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Alzheimer's Disease: Clinical Manifestations, Diagnostic Approaches and Therapeutic Interventions

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Abstract
Alzheimer's disease is the most prevalent cause of dementia and a progressive neurological illness. Memory, cognitive abilities, and the capacity to do basic everyday tasks are gradually destroyed by it. Today, dementia affects about 25 million individuals worldwide, with Alzheimer's disease accounting for the majority of cases. Mild, moderate, and severe are the three stages of the illness. Additionally, the symptoms differ depending on the stage. Vascular disease, Down syndrome, age, and family history are some of the reasons of this illness. Intracellular neurofibrillary tangles and extracellular amyloid plaques are the main causes. CT, MRI, and cognitive tests can be used to make a diagnosis. Partial glutamate antagonists and cholinesterase inhibitors are employed in the therapy. By engaging in certain hobbies like reading, writing, and learning foreign languages, it can be avoided. Over the past few decades, numerous drug candidates have been evaluated; however, a large proportion have failed in clinical trials, reflecting the complexity of the disease. Recent research efforts have focused on the discovery of novel biomarkers, improved cognitive and behavioural science assessment tools, early-stage patient inclusion, and innovative clinical trial methodologies to enhance the effectiveness of future therapeutic interventions. In the context of precision medicine, the integration of abnormal biomarkers with distinct brain- behaviour relationships and neuroimaging patterns may help in identifying individualized treatment strategies for patients within a personalized therapeutic approach. This concept suggests that, soon, different targeted therapies could be tailored for each patient based on their specific disease profile. This review highlights potential personalized treatment frameworks that may benefit individuals with Alzheimer's disease, along with various therapies aimed at disease progression that are currently being explored.

Keywords: Beta-Amyloid Plaques, Tau Protein, Alzheimer's Disease, Global Health, Pharmacological Treatment, Non-Pharmacological Treatment

Introduction

Alzheimer Disease

Alzheimer disease is a gradually worsening brain condition which slowly impairs memory, thinking capacity, and routine activities, making it the most common cause of impaired cognition worldwide. The illness gradually affects daily activities and quality of life, and in advanced stages patients may become completely dependent on caregivers for routine support. Memory disorder is a chronic neurological condition associated with progressive decline in cognitive abilities, which is more severe than the normal memory changes observed during aging [1]. Many neurological disorders are linked with occurrence of loss of cognitive abilities, among which progressive brain disorder accounts for the majority of cases worldwide. Nearly 50–70% of dementia cases are linked with Alzheimer's disease. Because of increased life expectancy and advancement in healthcare services, the global elderly population is continuously rising, which may further raise the incidence of dementia and other neurodegenerative disorders in the future. Forecasts indicate that by 2050, over 21% of the population would be over 60, creating a sizable old population of two billion. Illnesses correlated with aging, including cognitive disorder, have increased in frequency as the number of senior people rises. Memory loss, cognitive decline, and challenges with everyday tasks are the

hallmarks of neurological disorder, greatly prevalent kind of mental deterioration, a worsening and incurable neurological condition. Although the precise origin of AD is yet unknown, genetic factors are thought to be important. A smaller cerebral cortex and larger brain ventricles are the pathological results of neurofibrillary tangles and amyloid plaques spreading throughout the brain, which interferes with neuronal communication and causes nerve cell death [2].

Age, genetics, family history, smoking, drinking, and other elements associated with many risk factors for AD. Poor decision-making, inability to think clearly, misplacing items, difficulty moving, poor verbal communication, strange emotions, and total memory loss are all signs of AD. According to a study by the Alzheimer's Association research group, 66% of people with dementia have AD, and only 10% receive a timely diagnosis. The remaining 90% receive no diagnosis at all. Government records show that 121,404 deaths in the US in 2017 were officially attributed to AD. AD is predicted to affect 60 million people globally in the next 20 years. According to the World Alzheimer's Report, there will be 152 million Alzheimer's sufferers globally by 2050 [3].

