changes in intimacy and sexuality.
- ✓ Reassure the person of love and safety.

• End-of-life care: Moving the person, prevent hurting themselves, swallowing problems, skin problems, foot care.

• Future planning: Plan ahead in terms of health, legal and financial issues.

Pharmacological management in Alzheimer's disease:

Treatments [30]

Drug Therapy: There are two types of medication used to treat Alzheimer's disease: acetylcholinesterase inhibitors and N-methyl D-aspartate antagonists. The two types work in different ways.

Cholinesterase Inhibitors: There are lower levels of a chemical called acetylcholine in the brain of a person with Alzheimer's disease. Acetylcholine performs the function of sending messages between nerve cells. Cholinesterase inhibitors (CI) aim to increase acetylcholine availability in synaptic neurotransmission in order to treat memory disturbances. Currently, three CIs are being used as the first-line treatment in mild to moderate Alzheimer's disease: donepezil, rivastigmine and galantamine. While donepezil and rivastigmine are both selective inhibitors, galantamine inhibits both ACh and butyrylcholinesterase. A meta-analysis collaborating 13 randomized, double blind trials that were designed to evaluate the effectiveness and safety of CIs showed no improvement in ADL and behavior. In addition, donepezil and rivastigmine showed no significant difference in their impact on cognitive functions, ADLs and behavior. Overall, similar benefits were observed across all three drugs. It is known that CIs are unable to halt disease progression, but they have been found to have effects for a substantial period of time. As seen in a randomized double-blind trial, patients undergoing long-term treatment with donepezil showed no beneficial loss for up to two years. In addition, there may be some added benefits to increased doses of CIs given. In a randomized, double

blind, parallel-group, 48-week study conducted to determine the efficacy and safety of a rivastigmine patch of a higher dose, deterioration of ADLs was significantly reduced and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) was improved in patients treated with higher doses. Side effects as a result of CIs are minimal and are usually limited to gastrointestinal symptoms such as diarrhea, nausea and vomiting. The National Institute for Health and Care Excellence (NICE) has issued guidelines on the use of these drugs. NICE review drugs and decides whether they represent well enough value for money to be available as part of NHS treatment.

NMDA Receptor Antagonists: Memantine is a non-competitive NMDA receptor antagonist effective in the treatment of moderate-to-severe Alzheimer's disease. The modulation of NMDA receptors results in reduced glutamate-induced excitotoxicity. Its benefits were proven in a 28-week, double blind, parallel-group study, which showed that treatment significantly, reduced deterioration in patients. Most adverse reactions to the drug were not severe and were considered to be unrelated to the drug. The positive effect on cognitive function translates to behavioural improvements: patients were less agitated and required less assistance from caregivers Improvement of the behavioural and psychological symptoms related to dementia (BPSD) was also highlighted by a meta-analysis of 6 studies involving memantine treatment. The NICE guidance [2011] recommends use of memantine as part of NHS care for severe Alzheimer's disease. NICE also recommends memantine for people with moderate Alzheimer's disease who cannot take the cholinesterase inhibitor drugs because of side effects.

Antidepressants and Antipsychotics: BPSD is a common occurrence in Alzheimer's disease and a major source of burden on caregivers. CIs and memantine help to control these symptoms to a certain extent, but as patients continue to deteriorate, control by these drugs becomes insufficient. Depression is very common, especially in the early and late courses of the disease. Antidepressants such as: selective serotonin reuptake inhibitors (SSRI: citalopram, fluoxetine, paroxetine, sertraline, trazodone), tricyclic agents and combined serotonergic and noradrenergic inhibitors may be used to counter this. Discontinuation of antidepressants in demented patients in a double blinded, randomized, parallel-group placebo controlled trial showed significant increases in depression when compared to those who continued treatment. These results are indicative of the beneficial effects of antidepressants. A typical antipsychotic used in Alzheimer's disease include olanzapine, quetiapine and risperidone, which are used to treat psychosis and agitation. However, the use of such drugs appears to be controversial, with patients showing significant declines in cognitive function with antipsychotic drugs administration when compared to patients receiving the placebo.

Disease modifying treatments: While symptomatic treatments have proven helpful, it is the finding of a cure that is most vital. Since the amyloid hypo- thesis indicates that Aß generation and deposition from overexpressed APP cleavage make up the fundamental basis of Alzheimer's disease, interest centers on anti-amyloid therapies. These therapies result in decreased production of Aß, increased clearance of Aß and the prevention of Aß aggregation into amyloid plaques. Immunotherapy has also been an area of interest as it targets the clearing of Aß peptides, which can either directly or indirectly impact cognitive decline. Focusing on decreasing Aß generation, several methods can be employed to achieve this, mainly by targeting the amyloidogenic and nonamyloidogenic pathways. ß and secretases both compete for APP, with ß- and Y-secretase processing ultimately resulting in amyloid deposition and Y-secretase generating soluble APPSC. 2Inhibiting ß- and Y-secretases while simultaneously potentiating Y-secretase action would thus reduce Aß generation and deposition overall. Scientists believe that for most people, Alzheimer's disease is caused by a combination of genetic, lifestyle and environmental factors that affect the brain over time and eventually lead to damage of brain cells.

Less than 5 percent of the time, Alzheimer's is caused by specific genetic changes that virtually guarantee a person will tend to develop the disease. Although the causes of Alzheimer's aren't yet fully understood, its effect on the brain is clear leading to damage and shrinkage of brain cells. Alzheimer's disease damages and kills brain cells to a large extent. A brain affected by Alzheimer's disease has many fewer cells and many fewer connections among surviving cells than does a healthy brain. As more and more brain cells die, Alzheimer's disease leads to significant brain shrinkage and hence to memory loss.

Table no : Pharmacological management in Alzheimer's disease

Cognitive Symptoms	Drug class	Drug	Use	Side effects
	Cholinesterase Inhibitors	Donepezil Rivastigmine Galantamine	Mild to moderate AD Donepezil also used for severe AD	Mild to moderate gastro-intestinal disturbances including; nausea, vomiting and diarrhoea, urinary incontinence, dizziness, headache, syncope, bradycardia, muscle weakness, salivation, and sweating. Abrupt discontinuation may worsen cognition and behaviour in some patients.
	N-methyl-D-aspartate (NMDA)-receptor antagonists	Memantine	Moderate to severe AD	Constipation, confusion, dizziness, hallucinations, headache, cough and hypertension.
Non-cognitive symptoms	**Antipsychotics (Atypical)**	Clozapine Risperidone	Disruptive behaviour and psychosis in AD	Somnolence, extrapyramidal symptoms, abnormal gait, worsening cognition, cerebrovascular events, hypotension and increased risk of death.
	Antipsychotics (Typical)	Haloperidol	Disruptive behaviour and psychosis in AD	
	Antidepressants	Paroxetine Venlafaxine	Depression and anxiety in AD	Gastro-intestinal disturbances including; nausea, vomiting, dyspepsia, abdominal pain, diarrhoea and constipation, anorexia, anaphylaxis, arthralgia, myalgia, dry mouth, insomnia, tremor, dizziness, hallucinations, drowsiness and urinary retention.
Long-term pre-treatment - potential preventative option	**Non-steroidal antiinflammatory drugs (NSAIDS)**	Ibuprofen Indomethacin	Patients at risk of developing AD (Potential preventative option before cognitive impairment)	Gastro-intestinal disturbances including; discomfort, nausea, vomiting, diarrhoea and occasionally bleeding and ulceration, rashes, angioedema, bronchospasm, headache, dizziness, drowsiness, nervousness, depression, insomnia, vertigo, tinnitus, photosensitivity, haematuria and fluid retention.
	3-hydroxy-3-methylglutaryl coenzyme A–reductase inhibitors	Pravastatin Lovastatin	Patients at risk of developing AD (Potential preventative option before cognitive impairment)	Myositis, rhabdomyolysis, gastro-intestinal disturbances, pancreatitis, hepatitis, jaundice, sleep disturbance, headache, dizziness, depression, paraesthesia, asthenia, peripheral neuropathy, amnesia, fatigue, sexual dysfunction, thrombocytopenia, arthralgia, visual disturbance and alopecia.

