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A REVIEW ON HORIZONS IN ALZHEIMERS DISEASE AND ITS TREATMENT

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia among elderly individuals worldwide. This review provides a comprehensive overview of the pathophysiology, stages, symptoms, diagnosis, and treatment strategies associated with AD. The disease is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles, leading to neuronal degeneration, cortical atrophy, and cognitive decline. The amyloid cascade hypothesis explains the role of Aβ accumulation in triggering tau hyperphosphorylation, neuroinflammation, oxidative stress, and synaptic dysfunction. Alzheimers disease progresses through multiple stages, including preclinical stage, mild cognitive impairment, mild-to-moderate AD, and severe AD. Common symptoms include memory loss, language impairment, behavioral disturbances, and reduced spatial awareness. Diagnostic approaches involve clinical examination, neurocognitive assessment, magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebrospinal fluid biomarker analysis.Currently available pharmacological therapies include cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, along with the NMDA receptor antagonist memantine. India faces major challenges in the management of AD because of its rapidly increasing elderly population, lack of awareness, social stigma, and limited healthcare access. Recent advances in immune therapeutics, gene therapy, stem cell therapy, artificial intelligence, and machine learning offer promising future directions for early diagnosis and disease-modifying treatment strategies. However, challenges related to disease heterogeneity, drug delivery, and ethical concerns still remain. Continued research is essential for improving the diagnosis, treatment, and overall management of Alzheimer's disease.

Keywords Alzheimer's disease, Amyloid-β plaques, Neurofibrillary tangles, Dementia, Cognitive decline, Biomarkers, Neurodegeneration, Cholinesterase inhibitors.

INTRODUCTION

Dementia causes memory loss, difficulty in performing daily tasks, behavioral and emotional changes, and impaired cognition. Approximately 50 million people worldwide currently live with dementia, and this number is expected to rise to 152 million by 2050. Most cases occur in low- and middle-income countries, where nearly three-fourths of all affected individuals reside. Dementia is classified as primary, caused by aging and neurodegeneration, or secondary, resulting from other health problems. Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and Lewy body dementia are the most common primary types. Secondary causes include vascular problems, infections, injuries, and metabolic or chemical imbalance. The American Academy of Neurology recommends screening for hypothyroidism, vitamin B12 deficiency, and structural abnormalities in suspected cases of peripheral neuropathy. Studies have shown that factors such as poor literacy, malnutrition, heart disease, and metabolic disorders increase the risk of dementia. Addressing these issues may help prevent memory loss and reduce the risk of Alzheimer's disease.[1]

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most common cause of dementia. It leads to memory loss, confusion, behavioral changes, and difficulty communicating. The main pathological features are amyloid-β (Aβ) plaques and neurofibrillary tangles formed by the abnormal accumulation of tau proteins. Tau, which normally stabilizes microtubules, becomes hyperphosphorylated by enzymes such as GSK-3β, causing tangles and neuronal damage. Amyloid plaques consist of Aβ oligomers that disrupt brain signaling and trigger neuronal death long before symptoms appear. Factors such as oxidative stress, mitochondrial dysfunction, and neuroinflammation further accelerate neurodegeneration in Alzheimer's disease.[2]

Types of Dementia

1. Alzheimer's Disease (AD):

The most common type of dementia is caused by amyloid-β plaques and tau tangles, leading to progressive memory loss and cognitive decline.

2. Vascular Dementia:

Results from reduced blood flow to the brain due to stroke or vessel damage, causing problems with thinking, reasoning, and memory.[3]

3. Lewy Body Dementia (LBD):

Caused by abnormal deposits of alpha-synuclein (Lewy bodies) in the brain, leading to hallucinations, movement problems, and fluctuating alertness.[4]

4. Frontotemporal Dementia (FTD):

Affects the frontal and temporal lobes, leading to personality changes, poor judgment, and language

difficulties, often occurring at a younger age.[5]

5. Mixed Dementia:

Involves multiple causes, commonly Alzheimer's and vascular pathology, resulting in overlapping symptoms of both memory and reasoning impairment.[6]

6. Parkinson's Disease Dementia:

Occurs in later stages of Parkinson's disease, characterized by slowed thinking, visual hallucinations, and movement difficulties.[7]

7. Huntington's Disease Dementia

A genetic disorder causing brain cell death, resulting in movement disorders, mood changes, and gradual loss of thinking ability.[8]

8. Creutzfeldt–Jakob Disease (CJD):

A rare, fatal prion disease causing rapid mental deterioration, personality changes, and involuntary movements.[9]

9. Normal Pressure Hydrocephalus (NPH)

Caused by excess cerebrospinal fluid buildup, leading to walking difficulty, memory loss, and urinary incontinence; treatable with shunt surgery.[10]

10. Wernicke–Korsakoff Syndrome

Linked to thiamine (vitamin B1) deficiency, often due to alcoholism, causing confusion, poor coordination, and severe memory problems.[11]

