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DIAGNOSIS, MANAGEMENT AND TREATMENT OF ALZHEIMER'S DISEASE

Mr. Vishal Nanaware*[1], Mr. Atharva Pachange[2], Mr. Venkatesh Murkute[3], Prof. Lalita Khambait[4], Dr. Tushar Shelke[5]

[1,2,3]Research Scholar, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, India.

[4]Assistant Professor, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, India.

[5]Principal, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, India.

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***Corresponding Author**

Mr. Vishal Nanaware

Research Scholar, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, India.

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia in older adults. It impairs communication between neurons and ultimately causes neuronal death. Pathologically, it is characterised by extracellular senile plaques composed of β-amyloid (Aβ) deposits and intracellular neurofibrillary tangles composed of abnormally hyperphosphorylated tau protein. The prevalence of dementia rises sharply with age worldwide and places a heavy financial burden on society. AD arises from a complex interaction of genetic, environmental, and demographic factors. Late-onset AD is strongly influenced by advanced age and the APOE ε4 allele, whereas early-onset AD is associated with rare autosomal dominant mutations in the APP, PSEN1, and PSEN2 genes. Low educational attainment, physical inactivity, poor diet, smoking, cardiovascular comorbidities, and chronic sleep disturbance are additional risk factors. Clinically, AD presents with subtle short-term memory loss, followed by executive dysfunction, agnosia, apraxia, disorientation, language impairment (aphasia), and non-cognitive symptoms. Diagnosis rests on clinical history, cognitive screening (MMSE, MoCA), physical examination, and structural neuroimaging (MRI/CT), and is further refined by the ATN biomarker framework, which includes FDG-PET, amyloid-PET, and cerebrospinal fluid (CSF) measurements. Current pharmacological treatment relies mainly on acetylcholinesterase inhibitors and NMDA receptor antagonists for symptomatic relief, while

emerging research is examining disease-modifying immunotherapies that target the removal of Aβ plaques.

KEYWORDS: Alzheimer's disease; cholinesterase inhibitors; diagnosis; memantine; genetics and risk factors; biomarkers; pharmacological treatment.

1. INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder characterised by intracellular neurofibrillary tangles and extracellular senile (amyloid) plaques. It places an enormous financial strain on families and on healthcare systems worldwide. The main risk factors are age, genetic factors (including mutations in the APP, PSEN1, and PSEN2 genes and the APOE ε4 allele), Down syndrome, lifestyle choices, and cognitive reserve.

Symptoms progress from initial short-term memory loss to more general cognitive impairment, disorientation, apraxia, agnosia, language deficits (aphasia), and behavioural and psychological symptoms of dementia (BPSD). Diagnosis is based on medical history, cognitive tests (e.g., MMSE, MoCA), MRI/CT imaging, and modern biomarkers such as PET scans and CSF profiles (Aβ42, tau). Management combines pharmacological treatment (cholinesterase inhibitors and NMDA antagonists such as memantine) with non-pharmacological measures that emphasise daily routines, patient safety, behavioural techniques, and caregiver support.

Brain structure changes visibly as the disease advances (Figure 1). A healthy brain appears full and plump, with closely spaced gyri separated by narrow sulci. In mild AD, the gaps between the folds become noticeably wider, the cortical tissue begins to thin, and overall brain size starts to decrease. In severe AD, deeply hollowed-out spaces and marked atrophy are seen throughout the cortex, especially in the central and outer regions of the brain.



Figure 1: Comparison of a healthy brain with mild and severe Alzheimer's disease, showing progressive cortical atrophy.

2. PREVALENCE AND IMPACT OF ALZHEIMER'S DISEASE

Alzheimer's disease is a neurodegenerative disease that primarily affects the brain and progresses with age. As it gradually damages nerve cells, it causes problems with memory, thinking, learning, communication, and day-to-day activities. The illness was first described by Alois Alzheimer, a German neuropathologist and psychiatrist. AD is the most frequent cause of dementia in older adults; it begins slowly and worsens over time. Two pathological abnormalities characterise the disease:

A. Senile plaques. Senile (amyloid) plaques are abnormal extracellular deposits that form outside nerve cells. Their main component is β-amyloid (Aβ), derived from a larger protein known as amyloid precursor protein. Excessive β-amyloid accumulation is linked to neuronal damage, and the plaques interfere with normal communication between nerve cells.