Dosing of drugs used for Cognitive symptoms[31]

Cholinesterase Inhibitors:

Drug	Brand name	Initial dose	Usual range
Donepezil	Aricept, Aricept ODT	5mg daily in the evening	5-10mg daily in mild to moderate AD 10-23mg daily in moderate to severe AD
Rivastigmine	Exelon, Exelon Patch	1.5mg twice daily (capsule, oral solution) 4.6mg/day (transdermal patch)	3-6mg twice a day (capsule, oral solution) 9.5-13.3mg/day (transdermal patch)
Galantamine	Razadyne, Razdyne ER	4mg twice daily (tablet, oral solution) 8mg daily in the morning (extended-release capsule)	8-12mg twice a day (tablet, oral solution) 16-24mg (extended-release capsule)
Tacrine	Cognex	10mg four times a day	20-40mg four times a day

*ODT orally disintegrating tablet

N-methyl-D-aspartate (NMDA) Receptor Antagonist:

Memantine	Namenda, Namenda XR	5mg daily 7mg daily (extended-release capsule)	10mg twice daily 28mg daily (extended-release capsule)

Cholinesterase Inhibitor + NMDA Receptor Antagonist:

Memantine + Donepezil	Namzaric	28mg/10mg	14-28mg/10mg daily

Medications used in treating Noncognitive symptoms of Dementia:[32]

DRUGS	Suggested Dosage in Dementia (mg/day)	Indications
Antipsychotics Haloperidol Olanzapine Quetiapine Risperidone	 0.5-4mg 2.5-10mg 12.5-200mg 0.25-2mg	Psychosis: hallucinations, delusions, suspiciousness Disruptive behaviours: agitation, aggression
Antidepressants Citalopram Fluoxetine Mirtazapine Paroxetine Sertraline Trazodone Venlafaxine	 10-20mg 5-20mg 15-45mg 10-40mg 50-200mg 75-400mg 37.5-150mg	Depression: poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, agitation
Anticonvulsants		

Carbamazepine	100-1000mg	Agitation or aggression
Others		
Buspirone	10-45mg	Disruptive behaviours
Oxazepam	10-60mg	Disruptive behaviours
Selegiline	10mg	Disruptive behaviours, agitation, anxiety, depression

- Strategies for treatment of psychotic or behavioural symptoms should include both environmental and pharmacologic interventions (e.g: antipsychotics, antidepressants, mood stabilizers, and anxiolytics).
- The potential harm to the patient or caregiver should be used as a guide for selecting the appropriate intervention.
- Despite, the widespread nature of noncognitive symptoms in AD, until recently little research has been conducted in these patients. Data from clinical trials of antidepressants and antipsychotics are now emerging, although more research is needed.

General guidelines governing therapy can be summarized as follows: use reduced doses, monitor closely, titrate dosage slowly, and document carefully. [33]

Current management of AD:

A multifactorial tailored management of AD is attempted nowadays based in the following components:

1. Open physician, caregiver, and patient communication: a sincere and successful conveying of information and feelings between them will offer opportune identifying of symptoms, exact evaluation and diagnosis, and suitable guidance.

2. Behavioral approaches:

- Consistency and simplification of environment10;

- Established routines10;

- Communicative strategies such as calm interactions, providing pleasurable activities, using simple language and “saying no” only when safety is concerned10;

- Timely planning for legal and medical decisions and needs10;

- Cognitive behavioral therapy14,15;

- Exercise therapy, light therapy, music therapy.14,15

3. Caregiver support:

- Planned short rest periods for the caregiver;

- Psychoeducation including preparing for effects of dementia on cognition, function and behaviours, expectations, avoiding situations that can worsen the symptoms or increasing the dangers for safety and well-being

- Encouraging the development of support networks for the caregivers.10

4. Pharmacological interventions:

FDA-approved AD medications: The AChEIs donepezil, galantamine, rivastigmine, and the NMDA antagonist memantine are the only FDA-approved AD medications. [34]

The U.S. Food and Drug Administration (FDA) on 2 July 2024 approved the marketing authorisation for Kisunla (Donanemab) for adults with early symptomatic Alzheimer's disease (AD), which includes mild cognitive impairment (MCI) or the mild dementia stage of Alzheimer's disease. [6] Kisunla is administered as an intravenous infusion every four weeks. It works by reducing brain amyloid and slows cognitive and functional decline.

Donanemab is the second traditional approval of an Alzheimer's treatment by the FDA, after, Leqembi (Lecanemab) in July 2023, marking another milestone in the dementia treatment landscape.

Lecanemab and Donanemab are ant amyloid medicines approved for people with mild dementia due to Alzheimer's disease and mild cognitive impairment due to Alzheimer's disease. Lecanemab is given as IV infusion every two weeks. Each infusion lasts about an hour. These medicines reduce brain amyloid and modestly slow the decline in memory, reasoning and other thinking skills. Previously, Aduhelm (Aducanumab), received accelerated approval in June 2021.

Side effects of donanemab may include flu-like symptoms, nausea, vomiting, headache, and changes in blood pressure. Rarely donanemab can cause a life-threatening allergic reaction and swelling.

Side effects of Lecanemab can include fever, flu-like symptoms, nausea, vomiting, dizziness, changes in heart rate and shortness of breath. Other medicines may be given to manage these symptoms.

Both medicines may cause serious side effects that include brain swelling or small bleeds in the brain. These side effects are called amyloid-related imaging abnormalities, also known as ARIA. Rarely, this swelling or bleeding may cause: Headache, Confusion, Dizziness, Vision changes, Nausea, Stroke-like symptoms such as weakness, and numbness, Trouble walking, Seizures, Larger brain bleeds, Death. [35]

CURRENT LANDSCAPE IN TREATMENT RESEARCH FOR ALZHEIMERS DISEASE (AD):

- In the 2024 Alzheimer's disease drug development pipeline, there are 164 clinical trials assessing 127 drugs.
- There were 48 trials in phase 3 testing 32 drugs, 90 trials in phase 2 assessing 81 drugs, and 26 trials in phase 1 testing 25 agents.
- Of the 164 trials, 34% assess disease-modifying biological agents, 41% test disease-modifying small molecule drugs, 10% evaluate cognitive enhancing agents, and 14% test drugs for the treatment of neuropsychiatric symptoms.
- Drugs in the Alzheimer's disease drug development pipeline target a wide array of targets; the most common processes targeted include neurotransmitter receptors, inflammation, amyloid, and synaptic plasticity.
- The total development time for a potential Alzheimer's disease therapy to progress from nonclinical studies to FDA review is approximately 13 years

