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Unravelling Alzheimer's disease: Insights into pathophysiology, etiology, diagnostic approaches, and the promise of aducanumab, lecanemab, and donanemab

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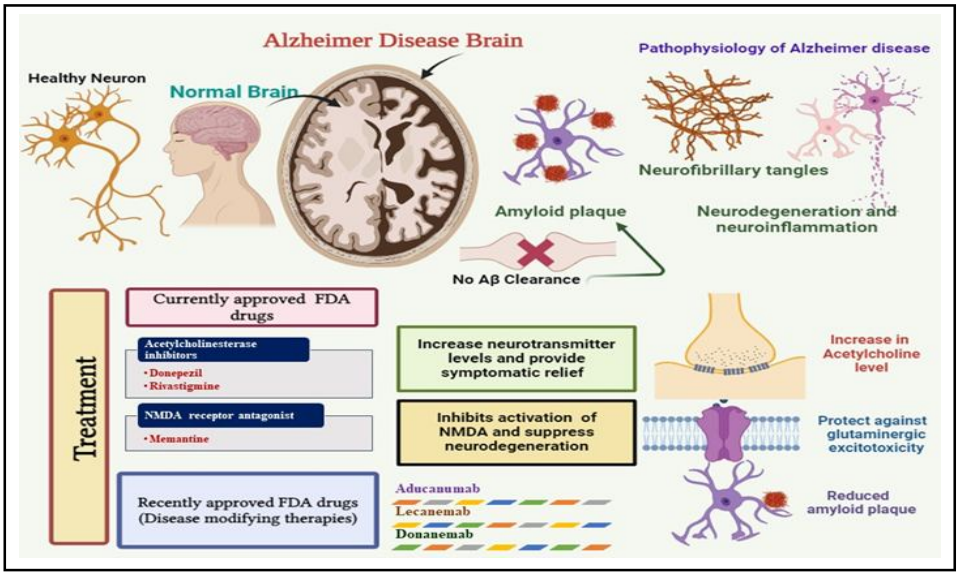
Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that profoundly affects cognitive function, leading to memory loss and behavioural changes, and it stands as the leading cause of dementia worldwide. The pathophysiology of AD involves the buildup of amyloid-beta (Aß) plaques and neurofibrillary tangles formed by hyperphosphorylated tau protein, which contributes to neuronal dysfunction, synaptic loss, and brain atrophy. These pathological changes disrupt neuronal communication, resulting in the cognitive deficits observed in affected individuals. The etiology of AD is complex, influenced by genetic factors such as mutations in the amyloid precursor protein (APP) and presenilin genes, with the apolipoprotein E (APOE-e4) allele being a significant risk factor for late-onset AD. Additional factors include aging, oxidative stress, and vascular health. Diagnosis usually involves clinical assessments, neuropsychological testing, and neuroimaging methods like MRI and PET, along with biomarker evaluations in cerebrospinal fluid (CSF) and blood. While current treatments primarily target symptoms through cholinesterase inhibitors and NMDA receptor antagonists, recent advancements in disease-modifying therapies such as aducanumab, lecanemab, and donanemab represent a significant shift in treatment strategies. Aducanumab, approved by the FDA in 2021, was the first monoclonal antibody aimed at reducing amyloid plaques, although, its clinical benefits remain under discussion. Lecanemab and donanemab have demonstrated promise in slowing cognitive decline by targeting early amyloid deposition. This review explores the complex pathophysiology, etiology, and diagnostic methods of AD, highlighting the potential of these innovative therapies to change the disease trajectory and improve outcomes for patients.



1. Introduction

Alzheimer's disease (AD) is a prevalent form of dementia, primarily affecting the elderly, with 60-80% of dementia cases attributed to this condition. It is characterized by the gradual loss of memory, cognitive function, and intelligence. Despite its widespread impact, AD currently has no cure, making it one of the most significant

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health concerns globally. The progression of AD is slow and insidious, with the final diagnosis often taking years. In seniors, the disease not only leads to oxidative stress but also causes permanent and progressive behavioural changes (Mohammed *et al.,* 2024).The historical understanding of AD dates back to the early 20th century. In 1910, Emil Kraepelin published a comprehensive account of cases marked by severe cellular transformations, including widespread plaques and the loss of approximately one-third of the cerebral cortex. Kraepelin's observations played a pivotal role in defining the disease at a time when its medical description was still unclear. Dr. Alois Alzheimer first identified the disease in 1906, describing the case of Auguste deter. However, the clinical definition of AD remained somewhat ambiguous until later developments. In 1907, Proskin further described Alzheimer's findings, noting the presence of senile plaques and neurofibrillary tangles. Although, arteriosclerosis was not overtly detected in clinical examinations, its role could not be completely ruled out. Later, in 1998, scientists from the Max Planck Institute and the University of Munich reanalyzed the brain of the first Alzheimer's patient, offering new insights into the disease's pathology. Further histological analysis by Dr. Gerber and his team in 1997 confirmed the presence of amyloid plaques, supporting Alzheimer's groundbreaking discoveries (Mohammed *et al.,* 2024).