B. Neurofibrillary tangles. Neurofibrillary tangles are abnormal structures found inside nerve cells and are composed mainly of an abnormal form of the protein tau. In healthy neurons, tau helps stabilise microtubules. In AD, tau undergoes abnormal modification and twists into fibres, and the resulting tangles hamper the transport of nutrients and other materials within neurons. Affected neurons may eventually die, and neurotransmitter systems may also be affected as the illness worsens.[1]

Prevalence of dementia and AD. Prevalence is the proportion of individuals in a population who have a disease at a particular time. Dementia becomes much more common with age, and as the world's population ages, the number of people with dementia is expected to rise sharply. The number of people with dementia worldwide is projected to double approximately every 20 years, reaching 81.1 million by 2040.[2]

Global social impact. Dementia has a major social and financial impact; its cost to society worldwide has been estimated at US$422 billion.[3]

AD in elderly people. In a study from Hong Kong, the reported prevalence of dementia among people aged 70 years or older.[4] In addition, 17.4% of people were reported to have mild or very mild dementia.[5]

Benefits of delaying disease onset. Even a small delay in the onset of AD could substantially affect the population as a whole. It has been estimated that an intervention delaying the onset

of AD by an average of two years could reduce the number of affected people by about two million after 50 years.[6]

3. EPIDEMIOLOGY

In the United States, dementia affects about 8% of people aged 65 years or older, and this rate roughly doubles when milder forms of dementia or cognitive impairment are included. Prevalence is strongly age-dependent and approximately doubles every five years, rising from about 1% between the ages of 65 and 70 to about 30% after the age of 85. AD is the most prevalent dementing illness in the United States.[7]

4. COST OF ALZHEIMER'S DISEASE

The cost of AD extends far beyond medication and medical care. As the disease progresses, patients need increasing medical attention, supervision, help with everyday tasks, and long-term care. The economic burden therefore consists of direct, indirect, and intangible costs. Earlier estimates put the annual cost of AD to the US economy at close to US$100 billion, including long-term and medical care, lost productivity, and family care; however, this figure is significantly lower than the present burden.

4.1 Direct costs. Direct costs are expenses directly related to the care and treatment of a person with AD. They include medical consultations, diagnostic testing, prescription drugs, hospital stays, long-term care, equipment and home modifications, day care, and support services. Excluding the economic value of unpaid caregiving, the Alzheimer's Association projects that health and care costs for Americans with AD or other dementias will total approximately US$409 billion by 2026.

4.2 Indirect costs. Indirect costs are losses resulting from the patient's inability to work and from the need for family members to provide care, such as lost productivity, caregiver income loss, and transportation expenses. Unpaid care has a major economic impact. According to WHO estimates, dementia cost the global economy approximately US$1.3 trillion in 2019, with informal care from family and friends accounting for about half of this amount.

4.3 Cost rises with disease progression. Costs typically rise as AD worsens. Studies from India likewise show that the cost of dementia care increases with severity. In one study, annual household costs ranged from ₹45,600 to ₹2,02,450 in urban areas and from ₹20,300 to

₹66,025 in rural areas, depending on severity, with informal care accounting for a large share of total costs.

4.4 Economic burden in India. Because AD falls under the broader category of dementia, Indian economic studies usually report the costs of dementia rather than of AD specifically. A nationally representative Indian study estimated the annual household cost of dementia at approximately US$571 (2019 purchasing-power-adjusted dollars), with the value of unpaid care by family members, rather than direct medical expenditure, forming the largest component. Another Indian study reported yearly costs of about ₹78,288 for mild-to-moderate major neurocognitive disorder and about ₹1,67,808 for severe disease.[8]

5. RISK FACTORS

5.1 Genetic risk factors

Genetic factors strongly influence the risk of AD. Genes carry hereditary information from parents to offspring, and specific genetic variations can affect the likelihood of developing the disease. There are two main categories of genetic risk.

A. Familial Alzheimer's disease. Familial AD, also called autosomal dominant AD, is a rare form closely linked to inherited mutations in specific genes. Symptoms typically appear before the age of 65. Three genes are implicated: amyloid precursor protein (APP) on chromosome 21, presenilin 1 (PSEN1) on chromosome 14, and presenilin 2 (PSEN2) on chromosome 1. Although such mutations are rare, they raise the risk of AD substantially. If a parent carries a disease-causing mutation in one of these genes, each biological child has a 50% chance of inheriting it.[9, 10]

B. Sporadic (late-onset) Alzheimer's disease. Sporadic AD is the more common type. It usually has no single inherited cause and appears after the age of 65. It is influenced by several factors, including ageing, genetic variations, family history, metabolic and cardiovascular health, lifestyle, and environmental exposures. A person can develop AD even without a family history of the illness.

C. Apolipoprotein E (APOE). The APOE gene is one of the most important genetic risk factors for late-onset AD. It encodes apolipoprotein E, a protein that helps transport cholesterol and fats in the body. Three forms (alleles) are commonly discussed (Table 1).

Table 1: APOE alleles and their effect on Alzheimer's disease risk.

SR.NO	APOE allele	Effect on Alzheimer's risk
1	APOE ε2	May provide some protection against the disease.
2	APOE ε3	Most common form; generally regarded as the reference allele for risk.
3	APOE ε4	Increases the risk of developing Alzheimer's disease.

The APOE gene is inherited in two copies, one from each biological parent, so an individual may carry combinations such as ε2/ε3, ε3/ε3, or ε3/ε4. People with two copies of APOE ε4 are generally at higher risk than those with one copy. Nevertheless, APOE ε4 is a risk factor, not a guarantee of developing AD, and its effect differs between populations.