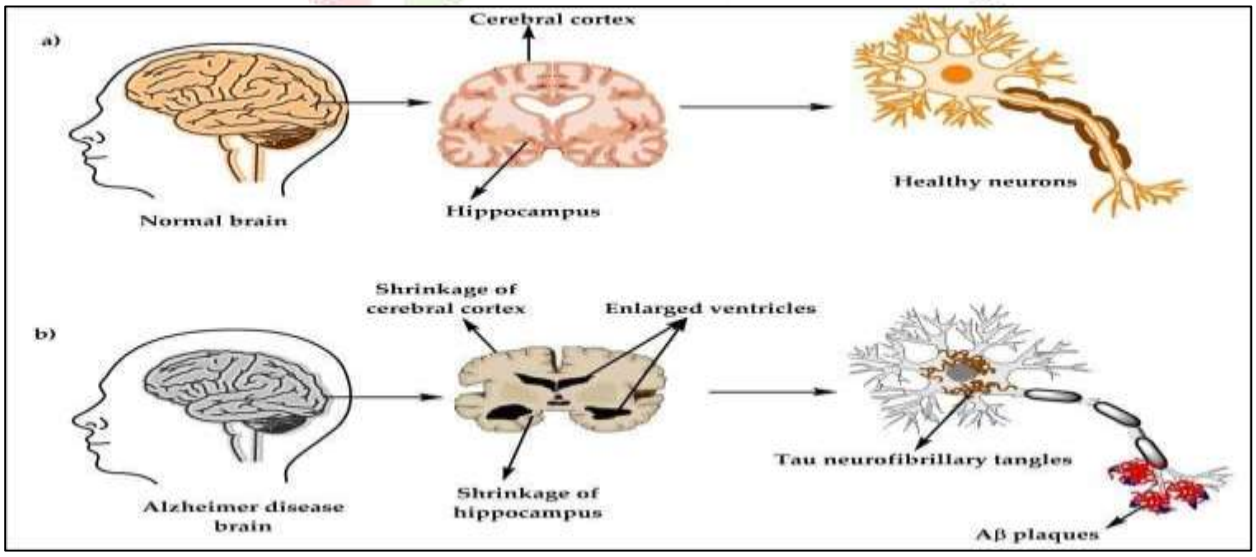


Figure 1: The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's disease (AD) brain.

PATHOPHYSIOLOGY

The hallmark pathological features of Alzheimer's disease (AD) are the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau (hyperphosphorylated tau, P-tau). These abnormalities cause neuronal dysfunction, synaptic loss, and cell death, leading to progressive cognitive decline. The major mechanisms involved include excitotoxicity, calcium imbalance, mitochondrial dysfunction, oxidative stress, and neuroinflammation.[12]

According to the amyloid cascade hypothesis, excessive accumulation of Aβ peptide in the brain initiates a series of neurodegenerative processes. Aβ peptides (36–43 amino acids long) are derived from amyloid precursor protein (APP), located on chromosome 21, via enzymatic cleavage. APP can undergo two processing pathways: the non-amyloidogenic pathway, involving α-secretase, which produces soluble APPα with neuroprotective functions, and the amyloidogenic pathway, involving β- and γ-secretases, which generate Aβ peptides. The γ-secretase complex includes presenilin 1 or 2, nicastrin, APH-1, and PEN-2. The imbalance favoring the amyloidogenic pathway leads to the formation of insoluble Aβ aggregates.[13]

Among the Aβ forms, Aβ42 is more hydrophobic and aggregation-prone than Aβ40, forming oligomers, fibrils, and plaques. These oligomeric Aβ species are particularly neurotoxic, damaging synaptic membranes and disrupting neurotransmission involving acetylcholine, dopamine, serotonin and norepinephrine. This synaptic dysfunction contributes to early stagecognitive impairment. Genetic mutations in APP and presenilin (PSEN1, PSEN2) genes increase Aβ42 production, explaining familial early-onset AD. [14]

The relationship between Aβ accumulation and tau pathology is central to the progression of AD. Aβ deposition induces hyperphosphorylation of tau through the activation of kinases such as GSK3β and CDK5, leading to NFT formation. Blurton-Jones and LaFerla (2006) proposed that Aβ may also promote tau pathology through neuroinflammatory cytokine release, proteasome dysfunction, and impaired axonal transport.[15]

Tau protein, encoded by the MAPT gene on chromosome 17, stabilizes neuronal microtubules. When hyperphosphorylated, tau loses its affinity for microtubules, aggregates into paired helical filaments, and forms neurofibrillary tangles (NFTs). This disrupts axonal transport and causes neuronal cell death. Studies have indicated that the density of NFTs correlates more closely with cognitive decline than amyloid plaque load, suggesting that tau pathology is a direct driver of neuronal loss.

Overall, AD pathogenesis involves a complex interplay between Aβ accumulation, tau hyperphosphorylation, neuroinflammation, oxidative stress, and mitochondrial impairment. The progressive synaptic and neuronal loss in the hippocampus and cortex underlies the characteristic

memory and cognitive deficits observed in Alzheimer's disease.[16]