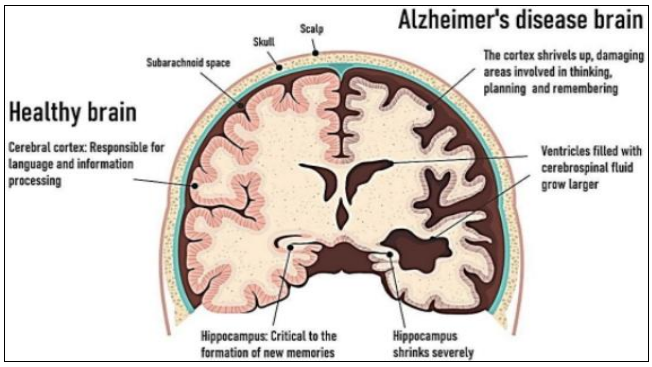

Fig 1: Difference between Normal Brain and Alzheimer Disease Brain

Sign and Symptoms

Development and trajectory of cognitive and functional changes decline, such as neuronal loss and cognitive impairments, are among the symptoms linked to AD. A leading cause of death for the elderly is AD. Globally, at least around 50 million individuals have been diagnosed with AD, and this number is projected to increase by 2050, that number is predicted to rise to 152 million. In the UK, the percentage of fatalities from cognitive disorder tripled from 4.23% to 12.53% during the preceding ten years. AD is thought to have a typical survival length of 8–10 years from diagnosis, with few exceptions where patients survived more than 20 years. In 2019, AD was the seventh most prevalent reason for death among those over 64 [4].

- Slow decline in memory that interferes with daily tasks, planning, and problem-solving.
- Difficulty performing routine activities that were previously familiar.
- Disorientation regarding time and place.
- Challenges in interpreting visual information or understanding spatial relationships.
- New language difficulties, such as problems with speaking or writing.
- Frequent loss of personal belongings and struggling to retrace steps.
- Reduced judgment or decision-making ability.
- Reduced participation in work and social engagements, or hobbies.
- Noticeable changes in mood, including irritability, depression, or anxiety.
- Alterations in personality, such as becoming more suspicious, fearful, or confused [5].

Reason and Risk for Alzheimer Disease

Several risk factors, including aging, genetics, head injuries, vascular illnesses, infections, and environmental variables (heavy metals, trace metals, and others), have been linked to AD. It is currently unclear what causes the pathological alterations in Alzheimer's disease (Aβ, NFTs, and synaptic loss). Several theories have been put forth to explain AD, but two are thought to be the primary cause: some contend that cholinergic function impairment is a significant risk factor for AD, while others propose that changes in the production and processing of amyloid β-protein are the primary initiating factor. However, there isn't yet a recognized theory to explain the pathogenesis of AD [6].