D. Family history. A person whose parent or sibling has AD may be more susceptible to the disease. This increased risk may reflect shared genetic variations, similar diet and lifestyle, common environmental exposures, and shared metabolic and cardiovascular risk factors.

E. Down syndrome. Individuals with Down syndrome are more likely to develop AD at a younger age. Down syndrome is caused by an extra copy of chromosome 21, which carries the APP gene. The extra genetic material may increase amyloid-beta production and contribute to amyloid build-up in the brain.[10–13]

5.2 Age

Age is the biggest known risk factor for AD, and the risk rises significantly with advancing age, especially beyond 65 years. Ageing is associated with the accumulation of neuronal damage and vascular changes in the brain. AD symptoms typically appear in people aged 65 years or older, and AD that develops before the age of 65 is defined as early-onset AD.[14]

5.3 Sex and gender

Sex- and gender-related factors may influence the observed risk of AD. More women than men are affected, which is partly explained by their longer average life expectancy. Hormonal changes during and after menopause are being investigated for possible links with brain health, although their precise role in AD risk remains unclear. In men, dementia risk may be influenced by smoking, cardiovascular risk factors, and other health-related exposures. Because AD is closely linked to advanced age, differences in life expectancy affect the numbers of men and women with the disease, and sex-related differences should not be attributed to a single factor.[15]

5.4 Education and cognitive reserve

Education may influence both the likelihood of dementia and the ability to adapt to changes in the brain.

A. Low level of education. Individuals with fewer educational opportunities may be more susceptible to dementia as they age. Education, however, is not a direct cause of AD.

B. Cognitive reserve. Cognitive reserve is the brain's capacity to maintain cognitive function despite injury or structural change. It can be built through reading, learning new skills, solving puzzles, learning a new language, taking part in educational activities, and mentally demanding work. Even with some brain changes, a person with higher cognitive reserve may continue daily functioning for longer.[7, 16]

5.5 Lifestyle-related risk factors

Lifestyle choices affect brain function and may raise the risk of dementia, including AD.

A. Physical inactivity. A sedentary lifestyle may make cognitive decline more likely. Regular exercise improves metabolic function, blood sugar control, cardiovascular health, and circulation. Walking, cycling, swimming, yoga, and household and outdoor activities can provide these benefits.

B. Unhealthy diet. A diet high in processed foods, refined carbohydrates, saturated fats, and excess salt may lead to obesity, diabetes, and cardiovascular disease, all of which are linked to a higher risk of cognitive decline. A balanced diet should include fruits and vegetables, whole grains, legumes and pulses, nuts and seeds, fish where appropriate, and unsaturated fats. No single food or diet can guarantee prevention of AD, but the Mediterranean-style diet is widely studied for its potential benefits to cognitive health.

C. Smoking. Smoking harms brain health and is linked to a higher risk of dementia. Possible mechanisms include blood vessel damage, reduced oxygen delivery to tissues, increased oxidative stress and inflammation, and a higher risk of stroke and cardiovascular disease. Avoiding tobacco is an important step in protecting long-term health.

D. Alcohol misuse. Prolonged or heavy alcohol use can damage the brain and raise the risk of dementia and cognitive decline. Excessive drinking can also cause liver disease, sleep problems, brain cell damage, and nutritional deficiencies. Some earlier studies suggested that

moderate drinking might be protective, but the evidence remains unclear. Alcohol should not be started as a means of preventing AD, and heavy consumption should be avoided.

E. Poor sleep. Poor sleep and sleep disorders may be linked to cognitive decline. Sleep supports healthy brain function and memory consolidation, and sleep disturbance may impair the brain's processes for clearing metabolic waste products. A regular sleep schedule and treatment of chronic sleep problems may support brain health.

F. Social isolation. Loneliness and lack of social interaction are linked to a higher risk of cognitive decline. Social activity supports communication skills, emotional stability, and mental stimulation.[17]

6. CLINICAL FEATURES OF ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive neurodegenerative condition and one of the main causes of dementia. It primarily affects memory, thinking, behaviour, communication, judgement, and the ability to carry out daily tasks. Clinical features usually appear gradually and subtly. In many patients, problems with short-term or recent memory are the first obvious sign, and other cognitive abilities and day-to-day functioning deteriorate as the illness advances. Symptoms and rate of progression vary considerably between individuals.

1. Cognitive and functional decline. The core clinical feature of AD is a progressive loss of cognitive abilities such as judgement, language, thinking and reasoning, executive function, and the capacity to carry out activities of daily living (ADL). Patients gradually lose independence and need more help from family members or caregivers. Affected activities include bathing, dressing, eating, cooking, shopping, taking medications as prescribed, handling finances, using phones or electronic devices, travelling independently, and maintaining hygiene.[18, 19]

2. Memory impairment. Memory impairment is typically one of the first and most noticeable symptoms. Patients initially struggle to recall recent experiences and recently acquired knowledge. Common signs include forgetting recent information, conversations, and appointments; asking the same question or repeating the same story; misplacing frequently used objects; forgetting the names of familiar people; difficulty learning new information; and, later, forgetting the names of family members.