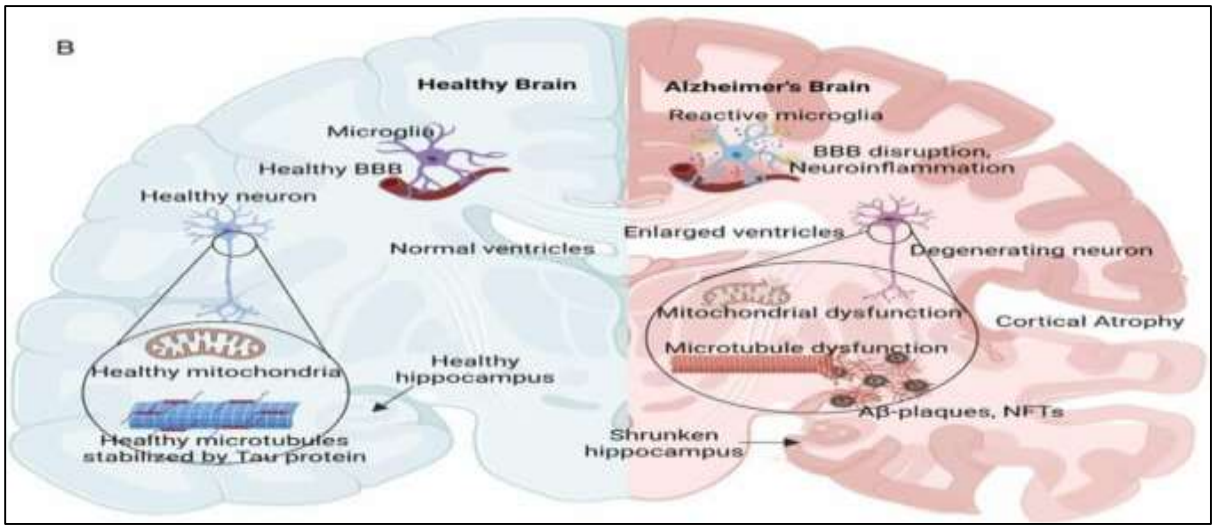


Figure 2: - Pathophysiology of Alzheimer's disease

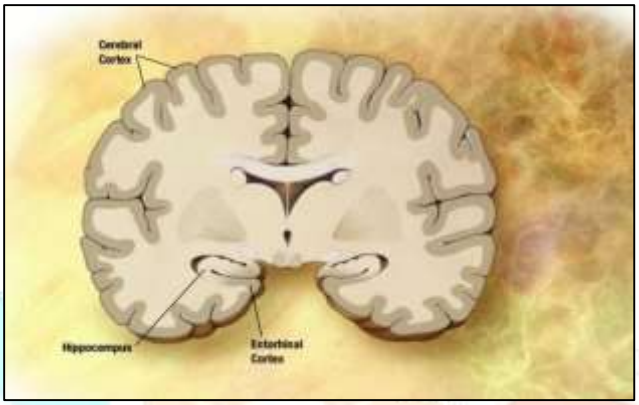
Despite recent progress, the true cause of this disease remains unknown. Apart from the well-known AI² aggregates and phosphorylated Tau, other potential triggers are surfacing as potential treatment targets.[17]

Disease stages

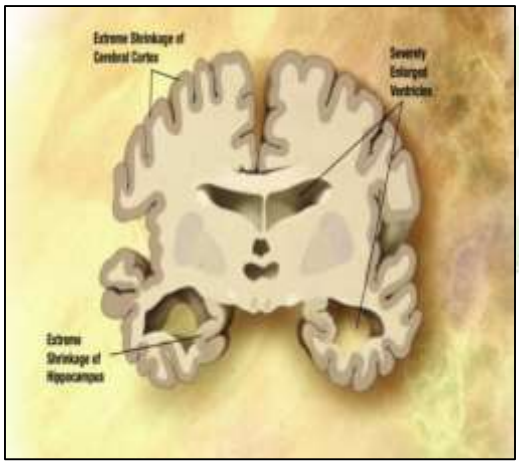
Table 1: Disease stages

Stage	Key brain area affects	Main Symptoms	Care needs
1. Preclinical / MCI (Mild Cognitive Impairment)	Entorhinal cortex, Hippocampus	- Memory loss begins (recent events) - Often no visible symptoms in preclinical stage - MCI shows subtle/intermediate issues	Usually independent
2. Mild Alzheimer's Disease	Memory, Language, Reasoning	- Persistent memory loss - Difficulty with daily tasks - Poor judgment, anxiety - Often diagnosed here	Mild assistance
3. Moderate Alzheimer's Disease	Language, Reasoning, Sensory Processing, Thought	- Confusion language issues - Trouble recognizing people - Behavioral changes (agitation, hallucinations, paranoia)	Significant care needed

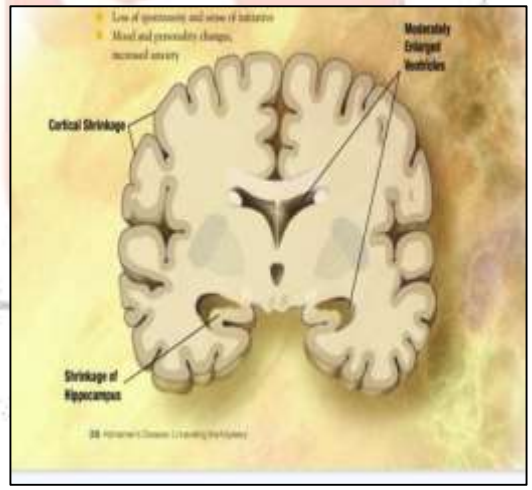
4. Severe	Wide spread brain shrinkage	- Loss of recognition and communication - Full care - Weight loss, seizures, infections - End-stage complications like aspiration pneumonia	Complete and continuous care required



Preclinical or Presymptomatic



Mild Alzheimer’s Disease



Moderate Alzheimer’s Disease

Figure 3: Progressive Brain Atrophy in Different Stages of Alzheimer’s Disease

Preclinical or Presymptomatic

In this early phase, people have no symptoms, yet there is strong proof in laboratories showing signs of Alzheimer's disease. Biomarkers can aid in the early diagnosis of Alzheimer’s disease. Low amyloid levels and increased tau protein in the cerebrospinal fluid can be markers but are not unique to Alzheimer’s disease. By analyzing factors such as ApoE4 status, cognitive test results, elevated tau levels in the cerebrospinal fluid, and structural MRI indicators of brain regions, researchers can forecast the transition

from the early stages to Mild Cognitive Impairment.[18]