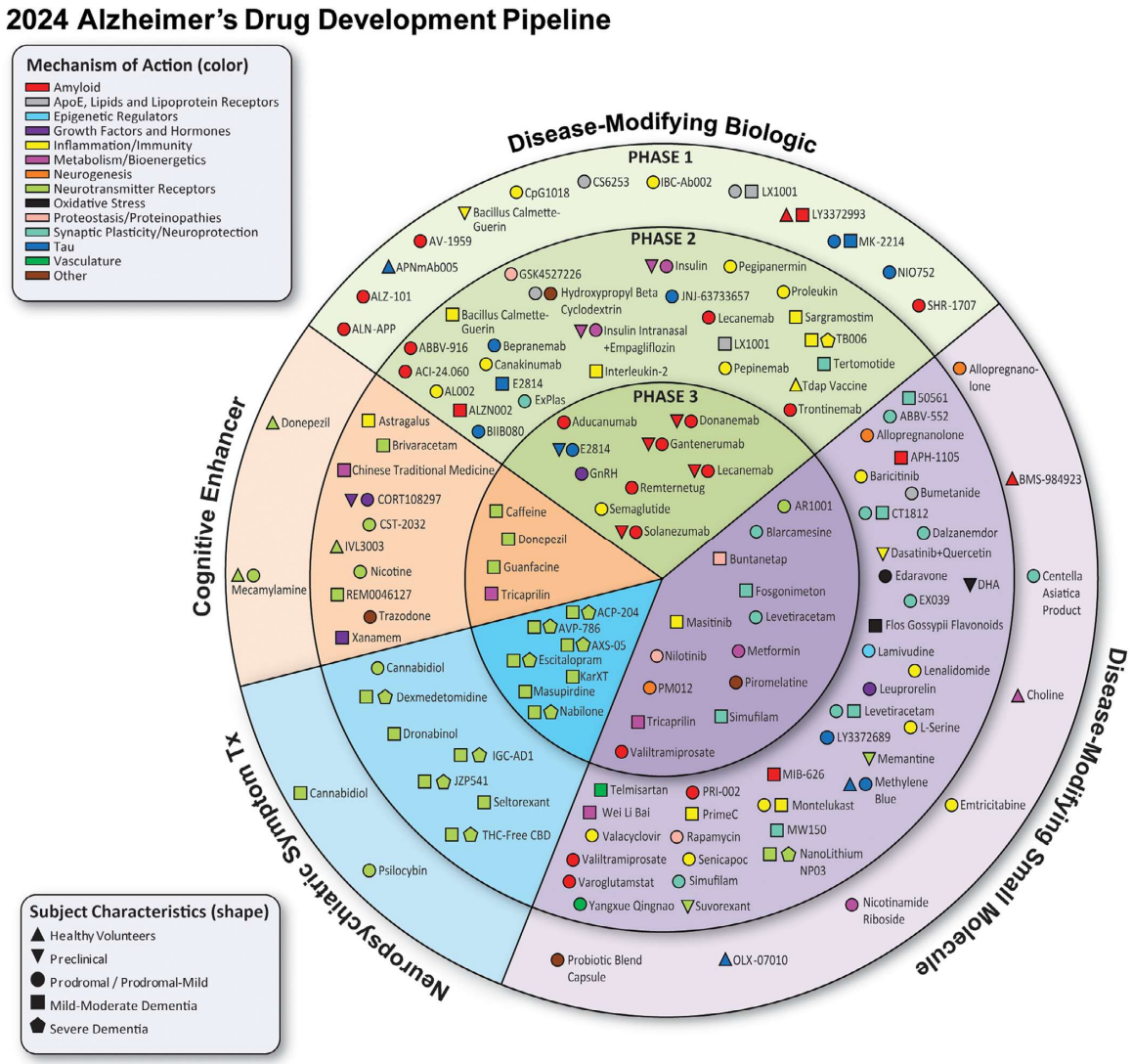


FIGURE: Agents in clinical trials for treatment of Alzheimer's disease on the Index Date of January 1, 2024, as recorded on clinicaltrials.gov. The inner ring shows Phase 3 agents; the middle ring includes Phase 2 agents; the outer ring presents Phase 1 therapies. Agents in green areas are biologics; those in purple areas are disease-modifying small molecules; agents in orange areas are symptomatic agents addressing cognitive enhancement; and those in the blue sections of the figure target behavioural and neuropsychiatric symptoms. The shape of the icon denotes the population of the trial; the color of the icon denotes the CADRO-based class of the agent (©J Cummings;Mde la Fleur, PhD, Illustrator).

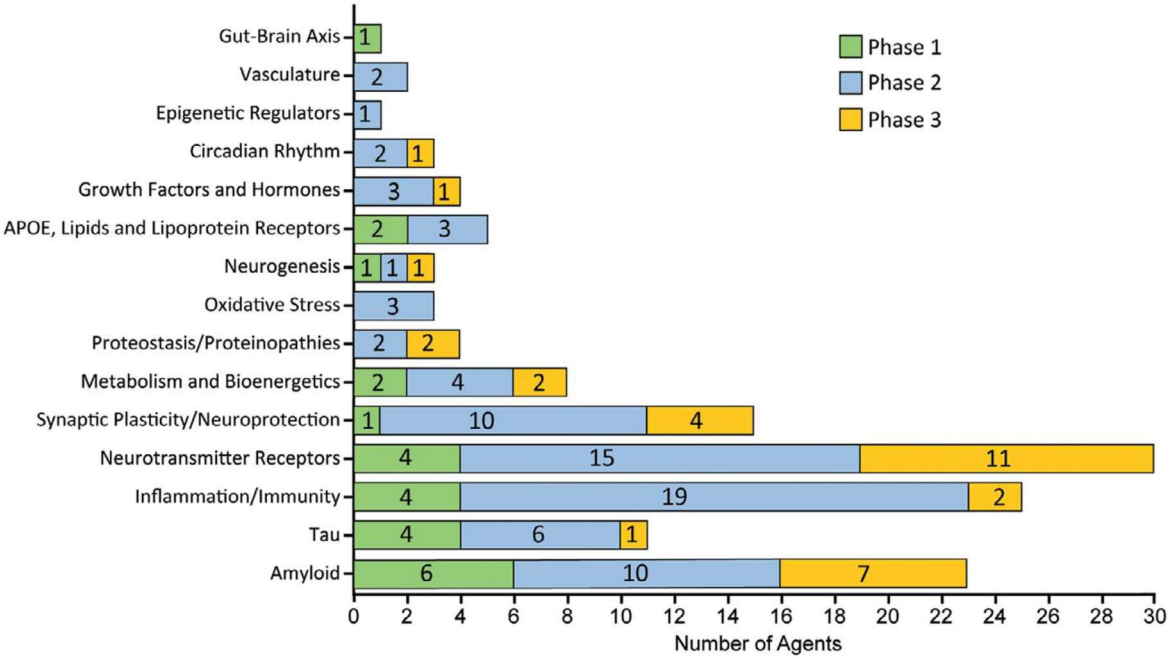


FIGURE : Alzheimer-related processes as categorized by the Common Alzheimer's Disease Research Ontology (CADRO) for agents in each phase of the Alzheimer's drug development pipeline (©J Cummings; Mde la Flor, PhD, Illustrator).

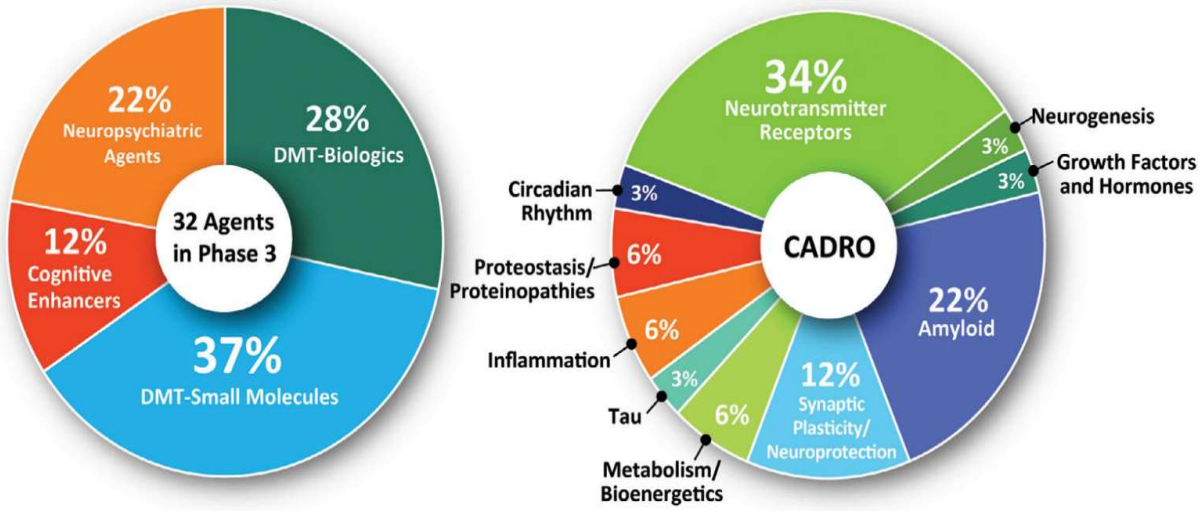


FIGURE 3 Mechanisms of action of agents in Phase 3 Alzheimer clinical trials as classified using 4 categories of therapeutic purpose (left) or the Common Alzheimer's Disease Research Ontology (CADRO) approach (right)(figure Cummings; DE la Flor, PhD, Illustrator).