3. Misplacing personal items. Because of memory and organisational problems, patients often put items in unusual places.[21]

4. Disorientation. Disorientation is the inability to recognise or understand one's own identity, surroundings, time, place, date, and day. It usually becomes more noticeable as the illness worsens.

5. Impaired thinking and reasoning. Abstract thinking and reasoning may gradually deteriorate. Patients may struggle to understand complex situations, solve problems, make decisions, grasp connections between concepts, plan, or follow instructions.[22]

6. Impaired judgement. Judgement deteriorates over time. Patients may make unsafe or inappropriate choices, such as giving money to strangers, overspending, making inappropriate purchases, dressing unsuitably for the weather, leaving stoves or electrical appliances on, or failing to recognise dangerous situations. As the condition worsens, supervision may be needed for important decisions.[21]

7. Impaired executive function. Executive functions are the mental skills needed to organise, plan, sequence, and complete tasks. Planning, organising, problem-solving, decision-making, multitasking, starting or finishing tasks, managing finances, and keeping a routine can all become difficult. A patient who once managed household or work tasks independently may eventually need help.[22]

8. Language problems. Language impairment is another significant clinical feature. Initially, patients may struggle to find the right words, forget names, pause frequently when speaking, follow conversations, understand complex sentences, and express ideas. It worsens as the disease advances: patients may repeat words or phrases, use incorrect words, have a limited vocabulary, struggle to understand others and to express themselves, and eventually develop aphasia. Aphasia is a language impairment caused by dysfunction of the brain regions that process language, and it can affect reading, writing, speaking, and comprehension of speech. It is usually more noticeable in the later stages of AD, although some patients have serious language problems much earlier.

9. Agnosia. Agnosia is the inability to recognise familiar objects, people, sounds, or other sensory information despite adequate sensory function. Patients may eventually lose the

ability to recognise family members, common household items, and their surroundings. For example, a patient may see a comb but be unable to work out its purpose.

10. Apraxia. Apraxia is the inability to carry out previously learned, purposeful movements despite adequate strength and coordination. Familiar tasks such as dressing, using cutlery, brushing teeth, housework, buttoning clothes, and preparing meals may become difficult. For example, a patient may be physically able to put on a shirt but not know the movements required.[21]

11. Personality changes. Personality changes may occur as AD advances. A previously composed person may become irritable, suspicious, withdrawn, apathetic, or agitated. These changes can be distressing for both the patient and family members.

12. Behavioural and psychological symptoms of dementia (BPSD). Behavioural and psychological symptoms are common in AD. Because they are distinct from the core cognitive impairments such as memory loss, they are also called non-cognitive symptoms.

Important BPSD include:

- **Agitation:** the patient may become restless, unable to stay still, and physically or verbally hostile. Agitation may become especially prominent during the course of the disease.
- **Depression and dysphoria:** an unpleasant emotional state that may include sadness, low mood, loss of interest, and social withdrawal.
- **Apathy:** lack of motivation, reduced interest, diminished emotional response, and reduced participation in activities. The patient may stop taking part in past interests or social activities.
- **Anxiety:** excessive worry, restlessness, and repeated requests for reassurance.
- **Irritability:** the patient may become easily irritated or angry, sometimes in response to trivial stimuli.
- **Withdrawal:** the patient may progressively withdraw from social interaction, stop going out with friends, avoid social gatherings, and spend time alone.
- **Disinhibition:** the patient may act inappropriately and lose normal social restraints, for example by making inappropriate remarks or touching, behaving impulsively, or performing socially unacceptable acts.

13. Delusions and suspicion. Some patients develop delusions or suspicions. They may wrongly believe that caregivers are hiding things from them, that someone has stolen their possessions, that a partner is unfaithful, or that others are trying to harm them. Memory loss and difficulty interpreting situations correctly can give rise to such beliefs.

14. Hallucinations. Some patients experience hallucinations, in which they see or hear things that are not there; other senses may also be involved. Not all patients have hallucinations, but they may be more common in advanced illness or when other conditions are present.

15. Repetitive behaviour. Patients may repeatedly ask the same question or carry out the same action, such as walking around the house, checking doors, or repeating a sentence. This behaviour may be linked to anxiety and memory loss.

16. Pacing and wandering. Some patients pace or wander. They may have difficulty navigating, get lost in familiar places, or leave the house without telling anyone.

17. Sleep disturbances and sundowning. Sleep disturbances are common. Patients may have an irregular sleep–wake cycle, difficulty falling asleep, frequent night-time waking, and daytime drowsiness. Sundowning is the worsening of confusion, agitation, or other behavioural symptoms in the late afternoon or evening, when the patient may become more confused, restless, anxious, irritable, or aggressive.