Mild Cognitive Impairment

In this phase, people have mild cognitive decline in their memory or other mental skills, such as thinking or speaking quickly. Although there are changes in their minds, these people still go to work, interact socially, and manage their daily tasks despite declining health. The progression rate from MCI to dementia is approximately 10% annually. The severity of impairment at the time of diagnosis increases the likelihood of progression of Alzheimer's disease (AD). Other known risk factors also contribute to its development.[19]

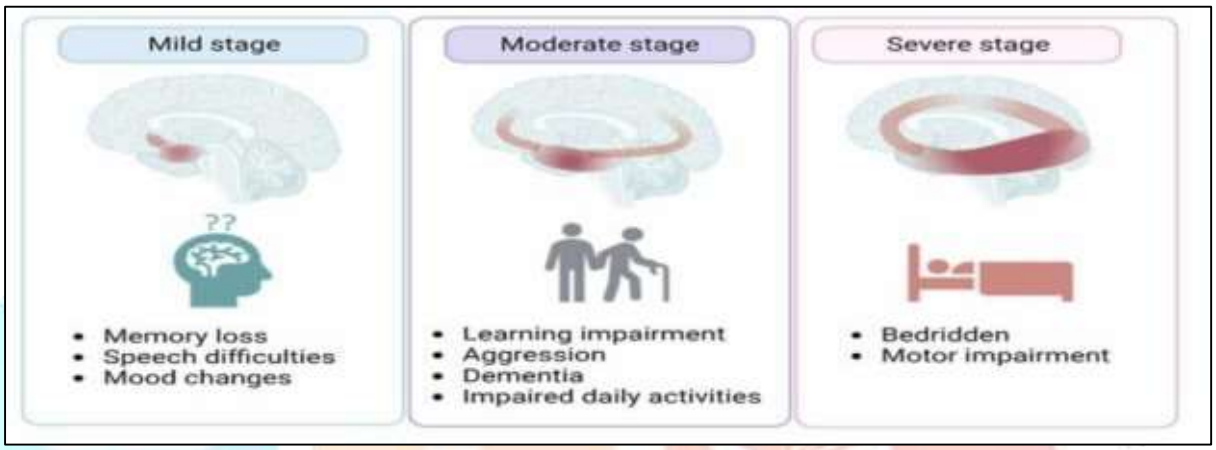


Figure 4: Alzheimer’s Disease Stages

Dementia

In this phase, people suffer from severe memory loss accompanied by significant speech difficulties, such as trouble naming objects (anomia), repeating incorrect words (paraphasia), less natural conversation flow, and often relying on indirect ways of talking to remember lost words. Additionally, reduced visuospatial skills result in difficulties navigating familiar areas and building tasks. A small proportion of patients with Alzheimer’s disease may have false beliefs about their conditions. Visual hallucinations often occur, but hearing voices and smelling things can also occur in patients with schizophrenia. Almost half of the patients exhibited disruptive behavior. Patients frequently alter their natural sleep and wake times during this phase, resulting in poor-quality rest. Motor vehicle accidents happen more often in people who have Alzheimer's disease.[20]