Table no :1 Agents in Phase 3 Alzheimer's disease drug development (clinicaltrials.gov accessed January 1,2024).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start Date	Estimated primary completion date
ACP-204	Neuropsychiatric symptom	Neurotransmitter Receptors	Selective antagonist/inverse agonist of5-hydroxytryptamine (serotonin) receptor subtype 2A	NCT06159673	ACADIA Pharmaceuticals	Nov 2023	Jan 2028
Aducanumab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody directed at plaques and oligomers	NCT04241068 NCT05310071	Biogen Biogen	Mar 2020 Jun 2022	Aug 2023 Dec 2025
AR1001	Disease-modifying small molecule	Neurotransmitter receptors	PDE5 inhibitor that reduces amyloid production and decreases inflammation in animal models of AD	NCT05531526	AriBio Co., Ltd.	Dec 2022	Dec 2025
AVP-786	Neuropsychiatric symptom	Neurotransmitter receptors	NMDA receptor antagonist, sigma 1 receptor agonist; serotonin and norepinephrine transporter inhibitor	NCT02446132 NCT03393520 NCT04408755 NCT04464564	Otsuka Pharmaceutical Development & Commercialization, Inc	Dec 2015 Jul 2020 Jul 2020 Sep 2020	Jul 2025 Dec 2023 Dec 2024
AXS-05	Neuropsychiatric symptom	Neurotransmitter receptors	NMDA receptor antagonist, sigma 1 receptor agonist; serotonin and norepinephrine transporter inhibitor	NCT04947553 NCT05557409	Axsome Therapeutics, Inc.	Jun 2021 Sep 2022	Jun 2023 Jun 2025
Blarcamesine	Disease-modifying small molecule	Synaptic plastic-ity/neuroprotection	Sigma-1 receptor agonist, M2 auto receptor antagonist	NCT04314934	Anavex Life Sciences Corp.	Oct 2019	Jul 2024
Buntanetap	Disease-modifying small molecule	Proteostasis/proteinopathies	Decrease protein translation	NCT05686044	Annovis Bio Inc.	Apr 2023	Feb 2024
Caffeine	Cognitive enhancement	Neurotransmitter receptors	Adenosine antagonist; non-specific phosphodiesterase inhibitor	NCT04570085	University Hospital, Lille	Mar 2021	Nov 2024
Donanemab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody specific for pyroglutamate plaque amyloid	NCT04437511 NCT05026866 NCT05508789 NCT05738486	Eli Lilly and Company	Jun 2020 Aug 2021 Oct 2022 Feb 2023	Apr 2023 Oct 2027 Apr 2027 Mar 2024
Donepezil	Cognitive enhancement	Neurotransmitter receptors	Acetylcholinesterase inhibitor; adipokine modulation	NCT04661280 NCT05592678	Assistance Publique—Hôpitaux de Paris The University of Texas Health Science Center at San Antonio	Feb 2022 Mar 2024	Aug 2026 Nov 2028
E2814	Disease-modifying biologic	Tau	Anti-tau monoclonal antibody	NCT01760005 NCT05269394	Washington University School of Medicine	Dec 2012 Dec 2021	Oct 2027 Jul 2027
Escitalopram	Neuropsychiatric symptom	Neurotransmitter receptors	Selective serotonin reuptake inhibitor	NCT03108846	JHSPH Center for Clinical Trials	Jan 2018	May 2024

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start Date	Estimated primary completion date
Fosgonimeton	Disease-modifying small molecule	Synaptic plastic-ity/neuroprotection	Hepatocyte growth factor (HGF); activates signaling via the hepatocyte growth factor (HGF)/MET receptor system; promotes survival of neurons enhances hippocampal synaptic plasticity	NCT04488419 NCT04886063	Athira Pharma	Sep2020 Jun 2021	Jul 2024 Jan 2027
Gantenerumab	Disease-modifying biologic	Amyloid beta Growth factors and	Anti-amyloid monoclonal antibody	NCT01760005	Washington University School of Medicine	Dec 2012	Oct 2027
GnRH	Disease-modifying biologic	Growth factors and hormones	Anti-aging	NCT04390646	Nelly Pitteloud	Aug 2020	Dec 2028
Guanfacine	Cognitive enhancement	Neurotransmitter receptors	Alpha-2 adrenergic agonist	NCT03116126	Imperial College London	Jan 2019	Dec 2022
KarXT	Neuropsychiatric	Neurotransmitter	Muscarinic cholinergic agonist with	NCT05511363	Karuna Therapeutics	Aug 2022	Mar 2025
	symptom	receptors	peripheral anticholinergic	NCT05980949		Jul 2023	Apr 2026
				NCT06126224		Dec 2023	Jul 2025
Lecanemab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody directed at amyloid protofibrils and amyloid plaques	NCT01760005 NCT03887455 NCT04468659 NCT05269394	Washington University School of Medicine Eisai Inc. Eisai Inc. Washington University School of Medicine	Dec2012 Mar2019 Jul 2020 Dec2021	Oct 2027 Sep 2027 Oct 2027 Jul 2027
Levetiracetam	Disease-modifying smallmolecule	Synaptic plasticity/ neuroprotection-	Modulator of the synaptic vesicle protein (SV2A) to reduce aberrant neuronal hyperactivity	NCT05986721	AgeneBio	Dec 2024	Jul 2028
Masitinib	Disease-modifying smallmolecule	Inflammation	Tyrosine kinase inhibitor; exhibits neuroprotection via inhibition of mast cell and microglia/macrophage activity	NCT05564169	AB Science	Jan 2024	Dec 2026
Masupirdine	Neuropsychiatric symptom	Neurotransmitter receptors	5HT6 receptor antagonist	NCT05397639	Suven Life Sciences Limited	Nov 2022	Jan 2025
Metformin	Disease-modifying Small molecule	Metabolism and bioenergetics	Insulin sensitizer	NCT04098666	Columbia University	Mar 2021	Mar 2026
Nabilone	Neuropsychiatric symptom	Neurotransmitter receptorsr	Synthetic cannabinoid; cannabinoid	NCT04516057	Sunnybrook Health Sciences Center	Feb 2021	Oct 2025

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start Date	Estimated primary completion date
Nilotinib BE	Disease-modifying Small molecule	Proteostasis/ Proteinopathies	Abl tyrosine kinase inhibitor; autophagy enhancer	NCT05143528	KeifeRx, LLC	Feb 2022	Dec 2025
Piromelatine	Disease-modifying Small molecule	Circadian rhythm	Melatonin and serotonin receptor agonis	NCT05267535	Neurim Pharmaceuticals Ltd.	May 2022	May 2024
PM012	Disease-modifying Small molecule	Neurogenesis	Upregulation of BDNF	NCT05811000	Mediforum Ltd., Co.	Nov 2020	Feb 2021
Remternetug	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT05463731	Eli Lilly and Company	Aug 2022	Oct 2025
Semaglutide	Disease-modifying biologic	Inflammation	GLP-1 agonist; anti-inflammatory and insulin sensitivity effects	NCT04777396 NCT04777409 NCT05891496	Novo Nordisk A/S	May 2021 May 2021 Jun 2023	Sep 2025 Sep 2025 May 2024
Simufilam	Disease-modifying smallmolecule	Synaptic plasticity/ neuroprotection -	Filamin A conformation stabilizer; disrupts the interaction of filamin A with the alpha 7 nicotinic acetylcholine receptor to reduce tau hyperphosphorylation and neurodegeneration; dependent on A-beta's signaling via the alpha 7 pathway	NCT04994483 NCT05026177 NCT05575076	Cassava Sciences, Inc.	Nov 2021 Nov 2021 Nov 2022	Oct 2024 May 2025 Jul 2026
Solanezumab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT01760005	Washington University School of Medicine	Dec 2012	Oct 2027
Tricaprilin	Cognitive enhancement	Metabolism and bioenergetics	Caprylic acid is metabolized to ketone bodies to create ketosis and stimulate mitochondria	NCT05809908	Cerecin	Jan 2024	Jan 2026
Valiltramiprosate	Disease-modifying smallmolecule	Amyloid beta	Prodrug of tramiprostate	NCT04770220	Alzheon Inc.	May 2021	May 2024

TABLE 2 Agents in Phase 2 Alzheimer's disease drug development (clinicaltrials.gov accessed January 1, 2024).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
50561	Disease-modifying smallmolecule	Synaptic plasticity/ neuroprotection -	RAC1 inhibitor (RAC family small GTPase inhibitors) enhance dendritic spine morphogenesis and synaptic plasticity	NCT05811442	Beijing Joekai Biotechnology	Apr 2023	May 2024
ABBV-552	Disease-modifying small molecule	Synaptic plastic-ity/neuroprotection	Synaptic vesicle glycoprotein 2A (SV2A) modulator	NCT05771428	AbbVie	Apr 2023	Jun 2024
ABBV-916	Disease-modifying biologic	Amyloid beta	Anti-amyloid antibody	NCT05291234	AbbVie	Aug 2022	Jan 2030