18. Aggression. Aggression may appear as the illness worsens. It can be physical, such as pushing, kicking, or hitting, or verbal, such as yelling, insulting, or arguing. It may be triggered by poor communication, confusion, fear, frustration, pain, or external circumstances.[21–25]

19. Loss of functional independence. Patients become progressively less independent as the disease advances. In the early stage, the patient may still be self-sufficient but may struggle with complicated financial tasks, work duties, planning, shopping, and managing medications. In the moderate stage, help may be needed with dressing, bathing, cooking, travelling, hygiene, and medication management. In the severe stage, patients eventually need continuous care and depend on caregivers for eating, dressing, bathing, toileting, and mobility.

20. Getting lost in familiar environments. Patients may become less able to navigate familiar surroundings and may get lost on the way to a previously known place, inside their own home, or in their neighbourhood. This is associated with deficits in orientation, memory, and visuospatial skills.

21. Progressive loss of communication. Communication becomes more difficult as AD advances. Patients may repeat words, give inappropriate or inadequate answers, have trouble following conversations, forget words, struggle to form sentences, and eventually have very limited speech. At this point they may be unable to communicate even basic needs effectively.[26]

7. CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE

The main symptoms of AD affect memory, thinking, language, judgement, behaviour, and the capacity to carry out daily tasks. The diagnostic process includes a thorough history, cognitive evaluation, physical and neurological examination, laboratory tests, brain imaging and, where appropriate, AD biomarkers.

7.1 Clinical diagnosis

Clinical diagnosis involves determining whether the patient's symptoms indicate cognitive impairment, whether the impairment interferes with day-to-day functioning, and whether AD is the most likely underlying cause. The first complaint is frequently forgetfulness, such as repeating questions, forgetting recent conversations or events, misplacing objects, or missing appointments. Other early features include difficulty finding words, organising or solving problems, making decisions, carrying out routine tasks, and behavioural or personality changes. Memory problems are frequently an early feature, although some patients first present with language, visuospatial, or executive difficulties. Family members and caregivers are especially important because the patient may not be aware of the severity of the cognitive changes.

7.2 Medical history

A detailed medical history is the first major step in diagnosis. The doctor obtains information from the patient, a family member or caregiver, and medical records, including the nature of the cognitive symptoms.

A. Course of illness. AD typically progresses gradually. The doctor assesses whether symptoms have remained constant, progressed gradually, progressed rapidly, or fluctuated significantly. A sudden onset raises the possibility of other causes such as delirium, stroke, drug side effects, or another illness.

B. Impact on everyday activities. The doctor asks about bathing, dressing, eating, cooking, shopping, handling money, taking medications, using transport, self-care, and household chores. This is especially important for distinguishing dementia from milder impairment.

7.3 Spectrum of cognitive states

Distinguishing dementia from other cognitive states is a crucial component of the diagnosis of AD.

A. Normal ageing. Some slight memory changes occur with age and do not indicate a neurodegenerative illness.

B. Subjective cognitive decline. The person or their family reports cognitive problems, but formal cognitive testing does not show significant objective impairment.

C. Mild cognitive impairment (MCI). MCI lies between normal cognition and dementia, with impairment in one or more cognitive domains such as memory, attention, executive function, or language. Objective testing shows the impairment, but overall independence is preserved and relatively simple daily tasks are usually maintained.

D. Dementia due to Alzheimer's disease. This is a more severe form of cognitive impairment in which cognitive decline impairs daily functioning. As the illness worsens, the patient may need help with money, medication administration, shopping, cooking, transportation, and personal care.

7.4 Cognitive assessment

Cognitive testing is an essential part of the assessment. The doctor evaluates memory (immediate and delayed recall, recognition), attention (span, simple mental tasks), language (word finding, comprehension, repetition), executive function (problem-solving, mental flexibility), and visuospatial skills (copying figures, drawing, spatial orientation). The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) are common screening tools, but they are not sufficient on their own to determine the cause of cognitive impairment. They remain important for identifying cognitive decline.

7.5 Physical and neurological examination

A thorough physical examination helps identify disorders that may contribute to or cause cognitive impairment. The neurological examination may assess muscle strength, reflexes, coordination, gait, sensory function, cranial nerves, and signs of focal neurological deficit. This is important because parkinsonism, focal deficits, abnormal gait, or marked behavioural change may indicate mixed pathology or another neurological disorder.

7.6 Psychiatric evaluation

Depression and other mental illnesses can produce cognitive symptoms. Anxiety, sleep problems, and social disengagement may be assessed. Because depression can sometimes cause concentration and memory problems that resemble dementia, it should be evaluated rather than automatically attributing cognitive symptoms to AD.

7.7 Laboratory investigations

Routine laboratory investigations are mainly intended to find other potentially treatable causes of, or contributors to, cognitive impairment. Depending on the clinical circumstances, tests may include a complete blood count, thyroid function tests, vitamin B12, and folate. Further tests, such as those for infections or other metabolic disorders, may be carried out when clinically indicated. The goal is to rule out alternative causes of cognitive impairment rather than to “prove” AD.

7.8 Structural brain imaging

Brain imaging is an essential part of the diagnostic procedure. Magnetic resonance imaging (MRI) is the primary structural imaging technique and can detect subdural collections, hydrocephalus, vascular disease, and other structural abnormalities. When MRI is unavailable, computed tomography (CT) can be used to detect significant structural abnormalities.