Symptoms

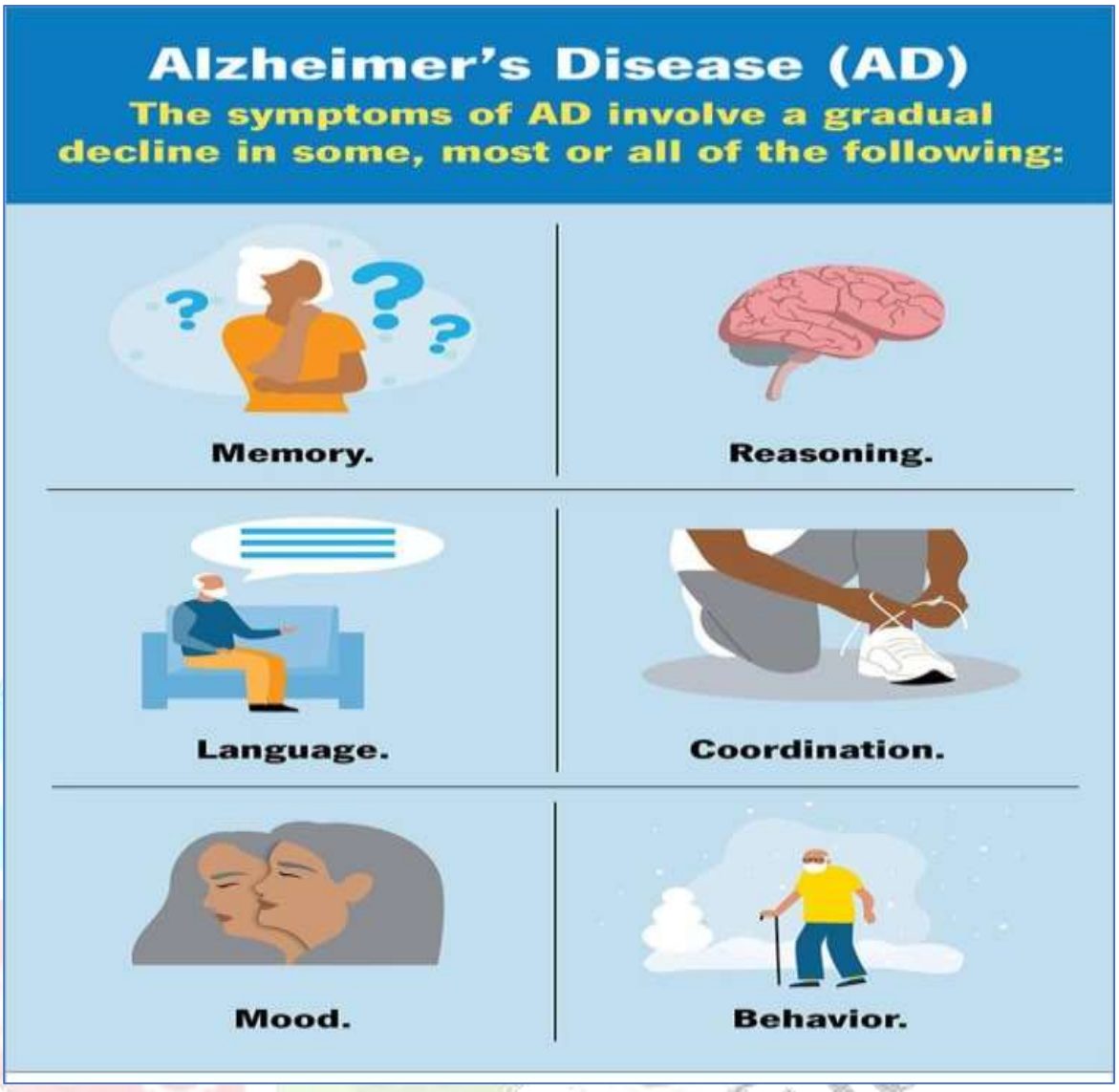


Figure 5: Symptoms for Alzheimer's Disease

Alzheimer's disease (AD) is characterized by a progressive decline in memory, reasoning, language, behavior, personality, and spatial understanding due to widespread neuronal damage in the cerebralcortex and the hippocampus. The onset is gradual, and symptoms worsen over time, leading to significant impairment in daily activities and social functioning.[21]

Memory Impairment:

Memory loss is the hallmark and earliest symptom of AD. Patients have difficulty remembering recent events, conversations, or appointments, while long-term memories may also fade as the disease progresses. Individuals often struggle to recognize familiar faces or recall names, locations, and important personal facts. [22] Unlike normal age-related forgetfulness, memory loss in AD progressively interferes with independent functioning of the patient. These changes are usually first noticed by family members or caregivers rather than the affected person.[23]

Reasoning and Problem-Solving Difficulties:

Individuals with AD frequently experience confusion and a reduced ability to think abstractly or plan ahead. Tasks such as following recipes, organizing activities, or making financial decisions become increasingly challenging as cognitive function declines. Decision-making slows significantly due to impaired executive functions caused by degeneration of the prefrontal cortex. As reasoning declines, individuals may find it difficult to assess risks, prioritize tasks, or adapt to new situations.[24]

Language and Communication Problems:

As the disease progresses, patients develop aphasia, which is the difficulty in finding words, naming objects, or following conversations. Speech becomes repetitive or disorganized, and understanding complex instructions becomes difficult for the individual. These deficits often contribute to social withdrawal and frustration.[25]

Behavioral and Personality Changes:

Behavioral symptoms, such as irritability, apathy, agitation, anxiety, and depression, are common. Some individuals develop delusions, hallucinations, or paranoia in the later stages. Disruption of sleep–wake cycles and wandering behavior are also frequently observed.[26]

Spatial and Visual Difficulties:

Patients may experience impaired spatial awareness, leading to disorientation in familiar places and difficulty in judging distances or recognizing landmarks. This contributes to increased risk of falls and accidents, including motor vehicle incidents.[27]

DIAGNOSIS:

Accurate and early detection of Alzheimer's disease is crucial for providing proper treatment, controlling symptoms, and creating tailored solutions for patients. Diagnostic strategies for Alzheimer's disease involve the integration of clinical evaluations, mental status tests, and sophisticated brain imaging techniques.