ACI-24.060	Disease-modifying biologic	Amyloid beta	Vaccine stimulates antibodies against amyloid beta protein	NCT05462106	AC Immune SA	Jun 2022	Jun 2026
AL002	Disease-modifying biologic	Inflammation	Monoclonal antibody targeting TREM2 receptors	NCT04592874 NCT05744401	Alector Inc.	Jan 2021 Jan 2023	Sep 2024 Sep 2025
Allopregnanolone	Disease-modifying small molecule	Neurogenesis	Allosteric modulator of GABA-A Receptors	NCT04838301	University of Arizona	Aug 2023	Apr 2025
ALZN002	Disease-modifying biologic	Amyloid beta	Autologous Beta-Amyloid Mutant Peptide-pulsed Dendritic Cells	NCT05834296	Alzamend Neuro, Inc.	Jul 2023	Mar 2028
APH-1105	Disease-modifying small molecule	Amyloid beta	Alpha-secretase modulator (amyloid precursor protein secretase modulator)	NCT03806478	Aphios	Jun 2023	Sep 2024
Astragalus	Cognitive enhancement	Inflammation	Undisclosed	NCT05647473	Fujian Medical University Union Hospital	Feb 2024	May 2025
Bacillus Calmette-Guerin	Disease-modifying biologic	Inflammation	Vaccine to stimulate resilience to Alzheimer-related processes	NCT05004688	Steven E Arnold, MD	Mar 2022	Oct 2023
Baricitinib	Disease-modifying small molecule	Inflammation	Janus kinase (JAK) inhibitor	NCT05189106	Massachusetts General Hospital	Dec 2022	Jul 2024
Bepranemab	Disease-modifying biologic	Tau	Anti-tau monoclonal antibody binding to central region of tau	NCT04867616	UCB Biopharma SRL	Jun 2021	May 2024
BIIB080	Disease-modifying biologic	Tau	Antisense oligonucleotide that inhibits translation of tau mRNA into the tau protein	NCT05399888	Biogen	Aug 2022	Nov 2027
Brivaracetam	Cognitive enhancement	Neurotransmitter receptors	Anticonvulsant with high affinity for synaptic vesicle protein 2A	NCT05899764	University of California, Los Angeles	Jun 2023	Jun 2028
Bumetanide	Disease-modifying small molecule	ApoE, lipids and lipoprotein receptors	Reversal of ApoE-specific AD signatures	NCT06052163	Stanford University	Oct 2023	Oct 2025
Canakinumab	Disease-modifying biologic	Inflammation	Anti-IL-1-beta monoclonal antibody	NCT04795466	Novartis Pharmaceuticals	Oct 2021	Mar 2024

Agent	**Therapeutic purpose**	**CADRO target**	**Mechanism of action**	**Clinical trial**	**Lead sponsor**	**Start date**	**Estimated primary completion date**
Cannabidiol	Neuropsychiatric	Neurotransmitter	Endocannabinoid receptor agonist	NCT05822362	University of Colorado,	Jan 2024	Apr 2028
Chinese Traditional Medicine	Cognitive enhancement	Metabolism and bioenergetics	Three herbs (Rhizoma Acori Tatarinowii, Poria cum Radix Pini, Radix Polygalae);mechanism unknown	NCT05538507	Peking UnionMedical College Hospital	Jun 2022	Jun 2024
CORT108297	Cognitive enhancement	Growth factors and hormones	Selective glucocorticoid receptor antagonist	NCT04601038	Johns Hopkins University	Jun 2021	Jun 2025
CST-2032	Cognitive enhancement	Neurotransmitter receptors	Noradrenergic agonist	NCT05104463	CuraSen Therapeutics, Inc	Apr 2022	Nov 2023
CT1812	Disease-modifying smallmolecule	Synaptic plasticity/ neuroprotection	Sigma 2 receptor antagonist; binds to sigma-2/PGRMC1 receptor and regulates Aβ oligomer-mediated synaptic toxicity	NCT03507790 NCT05531656	Cognition Therapeutics	Oct 2018 Jun 2023	Jul 2024 Apr 2027
Dalzanemdor	Disease-modifying smallmolecule	Synaptic plasticity/ neuroprotection	Enhnaces synaptic function through NMDA receptor blockade	NCT05619692	Sage Therapeutics	Dec 2022	Dec 2024

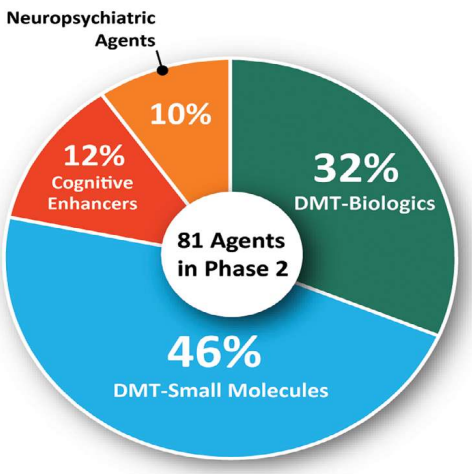
Dasatinib + Quercetin	Disease-modifying smallmolecule	Inflammation	Dasatinib induces apoptosis in senescent cells to allow their removal; quercetin is a flavonoid	NCT04685590 NCT04785300 NCT05422885	Wake Forest University Health Sciences James L. Kirkland,MD, PhD Lewis Lipsitz	Dec 2021 Jul 2022 May 2022	Jan 2025 Dec 2023 Jun 2024
Dexmedetomidine	Neuropsychiatric symptom	Neurotransmitter receptors	Presynaptic alpha-2 adrenoceptor agonist to inhibit release of norepinephrine	NCT06052254	Teikoku Pharma USA, Inc.	Dec 2023	Dec 2024
DHA	Disease-modifying smallmolecule	Oxidative stress	Omega 3 fatty acid; reduce amyloid production; improve synaptic function; antioxidant	NCT03613844	University of Southern California	Sep 2018	May 2024
Dronabinol	Neuropsychiatric symptom	Neurotransmitter receptors	CB1 and CB2 endocannabinoid receptor partial agonist	NCT02792257	Johns Hopkins University	Mar 2017	May 2024
Dronabinol + PEA	Neuropsychiatric symptom	Neurotransmitter receptors	Cannibinoid	NCT05239390	The Israeli Medical Center for Alzheimer's	Dec 2021	Jun 2023
Dronabinol + PEA	Neuropsychiatric symptom	Neurotransmitter receptors	Cannibinoid	NCT05239390	The Israeli Medical Center for Alzheimer's	Dec 2021	Jun 2023
Agent	**Therapeutic purpose**	**CADRO target**	**Mechanism of action**	**Clinical trial**	**Lead sponsor**	**Start date**	**Estimated primary completion date**
E2814	Disease-modifying biologic	Tau	Anti-tau monoclonal antibody	NCT04971733	Eisai Inc.	Jun 2021	Jul 2025
Edaravone	Disease-modifying Small molecule	Oxidative stress	Pyrazolone free-radical scavenger	NCT05323812	Treeway B.V.	Mar 2023	Jan 2024
EX039	Disease-modifying Small molecule	Synaptic plasticity/ neuroprotection	Inhibits D-amino acids oxidate to increase N-methyl-D-aspartate receptor activity	NCT05413655	Excelsior	Aug 2022	Aug 2025
ExPlas	Disease-modifying biologic	Synaptic plasticity/ neuroprotection	Plasma transfusion from exercise-trained donors	NCT05068830	Norwegian University of Science and Technology	Sep 2021	Sep 2024