7.9 Biomarker evaluation

Biomarkers that provide evidence of the biological mechanisms of AD are increasingly used in modern diagnosis.

A. Cerebrospinal fluid (CSF). CSF is obtained by lumbar puncture. Amyloid-beta 42 (Aβ42) and total and phosphorylated tau (p-tau) are the key biomarkers. Reduced CSF Aβ42

together with elevated total and phosphorylated tau is the typical AD-related pattern and indicates Alzheimer-type pathology.

B. Amyloid PET. Amyloid positron emission tomography (PET) shows abnormal amyloid deposition in the brain and can help identify Alzheimer-type amyloid pathology when the clinical diagnosis is unclear.

C. FDG-PET. FDG-PET assesses patterns of brain glucose metabolism and may, in some circumstances, help differentiate AD from other neurodegenerative conditions.

D. Tau PET. Tau PET can show abnormal tau accumulation and is becoming increasingly important in research and specialised diagnostic settings.

E. Blood biomarkers. Blood-based biomarkers measuring proteins such as phosphorylated tau and amyloid are evolving rapidly and are increasingly used in clinical diagnostic work-ups. Their use depends on the specific test, clinical setting, regulatory status, and available guidance. They should be interpreted as part of a thorough clinical evaluation and not as a replacement for clinical assessment.[27, 28]

8. BIOMARKERS IN ALZHEIMER'S DISEASE DIAGNOSIS

A biomarker is a measurable biological characteristic that provides information about a disease process. Biomarkers are valuable in AD because clinical symptoms such as memory loss, word-finding difficulty, impaired judgement, disorientation, and difficulty with daily activities may appear relatively late in the disease process. The ATN research framework, which consists of amyloid pathology (A), tau pathology (T), and neurodegeneration (N), is the standard framework of pathological biomarkers used to diagnose AD and distinguish it from other causes of dementia.

8.1 Neurodegeneration and functional biomarkers (FDG-PET). Fluorodeoxyglucose PET (FDG-PET) measures regional brain glucose metabolism to detect cellular loss and dysfunction. In AD, symmetrical hypometabolism (reduced glucose uptake) is seen mainly in the temporal and parietal lobes, and in later stages the metabolic decline spreads to the frontal lobes.[29–32]

8.2 Amyloid pathology biomarkers (PiB-PET). Pittsburgh compound B (PiB) PET maps the deposition of amyloid-beta plaques in living patients. In normal controls, tracer retention

is minimal and limited to white matter tracts, with none throughout the cerebral cortex. In AD patients, strong, diffuse tracer retention is seen in the frontal, parietal, and occipital cortices, indicating a high amyloid plaque burden. A positive PiB-PET scan strongly supports an AD diagnosis, but its diagnostic value must be evaluated together with clinical symptoms, since 10% to 30% of cognitively normal older people may also have positive amyloid scans, representing a preclinical, asymptomatic stage of the disease.[33–36]

8.3 Cerebrospinal fluid biomarkers. CSF biomarkers obtained by lumbar puncture provide highly sensitive molecular information when structural or metabolic neuroimaging is unavailable or inconclusive.

a. CSF Aβ42. CSF levels of soluble Aβ42 fall markedly because the protein aggregates into insoluble plaques within brain tissue instead of circulating freely.

b. CSF total tau (t-tau) and phosphorylated tau (p-tau). Cortical neurodegeneration and neurofibrillary tangle formation raise CSF levels of both t-tau and hyperphosphorylated p-tau.
c. Biomarker ratios. Diagnostic accuracy is maximised by combining these measurements into ratios (e.g., t-tau/Aβ42 or p-tau/Aβ42). For differentiating AD from disorders such as frontotemporal dementia (FTD), this combined approach gives a sensitivity of approximately 92% to 98% and a specificity of 83% to 95%.[37–39]

9. PHARMACOLOGICAL TREATMENT

9.1 Cholinesterase inhibitors (ChEIs)

ChEIs increase neurotransmitter activity by blocking acetylcholinesterase in the synaptic cleft. This slows the breakdown of acetylcholine released from presynaptic neurons and provides modest but clinically meaningful benefit in patients with mild-to-moderate disease.

A. Clinical efficacy. Over six to twelve months, ChEI treatment delays cognitive decline as measured by the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog), global clinical ratings, behaviour, and ADL. In mild-to-moderate cases, cognitive abilities improve within the first three months. Decline then resumes over three to nine months, but much more slowly than with placebo. At six months, ChEIs improved attention, thinking, memory, praxis, language comprehension, and communication by 2.7 points on the ADAS-cog compared with placebo. In a 52-week clinical trial (Farlow et al.), patients who started

rivastigmine at 26 weeks performed worse cognitively than those treated from the start, underscoring the importance of early optimisation of treatment.

B. Long-term effects. Open-label trials have demonstrated long-term benefits, following galantamine for up to 4 years, donepezil for up to 4.9 years, and rivastigmine for up to 5 years. In these cohorts, cognitive and functional decline occurred more slowly than expected.