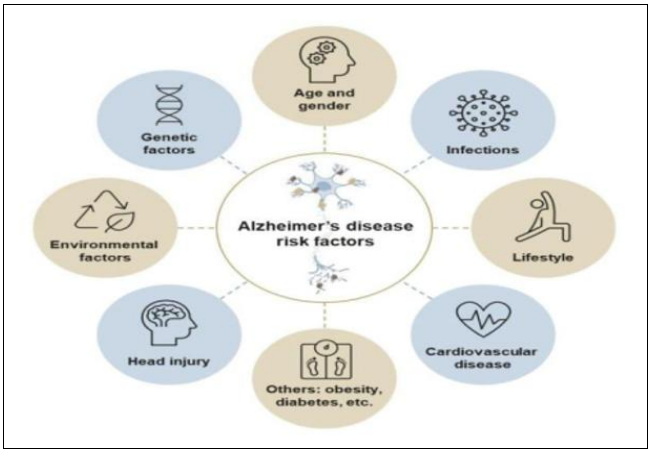

Fig 2: Reason and Risk for Alzheimer Disease

1. Aging: Advancing age is considered the predominant risk factor for Alzheimer's disease. Most AD patients have a late onset that begins beyond age 65, and younger people rarely have this condition. Aging is a complicated and irreversible process that affects many organs and cell systems. It is characterized by a decrease in brain weight and volume, a loss of synapses, and the enlargement of ventricles in certain regions along with SP deposition and NFT. Furthermore, a number of disorders, including glucose hypometabolism, cholesterol dishonesties, mitochondrial dysfunction, depression, and cognitive decline, may manifest as people age. It is challenging to differentiate the instances in early AD because these changes also occur in normal aging. Based on age of start, AD can be classified into two categories: early-onset AD (EOAD), a rare variety that accounts for 1–6% of cases. The majority of these instances are familial AD, which is defined as having multiple members in many generations with AD. EOAD often affects people between the ages of 30 and 60 or 65. The second kind, known as late-onset AD (LOAD), is more prevalent in people over 65. Families with a late-onset disease and those with a positive family history of AD may experience both forms [7].

2. Genetics: Based on age of start, AD can be classified into two categories: early-onset AD (EOAD), a rare variety that

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3. Environmental factor: Not all AD cases may be explained by aging or genetic risk factors. Air pollution, nutrition, metals, infections, and many other environmental risk factors can cause oxidative stress and inflammation, which raises the chance of developing AD. The most significant environmental variables and their connections to AD are listed here [9].

4. Air pollution: The influx of harmful chemical, physical, and biological matter into the air that alter the atmosphere's composition is what defines air pollution. It has been linked to cardiovascular and pulmonary conditions, and more recently, it has been linked to AD. The National Ambient Air Quality Standards (NAAQSs) in the United States have identified six air pollutants—ozone (O3), nitrogen oxides (NOx), carbon monoxide (CO), particulate matter (PM), sulphur dioxide (SO2), and lead—as posing a risk to human health. Exposure to high amounts of air pollution can cause damage to the olfactory mucosa and bulb in addition to the frontal brain region, similar to what is seen in AD, according to studies on animals and cellular models [10].

5. Diet: Analyses the nutritional deficiencies in AD have become more numerous in recent years. While saturated fatty acids and high calorie intake were linked to an increased risk of AD, several dietary supplements, including antioxidants, vitamins, polyphenols, and fish, were found to lower the risk. Food processing results in the degradation of heat-sensitive micronutrients (such as vitamin C and folates), significant water loss, and the production of hazardous secondary products (known as advanced glycation end products, or AGEs) from the non-enzymatic glycation of free amino groups in proteins, lipids, and nucleic acids. The capacity of AGEs to cause oxidative stress and inflammation by altering the structure and function of body proteins and cell surface receptors is known as their toxic effect [11].

6. Metals: Metals are found in both physiological systems and the natural world. They can be classified as toxicological metals, such as lead and aluminium, which have no biological role, and bio-metals, such as copper, zinc, and iron, which have physiological functions in living things. Processed foods, cosmetics, pharmaceuticals, medical preparations, and other sectors use aluminium extensively. Aluminium is attached to citrate molecules and plasma transferrin in the body, which can facilitate the movement of aluminium to the brain. Al builds up in the cortex, hippocampus, and cerebellum, where it interacts with proteins to produce misfolding, aggregation, and phosphorylation of highly phosphorylated proteins, such as tau protein, which is a hallmark of AD, according to studies [12].

7. Infections: Chronic infections of the brain and spinal cord are one of the risk factors for AD because they might lead to an accumulation of NFT and Aβ plaques. Dr. Itzhaki's research revealed that patients with ApoE-ε4 allele carriers have the DNA of the herpes simplex virus (HSV-1), which explains the elevated risk of AD. HSV-1 has the ability to multiply in the brain, which can lead to an increase in Aβ deposition and an activation of the inflammatory response, which can damage neurons and cause AD to gradually develop. However, the findings of and Balin's study have demonstrated the part that persistent bacterial infections play in AD. For instance, the accumulation of spirochete bacteria (Treponema pallidum) in the cerebral cortex induced syphilitic dementia, which resulted in catastrophic neurodegenerative illnesses with lesions resembling neurofibrillary tangles. Additionally, by activating astrocytes and cytotoxic microglia, the Chlamydia pneumonia bacteria can cause late-onset AD, interfere with calcium control and apoptosis, impair cognitive function, and raise the risk of AD [13].