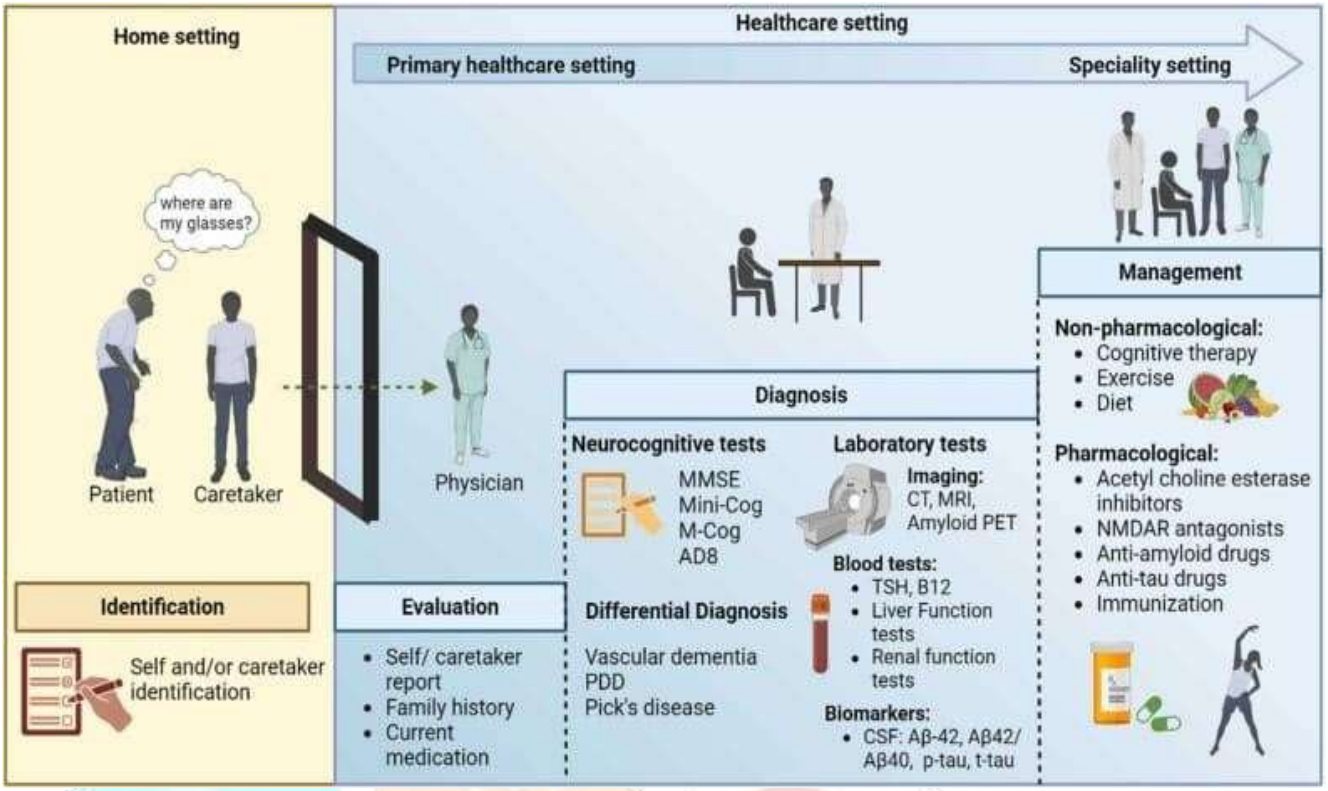


Figure 6: Clinical Pathway for Diagnosis

The steps involved in ad management can be divided into identity, evaluation, analysis, and control. The diverse tests/gear used in each step are shown in the respective columns. To begin with, cognitive adjustments and reminiscence impairments are identified by the patient or their caretaker. In a healthcare setting, the physician evaluates the affected person, their family history, and medicinal drug status, and refers them to a specialist. Neurocognitive checks, which include MMSE, Mini-Cog, M-Cog, AD8, Imaging strategies, which include MRI, Amyloid PET; biomarkers such as Aβ42/Aβ40 and p-tau; and diverse blood assessments are used in the prognosis of AD. Upon analysis, both pharmacological and non-pharmacological treatment are used for the control of advert.[28]

CURRENT DIAGNOSTIC STRATEGIES

A thorough examination of someone who might have trouble remembering things involves checking many tests that help understand why their mind is not working well and finding out if there is anything that can be fixed in their body. These assessments gather extensive health data through medical history, physical examinations, laboratory tests, and brain scans. Additional tools include neuropsychological tests and sophisticated brain-scanning methods. The specific reasons for severe brain problems were investigated after all possible changes were reversed. A history of multiple strokes may indicate vascular dementia. A past brain injury may indicate a serious condition called encephalopathy due to brain damage. Prolonged heavy drinking can lead to alcohol-related dementia. Adults older than 60 years who experience cognitive decline tend to have Alzheimer's disease as the primary reason for this change in mental function.[29]

Emerging Diagnostics

Finding better methods for diagnosing Alzheimer's disease (AD) has attracted much attention from researchers, and recent advancements in diagnostic tests have been observed over the past ten years. These improvements include increased use of positron emission tomography (PET) and magnetic resonance imaging (MRI), as well as the detection of biomarkers in cerebrospinal fluid (CSF) and more recently in serum.[30]

We examined 150 patients with dementia symptoms using the MMSE to determine an acceptable cutoff score for referral for diagnostic examinations. All patients underwent a thorough and uniform examination and identification through the Alzheimer's disease Patient Registry program. The doctors and psychologists agreed that dementia was diagnosed according to standard rules. After one year, the diagnosis was confirmed in 80 of 150 patients who had completed their follow-up (including 53 patients without dementia). We examined how well someone performed on their first memory test before they got sick and then determined whether that was correct when we found out what was wrong with them. The sensitivity, specificity, and predictive values were determined for MMSE scores ranging from 22 to 29. A cutoff score of less than 24 indicated a sensitivity of zero. Sixty three with a precision of zero. Sensitivity increased as the cutoff points increased. Educational level was a significant indicator of scores ≥ 27 in the multivariate analysis. An MMSE score of 26 or 27 should be used as a cutoff score for symptomatic populations with similar educational and socioeconomic backgrounds if the aim is to avoid missing the true cases. Low-prevalence population surveys might necessitate varying thresholds to determine if additional diagnostics are needed.[29]

MEDICATIONS

Table no 2: Medications for Alzheimes Disease

Sr. No.	Drug Name	class	Mechanism of Action	Use
1.	Rivastigmine	Cholinesterase Inhibitor	Increases acetylcholine level by blocking cholinesterase enzymes	Mild to Moderate AD
2.	Donepezil	Cholinesterase Inhibitor	Increases acetylcholine activity and supports nerve signaling	Mild to Severe AD
3.	Galantamine	Cholinesterase Inhibitor	Prevents breakdown of acetylcholine and improves memory function	Mild to Moderate AD
4.	Memantine	NMDA Antagonist	Protects brain cells by reducing glutamate toxicity	Moderate to Severe AD
5.	Ketamine	NMDA Antagonist	Blocks NMDA receptors to reduce nerve cell damage	Moderate to Severe AD
6.	Lecanemab	Amyloid Beta Targeting Drug	Targets amyloid-beta protein deposits in the brain	Early AD
7.	Aducanumab	Amyloid Beta Targeting Drug	Helps remove amyloid plaques from the brain	Early AD
8.	Donanemab	Amyloid Beta Targeting Drug	Binds to amyloid-beta and reduces plaque formation	Early AD / Clinical Trials
9.	Brexpiprazole	Antipsychotic Drug	Antipsychotic Drug Acts on serotonin and dopamine receptors to control agitation	Agitation in AD
10.	Donepezil + Memantine	Combination Therapy	Improves acetylcholine level and reduces glutamate toxicity	Moderate to Severe AD