Flos gossypii flavonoids	Disease-modifying small molecule	Oxidative stress	Antioxidant; anti-inflammatory	NCT05269173	Capital Medical University	Oct 2020	Jun 2024
GSK4527226	Disease-modifying biologic	Proteostasis/ proteinopathies	Monoclonal antibody to sortilin (SORT1) to improve lysosomal function	NCT06079190	GlaxoSmithKline	Oct 2023	Dec 2026
Hydroxypropyl Beta cyclodextrin	Disease-modifying biologic	ApoE, lipids and lipoprotein receptors	Modulates cholesterol transportation with secondary effects on amyloid, tau, and oxidative e stress	NCT05607615	Cyclo Therapeutics, Inc.	Sep 2022	Mar 2024
IGC-AD1	Neuropsychiatric symptom	Neurotransmitter receptors	Cannabinoid	NCT05543681	IGC Pharma LLC	Oct 2022	Jun 2025
Insulin	Disease-modifying biologic	Metabolism and bioenergetics	Decreases glucose resistance; increase insulin signaling in the brain	NCT05006599	Wake Forest University Health Sciences	May 2025	May 2029
Insulin + Empagliflozin	Disease-modifying biologic	Metabolism and bioenergetics	SGLT2 inhibitor (empagliflozin) and insulin combination therapy; decrease glucose resistance and increase insulin signaling in the brain	NCT05081219	Wake Forest University Health Sciences	Oct 2021	Oct 2026
Interleukin-2	Disease-modifying biologic	Inflammation	Restore function of regulatory T cells	NCT06096090	The Methodist Hospital Research Institute	Mar 2023	Dec 2025
IVL3003	Cognitive enhancement	Neurotransmitter receptors	Cholinesterase inhibitor	NCT05345509	Inventage Lab., Inc.	Apr 2023	Mar 2024
JNJ-63733657	Disease-modifying biologic	Tau	Monoclonal antibody targeted at soluble tau (mid-region of tau)	NCT04619420	Janssen Research & Development, LLC	Jan 2021	Mar 2025
JZP541	Neuropsychiatric symptom	Neurotransmitter receptors	Cannabinoid receptor agonists of the endocannabinoid system	NCT06014424	Sunnybrook Health Sciences Center	Sep 2023	Dec 2026
Lamivudine	Disease-modifying small molecule	Epigenetic regulators	Human immunodeficiency virus nucleoside analog reverse	NCT04552795	Bess Frost, PhD	Feb 2021	May 2023
Lecanemab	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody directed at amyloid protofibrils and amyloid plaques	NCT01767311	Eisai Inc.	Dec 2012	Feb 2025
Lenalidomide	Disease-modifying smallmolecule	Inflammation	Anti-inflammatory and immunomodulatory originally approved to treatmultiplemyeloma	NCT04032626 NCT06177028	St. Joseph's Hospital and Medical Center, Phoenix	Jul 2020 Jan 2024	Sep 2023 Jan 2026
Leuprorelin	Disease-modifying smallmolecule	Growth factors and hormone	Gonadotropin releasing hormone (GnRH) receptor agonist	NCT03649724	Weill Medical College of Cornell University	Nov 2020	Feb 2025
Levetiracetam	Disease-modifying smallmolecule	Synaptic plasticity/ neuroprotection	SV2A modulator enhancing synaptic plasticity	NCT03875638 NCT04004702	Beth Israel Deaconess Medical Center Walter Reed National MilitaryMedical Center	Aug 2019 Jan 2020	Aug 2023 Dec 2024

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
L-Serine	Disease-modifying Smalll molecule	Inflammation	Naturally-occurring dietary amino acid; inhibits toxic misfolding	NCT03062449	Aleksandra Stark	Mar 2017	Dec 2022
LX1001	Disease-modifying biologic	ApoE, lipids and lipoprotein receptors	Adeno-associated virus (AAV) gene transfer vector expressing the cDNA coding for human apolipoprotein E2 (APOE2) directly to the CNS/CSF of APOE4 homozygotes	NCT03634007	Lexeo Therapeutics	Nov 2019	Nov 2024
LY3372689	Disease-modifying Small molecule	Tau	O-GlcNAcase enzyme inhibitor	NCT05063539	Eli Lilly and Company	Sep 2021	Jul 2024
Memantine	Disease-modifying small molecule	Neurotransmitter receptors	NMDA receptor antagonist	NCT05063851	University of Virginia	Oct 2021	Dec 2025
Methylene Blue	Disease-modifying small molecule	Tau	Tau protein aggregation inhibitor	NCT02380573	The University of Texas Health Science Center at San Antonio	Jul 2015	Apr 2022
MIB-626	Disease-modifying smallmolecule	Amyloid beta	Sirtuin-nicotinamide adenine dinucleotide stimulator to enhance alpha-secretase	NCT05040321	Brigham and Women's hospital	Dec 2021	Apr 2024
Montelukast buccal film	Disease-modifying small molecule	Inflammation	Leukotriene receptor antagonist (LTRA); anti-inflammatory effects	NCT03402503	IntelGenx Corp.	Nov 2018	Feb 2024
MW150	Disease-modifying small molecule	Synaptic plastic-ity/neuroprotection	p38 alpha MAPK kinase inhibitor	NCT05194163	Neurokine Therapeutics	May 2022	Aug 2024
Nano Lithium NP03	Disease-modifying small molecule	Neurotransmitter receptors	Ion with effects on amyloid, oxidation, and inflammation	NCT05423522	Medesis Pharma SA	May 2022	Jan 2024
Nicotine transdermal patch	Cognitive enhancement	Neurotransmitter receptors	Nicotinic acetylcholine receptor agonist	NCT02720445	University of Southern California	Jan 2017	Aug 2025
Pegipanermin	Disease-modifying biologic	Inflammation	Neutralizes TNF-alpha	NCT05318976 NCT05522387	Inmune Bio, Inc.	Feb 2022 Feb 2023	Dec 2024 May 2026
Pepinemab	Disease-modifying biologic	Inflammation	Monoclonal antibody directed at semaphorin 4D; reduces inflammatory cytokine release	NCT04381468	Vaccinex Inc.	Jul 2021	Jun 2023
PRI-002	Disease-modifying smallmolecule	Amyloid beta	Interfereswith oligomerization of A-beta 42 to prevent formation and enhance reduction of A-beta oligomers	NCT06182085	PRInnovation GmbH	Dec 2023	Apr 2026

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
PrimeC	Disease-modifying small molecule	Inflammation	Combined product targeting inflammation, iron accumulation, impaired RNA regulation	NCT06185543	NeuroSense Therapeutics	Nov 2023	Nov 2025
Proleukin	Disease-modifying biologic	Inflammation	IL-2 immunomodulator	NCT05468073	Center Hospitalier St Anne	Oct 2022	Sep 2025
Rapamycin	Disease-modifying small molecule	Proteostasis/ proteinopathies	Autophagy enhancer; TOR inhibitor; immunomodulator	NCT04629495 NCT06022068	The University of Texas Health Science Center at San Antonio Karolinska Institutet	Aug 2021 Sep 2023	Dec 2023 Jan 2025
REM0046127	Cognitive enhancement	Neurotransmitter receptors	ModulatesOrai calcium (Ca2+) channel activity to normalize neuronal Ca2+ homeostasis	NCT05478031	reMYND	Jun 2022	Jun 2023
Sargramostim	Disease-modifying biologic	Inflammation	Hematopoietic growth factor granulocytemacrophage colony stimulating factor; anti-inflammatory	NCT04902703	University of Colorado, Denver	Jun 2022	Jul 2024
Seltorexant	Neuropsychiatric symptom	Circadian rhythm	Dual orexin receptor antagonist	NCT05307692	Janssen Research & Development, LLC	May 2022	Oct 2023
Senicapoc	Disease-modifying small molecule	Inflammation	Calcium-activated potassium channel inhibitor	NCT04804241	University of California, Davis	Mar 2022	Dec 2024
Simufilam	Disease-modifying Small molecule	Synaptic plasticity/ neuroprotection	Filamin A conformation stabilizer; disrupts the interaction of filamin A with the alpha 7 nicotinic acetylcholine receptor to reduce tau hyperphosphorylation and neurodegeneration; dependent on A-beta's signaling via the alpha 7 pathway	NCT05352763	Cassava Sciences, Inc.	May 2022	Oct 2025
Suvorexant	Disease-modifying Small molecule	Neurotransmitter receptors	Dual orexin receptor antagonist	NCT04629547	Washington University	May 2022	May 2026
TB006	Disease-modifying biologic	Inflammation	Monoclonal antibody targeting galactose-specific lectin (galectin) 3, a *β*-galactosidase-binding protein that activatesmacrophages; anti-inflammatory	NCT05476783	True Binding, Inc.	Sep 2022	Oct 2024
Tdap	Disease-modifying biologic	Inflammation	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine to stimulate inflammatory protection	NCT05183516	Mindful Diagnostics and Therapeutics, LLC	May 2023	Dec 2023