C. Global impression and response rates. A benefit of 4 points or more on the ADAS-cog indicates that up to 60% of patients respond to ChEI therapy. In nine clinical trials focusing on global impression, ChEI-treated patients were significantly more likely to improve than placebo groups. The pooled relative risks for clinical response were 1.88 for donepezil, 1.15 for galantamine, and 1.64 for rivastigmine. Three open-label evaluations and one randomised controlled trial found no significant difference in efficacy between galantamine or rivastigmine and donepezil.

D. Side effects and tolerability. ChEIs are usually well tolerated. The oral formulations of donepezil and galantamine are usually given once daily, whereas oral rivastigmine is usually given twice daily. The most common side effects are gastrointestinal (nausea, anorexia, vomiting, and diarrhoea) along with weight loss. Other common effects include dizziness, headache, fatigue, malaise, muscle cramps, asthenia, and bradycardia. Gradual upward dose titration over three months is strongly advised to minimise these effects.

Transdermal formulation. Rivastigmine is unique in being available as a transdermal patch, which reduces gastrointestinal distress. However, about 8% of patients experience skin reactions (pruritus and erythema), and 2% need permanent discontinuation. The patch should not be used in patients with active skin conditions.[40–46]

9.2 N-methyl-D-aspartate (NMDA) receptor antagonists

A. Mechanism. Glutamate is an essential neurotransmitter for learning and memory through long-term potentiation. Persistently high glutamate levels, however, cause excitotoxicity, which kills neurons. Memantine protects against harmful, prolonged glutamate levels while preserving the physiological glutamate activity needed for memory.

B. Efficacy. In moderate-to-severe AD, clinical trials show a small but significant improvement in behaviour, ADL, and cognition compared with placebo, and patients are less likely to experience delusions, agitation, irritability, or mood swings. Memantine may be

used together with ChEIs. In mild-to-moderate AD it shows only slight cognitive benefit and has no effect on ADL or global behavioural impression.

C. Dosing protocol. The suggested starting dose is 5 mg once daily, increased weekly in 5 mg increments up to a maximum maintenance dose of 10 mg twice daily.

D. Adverse reactions. Memantine is usually well tolerated. Uncommon adverse reactions include nausea, dizziness, confusion, somnolence, and hallucinations, which usually resolve when the dose is lowered or the drug is stopped.[47–49]

9.3 Antioxidants

Clinical evidence supporting antioxidants remains very limited, but several options have been examined.

A. Alpha-tocopherol (vitamin E) and selegiline. A randomised controlled trial found that these agents, alone or combined, could slow functional decline in moderately severe AD, delaying institutionalisation, loss of basic ADL, severe dementia, or death.

B. Clinical limitations. Vitamin E is cheaper than selegiline and has a lower chance of mild side effects, but it is suitable only for patients without cardiovascular risk factors, since data suggest increased mortality in people with underlying vascular disease.

C. Ginkgo biloba. Known for its anti-platelet properties, ginkgo was examined in a review of four RCTs, which found only slight cognitive benefit and no discernible effect on behaviour or ADL. It is generally not recommended for the management of AD and is associated with a risk of severe bleeding.[50–52]

9.4 Antipsychotics

Antipsychotic drugs are used only for neuropsychiatric symptoms, not for cognitive decline.

A. Indications. They are used to treat severe dementia-related hallucinations or distressing aggressive behaviour.

B. Conventional versus atypical antipsychotics. Older conventional antipsychotics such as haloperidol can worsen cognitive deficits, increase the risk of falls and related fractures, and carry a high risk of severe extrapyramidal symptoms (EPS) and heavy sedation. Atypical antipsychotics, which cause fewer EPS, are preferred for short-term behavioural stabilisation.

C. Safety. Although short-term adverse events are similar to placebo rates, antipsychotics carry a significant risk of stroke and increased mortality in older patients with dementia. Clinical consensus strongly recommends avoiding them where possible, particularly in patients with high cerebrovascular risk. However, an 18-month cohort study of elderly Chinese patients found no increased mortality with long-term use.[53]

10. NEW STRATEGIES IN ALZHEIMER'S DISEASE

A. Underlying pathology and current research targets. Current disease-modifying approaches are based mainly on the amyloid cascade hypothesis. A variety of mechanistic pathways are under investigation, including secretase modulators, immunotherapy, amyloid binders, metal-chelating agents, anti-inflammatory agents, and antioxidants.

B. Earlier clinical studies with unfavourable outcomes.

- **Hormones and steroids:** corticosteroids and oestrogens.
- **Non-steroidal anti-inflammatory drugs (NSAIDs):** rofecoxib, naproxen, ibuprofen, and indomethacin.
- **Other agents:** xaliproden, rosiglitazone, and tarenflurbil.