PRESENT SITUATION:

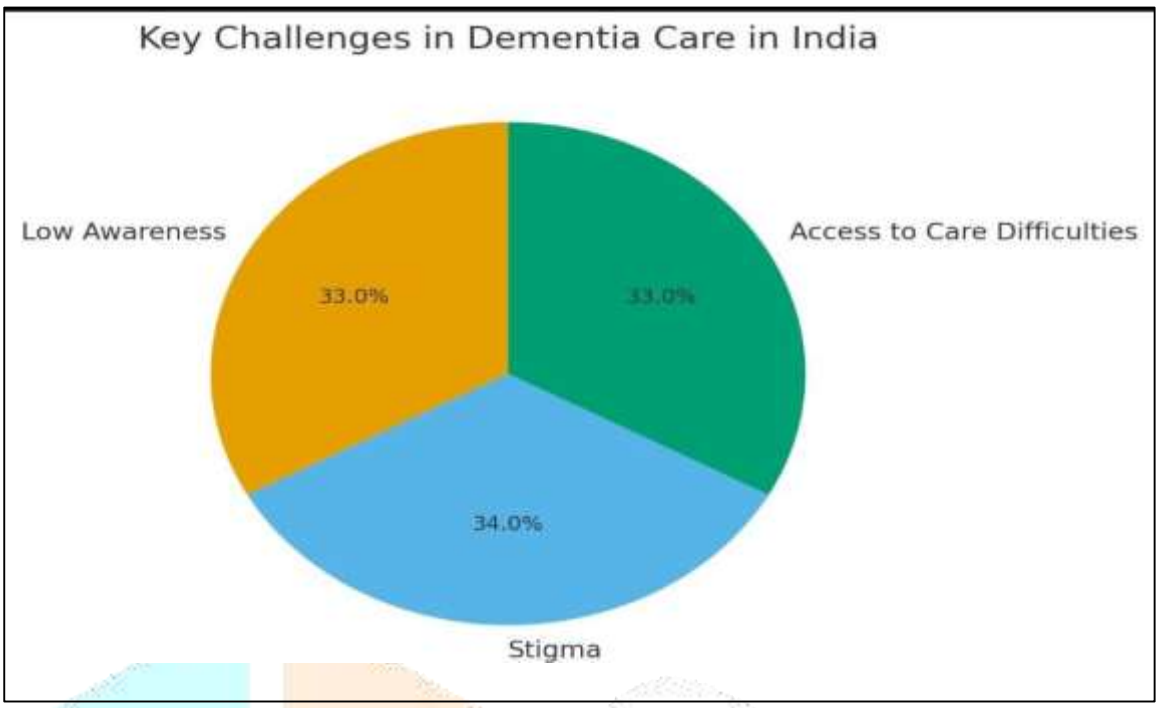


Figure 7: Present Situation for Alzheimer's Disease

India is the second most populated country in the world, with approximately 5.3 million people suffering from dementia. Only one in ten of these individuals receives a diagnosis, care, or treatment. There are many challenges in providing care and support to individuals with dementia and their caregivers. In addition, there is insufficient knowledge of dementia among the general public and the healthcare workers. Studies in India have shown that people with dementia face societal discrimination and are often neglected by their families. Social attitudes towards dementia make the experience difficult for those affected and their caregivers, making them feel isolated and judged. To understand how people perceive dementia, researchers spoke to groups of people in two different Indian cities, Chennai and Delhi. These groups included individuals with dementia, caregivers, healthcare workers, and the general public. They identified three main themes: low awareness, stigma, and difficulties in obtaining care. These issues arise from cultural and social beliefs. Even though each group had different experiences, they all used language that showed stigma towards dementia. These negative beliefs and lack of understanding often lead to poor-quality care. There is a need to increase awareness of dementia among all groups. The fact that participants recognized their lack of knowledge about dementia suggests they are open to learning more.[33]

APP ANALYSIS

Dementia is an irreversible brain disorder that primarily affects older adults, and the risk of developing dementia increases with age. It is the seventh leading cause of death worldwide. Individuals with dementia experience memory loss, confusion, wandering, and behavioral symptoms, such as agitation and aggression. As the disease progresses, patients lose their independence and rely on informal

caregivers, often family members. Studies show that people with dementia prefer home living, as it supports autonomy, enhances quality of life (QOL), and reduces costs. However, caregiving poses a heavy burden, requiring effective support solutions. Mobile technology offers potential assistance in improving the daily routines and QOL of both patients and caregivers. However, privacy and ethical concerns limit its acceptance. Research indicates a lack of dementia care technologies that meet user needs. This review analyzes mobile applications for dementia care, emphasizing usability, safety, privacy, and user-centered design to bridge existing technological and ethical gaps. [34]

Table No. 3: Comparative Features of Existing Dementia Care Apps [36,37,38,39,40,41]