8. Medical factors: Alzheimer's disease development is associated with a number of risk factors. To add to this list, cardiovascular disease (CVD), obesity, diabetes, and other diseases are common among older adults with AD. These disorders are all linked to an elevated risk of AD.

(i) Cardiovascular disease (CVDs): CVDs is considered a major contributing risk factor for AD. For example, stroke relates to a greater risk of dementia because it causes a loss of neural tissue, which intensifies the degenerative effect and affects tau and amyloid pathology. Additionally, embolisms brought on by atrial fibrillation result in stroke and a decline in neurocognitive and memory processes abilities. Additionally, cardiac failure impairs the heart's ability to pump blood, which results in an inadequate overall circulatory function and diminished cerebral blood flow, which causes insufficient oxygenation and neuronal damage. Cardiovascular disorders such as atherosclerosis, peripheral artery disease, impaired blood flow, and embolic events are thought to play a role in increasing susceptibility to Alzheimer's disease, as per the coronary heart disease hypothesis. Hypertension is linked to lumen narrowing and artery wall thickening, which lower brain tissue perfusion. In long-term cases, hypertension may also result in cerebral edema, all of which are risk factors for AD and CVD. It is possible to avoid and postpone AD by concentrating on the link between CVD and AD, which is a controllable risk factor.

(ii) Obesity and diabetes: The term "obesity" refers to excess body fat in people who consuming more calories than are expended, and it may be determined using the body mass index (BMI). Increasing body obesity is linked to a reduced blood flow to the brain, which can lead to vascular dementia, cerebral ischemia, and memory loss. Impaired glucose metabolism or diabetes, which is defined by elevated plasma glucose levels that damages peripheral tissues and vasculature, can be brought on by obesity, a poor diet, and other reasons. Because chronic hyperglycaemia increases amyloid-beta deposition, oxidative injury, mitochondrial abnormalities, and brain inflammation, it can cause cognitive impairment. Increased pro-inflammatory cytokine releases from isolated tissue, which activate lymphocytes and mononuclear phagocytes and ultimately cause systemic and local inflammation, are a hallmark of obesity. Insulin resistance, hyperinsulinemia, and ultimately hyperglycaemia is all facilitated by this inflammation. Type 2 diabetes mellitus, heart disease and oncological conditions are known risk factors for dementia and AD, and obesity is one of these conditions. Increased microglia, decreased synaptic plasticity, and compromised neurogenesis are all consequences of brain inflammation. Microglia have the ability to influence insulin receptor-mediated pathways,

substrate molecules and inhibit intracellular signalling cascades, which is crucial for brain function. As a result, changes in insulin activity may cause Aβ to build up and lessen the tau protein breakdown linked to AD [14].

Pathophysiology of Alzheimer's Disease:

Alzheimer's disease is a progressive neuronal degeneration in the brain, especially in areas responsible for memory and cognition including the hippocampus and cerebral cortex. The pathogenesis of Alzheimer's disease involves multiple interconnected processes that ultimately result in neuronal dysfunction and progressive neuronal degeneration.

1. Amyloid Beta Plaque deposition: This is considered one of the major pathological features of Alzheimer's disease. Amyloid Precursor Protein (APP) processing abnormalities are the primary cause of Alzheimer's disease. Alpha-secretase and gamma-secretase, a non-amyloidogenic route that stops plaque development, cleave APP under healthy conditions. However, in pathological situations, APP is sequentially cleaved by beta-secretase (BACE1) and gamma-secretase, which produces amyloid-beta peptides, especially the highly fibrillogenic A-beta_{1-42} form. The most neurotoxic species are known to be soluble oligomers, which are formed when these αA\beta\) monomers combine. These oligomers build up into insoluble fibrils over time, which eventually deposit as extracellular senile plaques. Severe synaptic malfunction, mitochondrial impairment, and persistent neuroinflammation caused by activated microglia are just a few of the negative downstream effects that are set off by this key accumulation [15].