C. Immunotherapy.

- **Active immunisation (AN-1792):** this vaccine was designed to target amyloid plaques, but 6% of patients who received it developed a serious form of encephalitis.
- **Passive immunisation (bapineuzumab):** in clinical data from Salloway et al., the monoclonal antibody bapineuzumab, given by intravenous infusion, showed a cognitive benefit in APOE ε4-negative patients but not in APOE ε4-positive patients. Phase III trials were planned at that time. Subsequent phase III trials, however, failed to show clinical benefit and the programme was discontinued.
- **Intravenous immunoglobulin (IVIg):** open-label use of IVIg, a form of passive immunotherapy, gave promising results. According to an earlier study by Relkin et al., about 75% of treated patients showed improvement or stabilisation of cognitive function on the MMSE. Later controlled trials, however, did not confirm a clear clinical benefit.

D. Recent developments

Newer anti-amyloid monoclonal antibodies, notably lecanemab and donanemab, have been shown to slow clinical decline in early AD and have received regulatory approval in several countries. Their use requires confirmation of amyloid pathology and monitoring for amyloid-related imaging abnormalities (ARIA), the risk of which is higher in APOE ε4 carriers.

11. NON-PHARMACOLOGICAL MANAGEMENT OF ALZHEIMER'S DISEASE

An essential component of treating Alzheimer's disease (AD) is non-pharmacological management. It seeks to enhance the patient's and the caregiver's everyday functioning, safety, independence, emotional health, and quality of life. As the illness worsens, it becomes more important and is used in conjunction with pharmaceutical treatment.

1. Behavioral Control: Problems like agitation, aggression, wandering, anxiety, sleep disturbances, and inappropriate behavior are managed with behavioral management techniques. Keep your surroundings peaceful and comfortable to prevent situations that set these off. Follow directions and make sure Don't argue with the patient or correct them excessively. Encourage the patient to engage in enjoyable and meaningful activities on a daily basis according to their interests. When appropriate, interventions should be tried before taking medication to treat behavioral symptoms.

2. Education and Counseling for Caregivers: In the long-term management of Alzheimer's disease, caregivers are crucial. They ought to get the right instruction and guidance regarding providing care. Education for caregivers can lower stress levels and enhance the standard of care.

3. Preventing Burnout and Stress in Caregivers: In Alzheimer's disease, caregiver stress and burnout are major problems. Emotional exhaustion can result from ongoing care. Regular breaks, delegating tasks to other family members, making use of community care services, attending caregiver support groups, and obtaining psychosocial support when necessary are some strategies. Because caregiver problems affect the patient's care, the caregiver's emotional health is vital.

4. Dementia Day-Care Centers: Patients may be directed to these facilities, where they can engage in suitable activities and receive supervision. These facilities offer caregivers periods of relaxation along with supervision, structured daily activities, and cognitive stimulation.

5. Caregiver and Family Support: Support groups are beneficial for caregivers and family members. These groups give people a chance to talk about their experiences, learn useful caregiving techniques, receive emotional support, and discuss available community and professional services.

6. Legal and Psychosocial Planning: A patient's capacity to make decisions may deteriorate as Alzheimer's disease advances. As a result, the patient and family should be consulted at the proper time regarding matters pertaining to mental competence, decision-making ability, guardianship, and future care planning. Financial decision-making, future living, designating a suitable guardian or representative, and future care planning are examples of important issues. The laws that are relevant in the patient's area should be followed when seeking advice.

7. Safety Measures: Because Alzheimer's patients may exhibit poor judgment, confusion, and wandering behavior, safety is especially crucial. Safety precautions include removing potentially dangerous items from the home, identifying patients who are at risk, utilizing medical alert systems or appropriate identification, and, when needed, communicating the patient's condition to dependable family members or caregivers. Planning ahead is important, particularly for patients who are prone to wandering.

8. Social and Psychosocial Support: Professional psychosocial support may be necessary for patients and their families. Medical social workers and other qualified professionals can assist with social planning, caregiver support, emotional resources, and suitable long-term options. When the family is struggling to meet the patient's needs, referral to suitable psychosocial services is especially helpful.

9. Preserving Independence: Patients should be encouraged to engage in activities that they are still able to do safely. Only when absolutely necessary should assistance be given; this includes eating on one's own while doing household chores, walking, engaging in physical activity or hobbies, and having fun. Self-worth, dignity, and quality of life can all be enhanced by independence.[55, 56]

12. CONCLUSION

Alzheimer’s disease is a progressive neurodegenerative disorder driven by the interplay of age, genetic susceptibility, and modifiable lifestyle and vascular risk factors. Early recognition, based on careful clinical assessment supported by neuroimaging and, increasingly, CSF, PET, and blood biomarkers, allows other causes of cognitive impairment to be excluded and the diagnosis to be made earlier. Cholinesterase inhibitors and memantine remain the mainstay of symptomatic treatment, while antipsychotics are reserved for severe behavioural symptoms because of their safety risks. Disease-modifying anti-amyloid

therapies are an important advance, but their benefits and risks require continued evaluation. Alongside drug therapy, caregiver support, patient safety, and the management of risk factors remain central to care, and the large and growing social and economic burden of AD underlines the need for early diagnosis and prevention.

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