App Name	Key Features	Uses	Limitations
MindMate	Memory games, daily activities, health tracking, music, exercise videos	Cognitive stimulation and routine management	No clinically validated cognitive tests; limited personalization
CogniCare	Caregiver education, tips, tasks, daily planning	Caregiver support, patient guidance	No India-specific content; limited shared dashboard features
Dementia Clock	Time/date reminders, medication alerts	Helpful for daily routines and medication scheduling	No personalized/adaptive reminders; lacks location-based alerts
Dementia Support	Basic reminders, notes, to-do lists	Provides basic memory support	No advanced safety features; no wandering detection
Alzheimer's Caregiver Buddy	SOS button, safety guidelines, caregiver resources	Emergency alerts and safety management	Limited GPS tracking or geofencing
Elevate (General Cognitive App)	Brain games, memory and focus training	General cognitive improvement	improvement Not dementia-specific; UI not designed for seniors
DonApp (Existing Dementia App)	Patient information, cognitive tests, notes, basic reminders	Simple dementia tracking and support	Lacks advanced modules (music therapy, behaviour log, safety alerts, geofencing)

Indian Need:

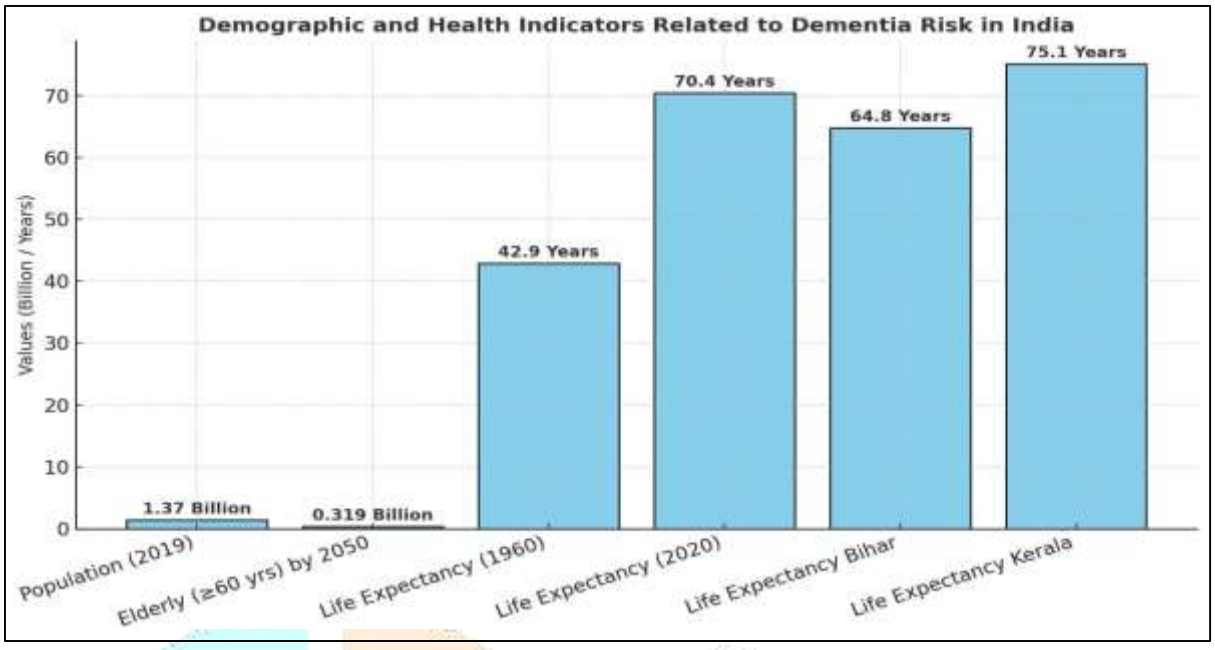


Figure 9: Demographic and Health Indicators Related to Dementia Risk in India

India, with a population of 1.37 billion (18% of the global total in 2019), is expected to surpass China as the most populous nation by 2023. The country faces rapid population aging, with individuals aged 60 years or older projected to constitute nearly 20% (319 million) of the total population by 2050, accounting for 15.4% of the global elderly population. This demographic shift results from increased life expectancy, from 42.9 years in 1960 to 70.4 years in 2020. As age is the strongest risk factor for dementia, India is expected to witness a major increase in dementia cases. The Alzheimer's and Related Disorders Society of India estimated dementia prevalence using South Asian data from the 2015 World Alzheimer Report and six Indian regional studies (2010), covering only six of the 36 states. Significant variations in life expectancy and health indicators exist across states, ranging from 64.8 years in Bihar to 75.1 years in Kerala. Recognizing these disparities, the Harmonized Diagnostic Assessment of Dementia for the Longitudinal Aging Study in India (LASI- DAD) was conducted as part of the national LASI project to estimate the prevalence of dementia, identify risk factors, and assess its social and economic burden. These findings are essential for effective dementia-related health policymaking in India.[42]

CONCLUSION:

Alzheimer's disease (AD) is a complex and gradually worsening brain disorder that mainly affects memory, thinking ability, and daily functioning in older adults. Although significant progress has been made in identifying its underlying biological processes and developing available treatments such as cholinesterase inhibitors and NMDA receptor blockers, difficulties still remain in achieving early detection and long-term management. With India's rapidly growing elderly population, the number of AD and dementia cases is expected to rise, highlighting the importance of national-level awareness programs, early screening, and accessible healthcare services. New research directions

— including immunotherapy, gene-based techniques, and stem-cell-driven approaches — offer encouraging possibilities for disease modification. Furthermore, integrating artificial intelligence and modern technological tools into Alzheimer's research may enhance diagnosis, treatment precision, and overall patient care outcomes in the future.

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