2. Neurofibrillary Tangles (Tau protein): Neurons' cytoplasm and axons frequently include tau protein, a microtubule-associated protein (MAP). In essence, it is a disordered protein that has a higher propensity to create self-aggregative β-sheet structures, which ultimately result in the production of NFT. Tau is an essential MAP that regulates and promotes tubulin assembly and neuronal activity, respectively, in order to stabilize microtubules. In this case, tau protein is receiving a lot of interest worldwide as a possible therapeutic target to treat AD because it is the cause of a wide range of neurodegenerative illnesses and tauopathies. Understanding tau and its biological structure is therefore a necessary requirement that may eventually lead researchers to develop successful treatment approaches to target tau.

3. Oxidative stress: The brain's cognitive processes depend on zinc, copper, and iron. However, the amounts of these metal ions in the AD brain have been discovered to be considerably higher. Aβ proteins are extremely vulnerable to these metal ions. Although the precise process by which Zn binds to Aβ proteins is not well documented, it is thought to engage with the imidazole ring of histidine derivatives. The direct binding of Cu and Fe to Aβ initiates the production of FRs. Cu's increased redox potential is thought to make it more prone to Aβ binding. Through a catalytic process, the Cu-Aβ complex interacts with molecular oxygen to create hydroxyl radicals and hydrogen peroxide. The imbalance between ROS/RNS and antioxidant levels in cells is referred to as oxidative stress. It contributes to microglial dysfunction in AD and interferes with the redox signalling system. The leaky electron transport chain (ETC) (complex I and III) in mitochondria is the primary source of ROS. Furthermore, non-heme iron enzymes like lipoxygenases (found in the cytoplasm), xanthine oxidase, cytochrome P450 monooxygenase, cyclooxygenase, and D-amino oxidase (found in the cytoplasm) C, an isoform of nitric oxide synthase (NOS) (found in neurons), NADPH oxidases (NOX) (found in the plasma membrane, and phagosomes of polymorphonuclear neutrophils, which are significant sources of ROS.

4. Neurotransmitter Deficiency: Acetylcholine (ACh), a neurotransmitter necessary for memory and learning, is severely deficient in Alzheimer's disease. This loss, which accounts for basic memory deficits and is the focus of current standard treatments, is caused by the progressive death of cholinergic neurons. Damage to cholinergic neurons present in the basal forebrain leads to reduction in acetylcholine levels within the brain. Since acetylcholine plays an important role in memory processing, learning and cognitive performance, its deficiency may contribute to progressive cognitive impairment in affected individuals. Reduced cholinergic transmission is therefore considered one of the major factors associated with memory dysfunction in Alzheimer's disease. For this reason, cholinesterase inhibitors are widely used to improve cholinergic activity and provide symptomatic relief in patients suffering from Alzheimer's disease [18].

5. Neuroinflammation: Persistent neuroinflammatory changes also contribute to development of Alzheimer's disease. The brain's astrocytes and microglial cells get activated when amyloid-β plaques build up. Inflammatory cytokines and other mediators are released by these activated immune cells, which exacerbate brain damage and the advancement of illness [19].