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
Telmisartan	Disease-modifying small molecule	Vasculature	Angiotensin II receptor blocker	NCT02085265	Sunnybrook Health Sciences Center	Mar 2014	Sep 2023
Tertomotide	Disease-modifying biologic	Synaptic plastic-ity/neuroprotection	Human telomerase reverse transcriptase (hTERT) mimic	NCT05189210	GemVax & Kael	Oct 2022	Jul 2023
THC-free cannabidiol	Neuropsychiatric symptom	Neurotransmitter receptors	Cannabinoid	NCT04436081	Eastern Virginia Medical School	Feb 2021	Mar 2024
Trazodone	Cognitive enhancement	Circadian rhythm	Serotonin reuptake inhibitor	NCT05282550	Johns Hopkins University	Jan 2023	Mar 2027
Trontinemab	Disease-modifying biologic	Amyloid beta	Monoclonal antibody directed at plaques and oligomers; “brain-shuttle” gantenerumab	NCT04639050	Hoffmann-La Roche	Mar 2021	Sep 2027
Valacyclovir	Disease-modifying small molecule	Inflammation	Anti-viral against HSV-1 and −2; reduces vira-related ‘seeding’ of amyloid plaque deposition	NCT03282916	Columbia University	Feb 2018	Dec 2024
Valiltramiprosate	Disease-modifying small molecule	Amyloid beta	Aggregation Inhibitor	NCT04693520	Alzheon Inc.	Sep 2020	Jul 2023
Varoglutamstat	Disease-modifying small molecule	Amyloid beta	Glutaminyl cyclase (QC) enzyme inhibitor to reduce production of pyroglutamate Aβ	NCT03919162 NCT04498650	Vivoryon Therapeutics N.V.	Nov 2021 Jul 2020	Nov 2023 Jan 2024
Wei Li Bai	Disease-modifying Small molecule	Metabolism and bioenergetics	Not specified; reported to regulate metabolism, improve blood circulation, and exert anti-inflammatory and antioxidant effects	NCT05670912	Capital Medical University	Oct 2022	Nov 2024
Xanamem	Cognitive enhancement	Growth factors and hormones	11-beta-hydroxysteroid dehydrogenase type 1 inhibitor	NCT06125951	Actinogen Medical	Dec 2023	Dec 2025
Yangxue Qingnao pills	Disease-modifying small molecule	Vasculature	Cerebral blood flow enhancer; traditional Chinese herbal medicine	NCT04780399	Dongzhimen Hospital, Beijing	Nov 2021	Mar 2024



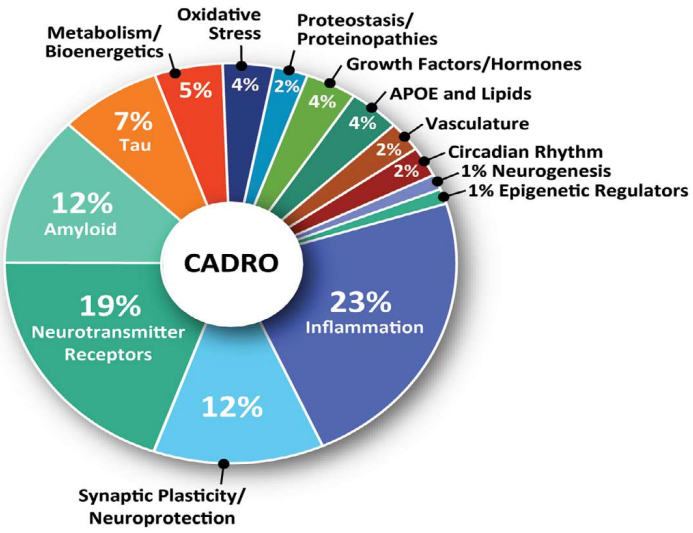


FIGURE 4 Mechanisms of action of agents in Phase 2 Alzheimer clinical trials as classified using 4 categories of therapeutic purpose (left) or the Common Alzheimer's Disease Research Ontology (CADRO) approach (right)(figure©J Cummings;Mde la Flor, PhD, Illustrator).

TABLE 3 Agents in Phase 1 Alzheimer's disease drug development (clinicaltrials.gov accessed January 1, 2024).

Agent	Therapeutic purpose	CADRO target	Mechanism of action	Clinical trial	Lead sponsor	Start date	Estimated primary completion date
Allopregnanolone	Disease-modifying Small molecule	Neurogenesis	Allosteric modulator of GABA-A Receptors	NCT03748303	University of Arizona	Oct 2019	Dec 2022
ALN-APP	Disease-modifying biologic	Amyloid beta	RNAi to decrease APP and downstream Aβ-related events	NCT05231785	Alnylam Pharmaceuticals	Feb 2022	Jul 2025
ALZ-101	Disease-modifying	Amyloid beta	Amyloid beta-directed vaccine	NCT05328115	Alzinova AB	Sep 2021	Dec 2023
AV-1959	Disease-modifying biologic	Amyloid beta	Anti-amyloid vaccine	NCT05642429	Institute for Molecular Medicine	Feb 2023	Feb 2026
Bacillus Calmette-Guerin	Disease-modifying biologic	Inflammation	Vaccine to stimulate resilience to Alzheimer-related processes	NCT06078891	Tamir Ben-Hur	Jul 2023	Jul 2024
BMS-984923	Disease-modifying Small molecule	Amyloid beta	Silent allosteric modulator (SAM) of mGluR5	NCT05804383 NCT05817643	Allyx Therapeutics	Mar 2023 Jan 2023	Oct 2024 Feb 2023
Cannabidiol	Neuropsychiatric symptom	Neurotransmitter Receptors	Cannabinoid	NCT04075435	Mclean Hospital	Jan 2021	Sep 2024
Centella asiatica product	Disease-modifying Small molecule	Synaptic Plasticity/ Neuroprotection	Antioxidant and anti-inflammatory agent with synaptic and neuroprotective effects	NCT05591027	Oregon Health and Science	Dec 2022	Nov 2024
Choline	Disease-modifying small molecule	Metabolism and Bioenergetics	Stabilizes the lipid metabolism and concomitantly restoring normal cell function by increasing phosphatidylcholine activity via the Kennedy pathway	NCT05880849	Paul E Schulz	Jun 2023	Jun 2025
CpG1018	Disease-modifying biologic	Inflammation	Toll-like receptor nine agonist leading to reduced Aβ plaques and tau pathology	NCT05606341	NYU Langone Health	Mar 2023	Nov 2024
CS6253	Disease-modifying biologic	ApoE, Lipids and Lipoprotein Receptors	Adenosine triphosphate-binding cassette transporter A1 (ABCA1) transfers lipids to ApoE, and increases clearance of A-beta from the brain	NCT05965414	Artery Therapeutics, Inc.	Oct 2023	Sep 2024
Donepezil	Cognitive enhancement	Neurotransmitter Receptors	Cholinesterase inhibitor	NCT06127368	G2GBio, Inc.	Jan 2024	Sep 2024
Emtricitabine	Disease-modifying Small molecule	Inflammation	Nucleoside reverse transcriptase inhibitor (NRTI)	NCT04500847	Butler Hospital	Dec 2021	Mar 2024
Agent	**Therapeutic purpose**	**CADRO target**	**Mechanism of action**	**Clinical trial**	**Lead sponsor**	**Start date**	**Estimated primary completion date**

IBC-Ab002	Disease-modifying biologic	Inflammation	Anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitor	NCT05551741	Immunobrain Checkpoint	Feb 2023	Oct 2024
LX1001	Disease-modifying biologic	ApoE, Lipids and Lipoprotein Receptors	Adeno-associated virus (AAV) gene transfer vector expressing the cDNA coding for human apolipoprotein E2 (APOE2) directly to the CNS/CSF of APOE4 homozygotes	NCT05400330	Lexeo Therapeutics	May 2023	Nov 2028
Mecamylamine	Cognitive enhancement	Neurotransmitter Receptors	Nicotinic antagonist	NCT04129060	University of Vermont	Mar 2020	Mar 2024
MK-2214	Disease-modifying biologic	Tau	Anti-tau monoclonal antibody	NCT05466422	Merck Sharp & Dohme LLC	Sep 2022	May 2025
Nicotinamide Riboside	Disease-modifying small molecule	Metabolism and Bioenergetics	Mitochondrial function enhancer and antioxidant	NCT04430517	Mclean Hospital	Mar 2022	Apr 2025
NIO752	Disease-modifying biologic	Tau	Anti-tau antisense oligonucleotide	NCT05469360	Novartis Pharmaceuticals	Feb 2023	Oct 2024
OLX-07010	Disease-modifying small molecule	Tau	Inhibits tau self-aggregation	NCT05696483	Oligomerix, Inc	Jan 2023	Dec 2024
Probiotic Blend Capsule	Disease-modifying Small molecule	Gut-Brain Axis	Inflammation/immunity	NCT06181513	University of Nicosia	Dec 2022	Jul 2024
Psilocybin	Neuropsychiatric symptom	Neurotransmitter Receptors	Psychedelic	NCT04123314	Johns Hopkins University	Mar 2021	Dec 2024
Remternetug	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT04451408	Eli Lilly and Company	Jul 2020	Aug 2024
SHR-1707	Disease-modifying biologic	Amyloid beta	Anti-amyloid monoclonal antibody	NCT06114745	Atridia Pty Ltd.	Jan 2024	Nov 2025