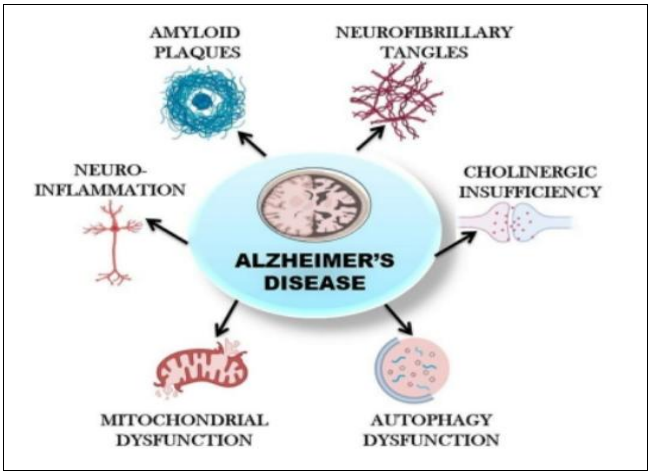

Fig 3: Pathophysiology of Alzheimer's Disease

Table 1: Stages of Alzheimer Disease

Stage	Clinical Description	Cognitive and Behavioural Features	Functional Status
Stage 1	No cognitive impairment	No measurable deficit: preclinical	Fully independent
		Neuropathological changes may begin	
Stage 2	Low-level cognitive decline	Subjective forgetfulness; weak memory lapses	independent
Stage 3	Mild cognitive impairment (MCI)	Noticeable memory decline, difficulty in concentration and word recall	Independent but reduced efficiency in complex tasks
Stage 4	Mild dementia (Early AD)	Impaired recent memory, difficulty with calculations and planning	Needs assistance in complex activities
Stage 5	Moderate dementia	Disorientation to time/place, behavioural symptoms (anxiety, irritability)	Requires help with daily activities
Stage 6	Moderately severe dementia	Severe memory loss, personality changes, difficulty recognizing relatives	Dependent for most activities
Stage 7	Severe dementia (late AD)	Loss of verbal ability, motor impairment, dysphagia	Completely dependent; full-time care required

Stage 1 - Memory-related disorder has a pathobiological onset that is clinically silent. A prognostically concerning stage known as age-related deterioration of cognitive abilities occurs in the precenting year patients start to exhibit decline in memory that surpasses that of their age-peers, and it takes several additional years prior to cognitive deterioration to a level that is effectively incapacitating, signalling the clinical onset of dementia. Neurofibrillary tangle development continues to progress, roughly in tandem with brain shrinkage and increasing dementia severity, whereas amyloid fibril accumulation, one of the two distinguishing neuropathological hallmarks of AD, is almost peaks during the stage of MCI stage. There is currently no proven method to delay the condition, and many have voiced concerns about the effectiveness of current anti-amyloid treatments in patients based on preliminary studies [20].

Stage 2 - Slight memory lapses, such as forgetting names, misplacing objects, or having trouble recalling well-known words, are indicative of Stage 2 (low-level Cognitive Decline). A person may have little memory problems at this point, such as forgetting where they put commonplace items or occasionally having trouble finding the proper word, but these changes are typically undetectable on routine medical examinations or unnoticed by friends and family.

Stage 3 - The earliest stage of Alzheimer's disease symptoms is known as mild cognitive impairment, or MCI. Although friends and family are aware of memory and cognitive issues, they are not yet severe enough to impede with complex routine activities or independent daily functioning. Word-finding difficulty and reduced work efficiency may also be observed during this stage. These changes are often first noticed by family members or colleagues [21].

Stage 4 - This stage includes moderate impairment in cognitive function with more evident memory deficits. People may develop reduced ability to manage handling complex tasks such as financial management, remembering recent events and organizing daily activities. Mild behavioural alterations and reduced awareness of current situations may also develop during this stage of Alzheimer's disease [21].

Stage 5 - Confusion and memory loss are more noticeable in Stage 5 (Moderately Severe Cognitive Decline). People may become confused about time and location and forget crucial personal information like their address or phone number. Daily chores like choosing proper clothing may require assistance [22].

Stage 6 - Significant memory loss and behavioural abnormalities are linked to Stage 6 (Severe Cognitive Decline). In addition to experiencing symptoms like agitation, anxiety, wandering behaviour, and sleep difficulties, patients may forget the names of close family members. Many daily tasks, such as dressing and taking a shower, require assistance.

Stage 7 - The last stage of Alzheimer's disease, known as Stage 7 (Very Severe Cognitive Decline), is when people can no longer converse clearly or carry out simple motor tasks. At this point, people need round-the-clock care and become incapable of responding to their environment, conversing, or controlling simple bodily movements [23].

Diagnosis of Alzheimer's Disease: The diagnosis of Alzheimer's disease is a multi-step procedure. In order to detect biological indicators such as tau tangles and amyloid plaques, doctors employ blood tests, spinal taps, or brain scans in addition to assessing symptoms, medical history, and cognitive abilities.