Complications of Alzheimer's Disease:

As Alzheimer's Disease is a progressive neurodegenerative disorder that primarily affects memory and cognitive function. The pathogenesis of AD involves complex mechanisms, including the accumulation of amyloid-beta plaques and tau protein tangles, leading to neuronal damage, inflammation and oxidative stress. These underlying processes contribute to several systemic and neurological complications:

1. Cognitive decline and dementia: Aβ Plaque deposition disrupts synaptic function, while tau tangles interfere with microtubule stability within neurons, impairing intracellular transport. Neuronal loss in areas like the hippocampus affects memory and learning, leading to cognitive deficits and progressive dementia.
2. Behavioural and Psychiatric complications: Neurodegeneration in the frontal and temporal lobes leads to changes in mood, behaviour and personality. Neurotransmitter imbalances (especially acetylcholine and serotonin) contribute to symptoms like agitation, depression, anxiety and psychosis.
3. Seizures: Increased excitotoxicity and loss of inhibitory neurons disrupt the balance of excitation and inhibition in the brain, leading to hyper excitability and a higher risk of seizures, especially in later stages of Alzheimer's

4. Infections: Immobility, reduced immune function and swallowing difficulties predispose patients to infections. Additionally, the autonomic dysfunction seen in AD can contribute to urinary retention, promoting urinary tract infections.
5. Malnutrition and dehydration: Impaired cognitive and motor functions affect eating and drinking habits. Swallowing difficulties due to cortical atrophy in the motor regions increase the risk of aspiration and reduce nutritional intake.
6. Falls and Fractures: Loss of coordination, muscle weakness and poor balance due to AD-related motor dysfunctions contribute to a higher risk of falls. Impaired visuospatial skills exacerbate this, increasing fracture risk and related complications
7. Sleep disturbances: AD disrupts circadian rhythms and melatonin production, resulting in altered sleep patterns. Damage to the hypothalamus, which regulates the sleep walk cycle, may lead to insomnia, nocturnal wandering and daytime sleepiness.
8. Cardiovascular complications: AD is associated with chronic inflammation, oxidative stress and vascular dysfunctions. These factors increase the risk of cardiovascular diseases, which may exacerbate brain damage and cognitive decline through reduced cerebral blood flow.
9. Death: AD is ultimately fatal, with pneumonia being a common cause of death due to weakened respiratory function, aspiration risk and a high rate of infections.
10. In summary, AD complications stem from a combination of direct neuronal damage, altered neurotransmission and systemic effects, all of which interact to increase morbidity and mortality in affected individuals.

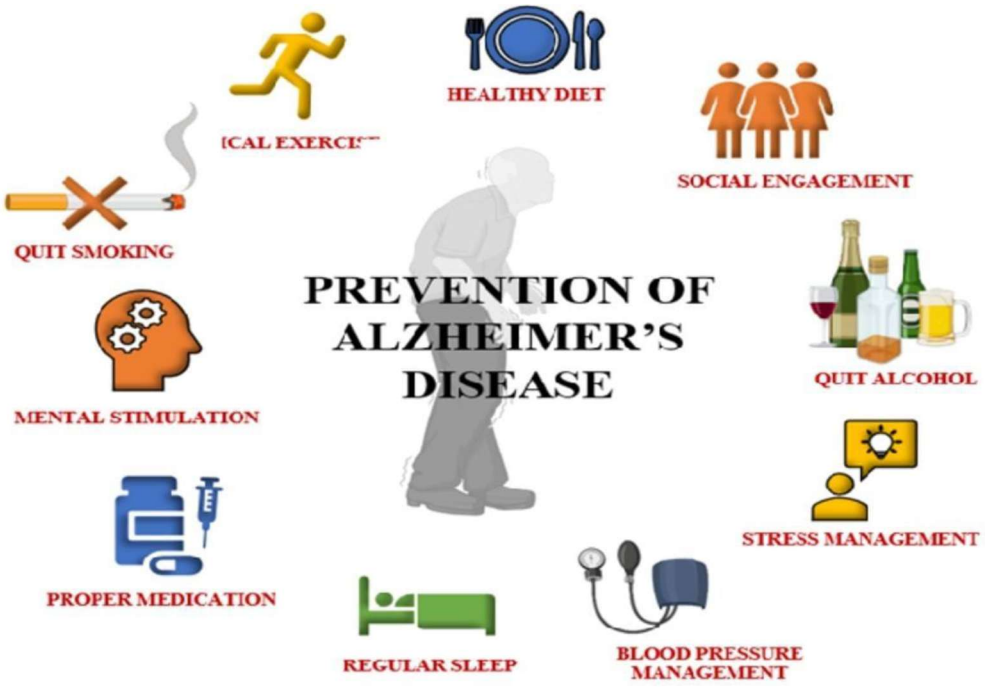
PREVENTIVE MEASURES OF ALZHEIMERS DISEASE:

 Preventive measures for Alzheimer's disease are multi factorial approach, focusing on lifestyle modifications, management of health conditions as well as cognitive involvement.

 Some of the important preventive measures include: -

- **Physical activity**: Regular aerobic exercises (like walking, swimming, cycling, jogging), strength training exercises (such as weight lifting), balance and flexibility exercises (such as yoga, tai chi etc) has been associated with improvement of brain health by increasing brain volume and improved blood flow to brain cells.
- **Balanced Diet**: DASH (Dietary approaches to stop Hypertension) therapy rich in fruits (bananas, blueberries, raspberries, oranges, grapes etc), vegetables (green leafy vegetables such as spinach, kale, broccoli, carrot, bell peppers, sweet potatoes etc), whole grains (oats, brown rice, barley, millet etc), may lower risk of Alzheimer's disease.
- **Cognitive stimulation**: Engaging mind in activities such as reading, puzzle solving, learning new skills may reduce risk of Alzheimer's disease.
- **Engagement in social activities:** Being with friends, involvement in fun activities, spending time with family with reduce risk of Alzheimer's disease.
- **Good cardiovascular health:** Maintaining good cardiovascular health by controlling Hypertension, Diabetes mellitus, obesity will reduce risk of Alzheimer's disease.
- **Stay away from alcohol and smoking:** As these have direct impact on declining of cognitive health, these are to be avoided.
- **Proper sleep:** Lack of sleep will have higher impact on cognitive impairment, so improve quality of sleep will reduce risk of Alzheimer's disease (1)

- **Cholesterol levels:** Diet rich in saturated fats (butter, cakes, fried snack items, coconut oil etc) can raise LDL cholesterol which is dangerous, whereas diets rich in omega 3 fatty acids (such as fishlike salmon, tuna, nuts and seed such as flaxseeds, chia seeds, yoghurt, kidney beans etc) may help in maintaining healthy cholesterol levels and support brain health. (2)
- **Adherence to medications:** Improved adherence to medications will improve cognitive outcomes. It can be done by use of aids such as pill organizers, alarms, reminders etc, educating the patient regarding benefits of medications, potential side effects and performing a regular follow up. (3)
- **Stress management:** Practices such as mindfulness meditation, yoga, deep breathing exercises helps to reduce stress and improve emotional wellbeing [4]



Conclusion:

a. Alsheimer's disease is the most common form of Dementia in Older adults. Alsheimer's disease has proven to be a very Complicated and stressful disease. There is no cure and it is often difficult to diagnose. AD is related to aging, Environmental and life-style issues. In some cases, there are genetic risks and factors.

b. Research is increasingly focusing on early intervention and prevention, with the goal of delaying or preventing the onset of AD in at risk-individuals. In 2024, AD drug development Pipeline, there are 164 clinical trials assessing 127 drugs target a wide array of targets include Neurotransmitter receptors, Inflammation, Amyloid and synaptic plasticity.

c. An Important area of Research in the development of Disease modifying therapies that target the underlying mechanism of AD currently being investigated in clinical trials. Immunotherapies including active and passive vaccines, Gene therapy by modifying

the Expression of genes involved in disease process. Stem cell therapy offers the potential to regenerate damaged neural tissue and restore cognitive function in individuals with AD.

d. Preventive strategies focused on modifiable risk factors, such as diet, Excise and cognitive Engagement are increasingly recognized as critical in the fight against AD. Life-style Interventions, including dietary changes, physical activity and cognitive training are being tested to determine their effectiveness in preventive AD.

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