1. Clinical Assessment: The clinical evaluation methodology was created to give medical professionals the bare minimum of information required to diagnose AD with confidence. Reliable, validated, or time-honoured measures are included in the battery. A general physical and neurologic examination of the patient, brief cognitive scales, and semi structured interviews with the patient and an informant are used to gather information. Prior injuries, diseases, and depressive symptoms are all questioned. Additional inquiries address the duration of the dementing process, drugs that may exacerbate symptoms, and the history of potential dementia signs. We use the Short Blessed to assess orientation, memory, and focus, and a modified Blessed Rating Scale for Dementia to assess informant-reported changes in instrumental and basic activities of daily living.

2. Cognitive Tests: There is an urgent need to quickly, affordably, and highly sensitively detect and monitor mild cognitive change during the preclinical stage of Alzheimer's disease (AD). At the same time, the field of digital cognitive assessment is changing quickly due to the advancement of technology, the rise in tech adoption among older adults, and the necessity of remote digital assessment due to external events like COVID-19. Here, we give a brief overview of the state of digital cognitive testing for

preclinical AD, covering several device platforms and assessment methods, validation levels, and implementation issues. We concentrate on publications, grants, and recent conference proceedings that explicitly investigate the connection between digital cognitive tests and recognized preclinical AD biomarkers (such as tau and amyloid beta) in people who are clinically normal (CN). Numerous digital tests were found on various platforms (such as smartphones and digital pens) [24].

3. Brain imaging Techniques: For the diagnosis of Alzheimer's disease (AD), brain imaging is essential. It visualizes characteristic protein accumulations such tau tangles and amyloid-beta plaques and detects structural shrinkage and functional alterations. Imaging methods such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans are commonly used to identify structural abnormalities in the brain, including cerebral atrophy and reduction in hippocampal volume. In certain cases, Positron Emission Tomography (PET) scans are also utilized to detect amyloid plaque deposition and to assess functional changes associated with neurodegeneration [25].

4. Biomarkers: The application of biomarkers in the diagnosis of Alzheimer's disease is increasing progressively**.** The degenerative alterations linked to Alzheimer's disease may be indicated by the presence of tau and amyloid- beta proteins in cerebrospinal fluid (CSF). Particularly in the early phases of the illness, these indicators aid in increasing the precision of diagnosis [26].

Non- pharmacological treatment of Alzheimer Disease:

These days, an attempt is made to manage AD in a multifactorial manner based on the following elements:

1. Open communication between doctors, caregivers, and patients: a genuine and effective exchange of information and emotions between them will provide timely symptom identification, precise evaluation and diagnosis, and appropriate counsel [29].

2. Behavioural approaches

- Establishing routines.
- Consistency and simplification of the environment.
- Various communication techniques include maintaining calm interactions, providing engaging activities, using simple and clear language, and limiting refusal only in situations where safety is at risk.
- Timely assessment of the patient is essential for medical and legal requirements.
- judgments Exercise, light, and music therapy.
- cognitive behavioural therapy.

3. Lifestyle modification and supportive care:

- Frequent exercise and physical activity enhance cognitive performance and reduce cognitive aging.
- A healthy, well-balanced diet—especially the Mediterranean diet—may promote brain function.
- Cognitive talents can be maintained by engaging in mental stimulation activities like reading, puzzles, and memory exercises.
- Maintaining general brain health in Alzheimer's sufferers also depends on getting enough sleep and managing stress [27].

Pharmacological Treatment of Alzheimer's Disease:

1. Cholinesterase inhibitors: According to the cholinergic theory of Alzheimer's disease, early dysfunction of cholinergic neurons in the basal forebrain contributes to decline in memory, cognition, and neuropsychiatric functions, primarily due to loss of acetylcholine neurons and decreased activity of enzymes responsible for its metabolism. It has been suggested that employing CIs to postpone the breakdown of acetylcholine between the synaptic cleft will improve cholinergic transmission. As of right now, three CIs have been approved to treat mild to moderate AD: galantamine (Janssen, Beerse, Belgium), rivastigmine (Novartis, Basel, Switzerland), and donepezil (Pfizer, New York, NY, USA) [Farlow, 2002]. According to related systematic reviews, donepezil had a reduced incidence of gastrointestinal side effects than rivastigmine and galantamine, including nausea, vomiting, diarrhoea, and cramping in the abdomen [Alva and Cummings, 2008]. A higher therapeutic dose was linked to a higher incidence of side effects. However, if a cautious and slow titration regimen lasting more than three months is employed, galantamine and rivastigmine might be as tolerable as donepezil. Some caregivers preferred the topical version of rivastigmine, which offers a lower dose with fewer side effects but comparable efficacy [28].

2. Antagonist of N-methyl-D-aspartate: Memantine is an additional treatment option for moderate to severe AD (Lundbeck, Valby, Denmark). This medication is a moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) antagonist which is considered to safeguard neurons against excitotoxic injury. A persistent, low-level release of glutamate results from disruptions in the brain's glutamatergic system in Alzheimer's disease. This causes NMDA receptors to become overactive, which lets too much calcium into the neurons. This long-term calcium inflow causes excitotoxicity, a process that destroys and damages brain cells [29].

3. NMDA Receptor Antagonist: N-methyl-D-aspartate (NMDA) receptors are ligand-gated ion channels that are activated by excitatory neurotransmitters. These N-methyl-D-aspartate receptors (NMDAR) are involved in excitatory neurotransmission in the central nervous system because they are mostly located at excitatory synapses. Open NMDARs not only produce an electrical signal but also cause calcium influx, which is necessary for neuroplasticity in learning and memory as well as synaptic signaling. On the other hand, excitotoxicity and cell death are caused by activation of extra synaptic NMDARs, which may be a mechanism of neurodegeneration in Alzheimer's disease (AD). The pathophysiology of AD includes abnormalities in both structure and function. Senile plaques of A and neurofibrillary tangles of phosphorylated tau, as well as a marked loss of synaptic profiles, are among the many structural abnormalities that the brain experiences as AD progresses. There is currently no known cure for AD. There are some treatments, though. Alzheimer's Disease Drugs from the National Institute on Aging Two categories of FDA-approved prescription medications that are currently utilized to treat AD patients are listed in the Fact Sheet [30].

Table 2: Pharmacological Treatment of Neurological condition

Drug class	Drug name	Mechanism of action	indication	Therapeutic Effect
Cholinesterase Inhibitors	Donepezil	Acetylcholinesterase Inhibit → Acetylcholine	Mild–Moderate AD	Memory & cognition improve
	Galantamine	Ache inhibition + nicotinic receptor Modulation	Mild–Moderate AD	Cognitive support
NMDA Receptor Antagonist	Memantine	Blocks excess Glutamate (NMDA receptor)	Moderate– Severe AD	Prevents excitotoxicity
Anti-Amyloid Monoclonal Antibodies	Aducanumab	Reduces amyloid-β plaques	Early AD	Disease-modifying approach
	Lecanemab	Targets soluble amyloid protofibrils	Early AD	Slows progression
Supportive/ Symptomatic Drugs	Antidepressants	Serotonin Modulation	Depression in AD	Mood stabilization
	Antipsychotics	Dopamine blockade	Agitation (short-term)	Use cautiously

Conclusion

Alzheimer's disease is a slowly advancing neurological disorder that mainly affects memory, cognition and behavioural functions in aged population. The disease is associated with neuronal degeneration, oxidative stress, amyloid beta plaque formation and tau protein abnormalities, which ultimately lead to decline in cognitive function and memory loss. Patients suffering from Alzheimer's disease often experience difficulty in performing daily activities and gradual decline in mental function. Currently available therapies such as cholinesterase inhibitors and NMDA receptor antagonists provide only symptomatic relief and are not able to completely cure or reverse the progression of disease. Due to limitations of currently available therapies, researchers are focusing on alternative treatment approaches with improved safety and therapeutic potential. Herbal drugs possessing antioxidant and neuroprotective properties may provide protective effects in management of cognitive impairment disorder. The present review emphasizes the importance of herbal therapy in neurodegenerative disorders. Further experimental and clinical studies on polyherbal formulations may contribute to development of effective therapies for neurodegenerative disorders.

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