Since then, research into AD has evolved significantly, leading to a deeper understanding of its molecular mechanisms. The identification of genetic factors, such as mutations in the APP and presenilin genes, has paved the way for genetic screening and risk assessment. The role of the apolipoprotein E(APOE-ε4) allele has also been extensively studied, establishing it as a major risk factor for late-onset AD. Advances in neuroimaging techniques, including positron emission tomography (PET), have facilitated the visualization of amyloid deposition in living patients, enabling earlier diagnosis. Recent studies have focused on the role of neuroinflammation and tau pathology, further elucidating the complex interplay of factors contributing to disease progression. Ongoing clinical trials for disease-modifying therapies, such as aducanumab, lecanemab, and donanemab, aim to target amyloid-beta and tau proteins, representing a shift towards innovative treatment strategies that may alter the disease course. Continued research into biomarkers and the underlying pathophysiology promises to enhance our understanding of AD and improve diagnostic and therapeutic approaches.

1.2 Epidemiology and prevalence of Alzheimer's disease

Alzheimer's disease poses a significant global health challenge, currently affecting approximately 24.3 million people worldwide. This figure accounts for a substantial portion of the estimated 57.4 million cases of dementia globally. As the population ages, the prevalence of dementia, including AD, is projected to nearly double every two decades. By 2030, it is anticipated that there will be around 78 million cases of dementia, and this number could rise to approximately 139 million by 2050 (Leverton and Pui Kin Kor, 2023).

In India, the rise in dementia cases has been particularly alarming, increasing from about 4.14 million in 2010 to 8.8 million in 2019. Projections indicate that by 2050, India could rank second in the world for the number of dementia cases, with an estimated 13.01 million individuals affected. This projection places India ahead of both the United States and Japan in terms of prevalence (Lee *et al*., 2023; Zhao *et al*., 2023; Vellingiri, 2023; Thomas *et al*., 2023).

In the United States, the Alzheimer's association estimates that approximately 6.9 million Americans aged 65 and older are living with AD as of 2024 (Nitrini, 2024). China holds the highest number of AD cases globally, with around 9.83 million cases reported in individuals aged 60 and above in 2021 (Hu *et al.,* 2024).The incidence of Alzheimer's disease increases significantly with age, approximately doubling every 10 years after the age of 60. In 2019, the worldwide economic impact of dementia was estimated at 1.3 trillion US dollars. A substantial portion of these costs, around 50%, is attributed to the contributions of informal caregivers. These caregivers play a critical role in patient support, devoting an average of 5 h per day to care and supervision, which underscores the extensive personal and financial toll the disease, takes on families and healthcare systems globally (World Health Organization, 2023).

2. Aetiology and risk factors of Alzheimer's disease

Understanding Alzheimer's disease aetiology involves examining genetic, environmental, lifestyle, and acquired risk factors that contribute to the disease's onset and progression.

2.1 Genetic factors

i. **Deterministic genes:** Specific genetic mutations directly lead to Alzheimer's, particularly in early-onset familial cases. Key genes include:

- **Amyloid precursor protein (APP):** Mutations here increase the production of amyloid-beta peptides, contributing to plaque formation in the brain.
- **Presenilin 1 (PS1) and presenilin 2 (PS2):** These genes are involved in the enzymatic processing of APP. Mutations in these genes also lead to increased amyloid-beta production, accounting for a small percentage of familial AD (<5%)(Cleveland clinic).

ii. **Risk genes:** The most notable risk gene is

- **Apolipoprotein E (ApoE)**: Specifically, the e4 allele significantly raises the risk of developing AD. Individuals with one e4 allele are three times more likely to develop the disease, while those with two ε4 alleles have a 6.5 times higher risk. Approximately 50% of individuals with AD have at least one copy of the ApoE ε4 allele.

2.2 Acquired risk factors

i. **Cerebrovascular diseases:** Vascular health plays a crucial role in cognitive decline. Conditions such as:

- **Ischemic infarcts:** Both small and large infarcts can contribute to dementia.
- **Vasculopathies:** Changes in blood vessels and white matter integrity are known to increase AD risk. Postmortem studies show a high prevalence of vascular pathology in AD patients, indicating a potential interaction between cerebrovascular health and amyloid accumulation.

The "double-stroke" theory suggests that vascular risk factors lead to dysfunction in the blood-brain barrier, reduced cerebral blood flow, and neuronal damage. This process promotes both the accumulation of amyloid-beta and tau hyperphos phorylation, accelerating neurodegeneration (Love and Miners, 2016).

ii. **Hypertension:** Elevated blood pressure is linked to an increased risk of AD. Longitudinal studies indicate that hypertension, particularly during middle age, negatively affects cognitive performance later in life. It can lead to:

- Vascular wall changes, resulting in ischemia and neuronal injury.
- Increased expression and accumulation of amyloid precursor protein (APP) and amyloid-beta (Skoog and Gustafson, 2006).

iii. **Type 2 diabetes:**This condition has a well-documented association with AD. Potential mechanisms include:

- **Insulin resistance:** Impaired insulin signalling can stimulate the activity of enzymes involved in amyloid-beta production.
- **Chronic inflammation:** Diabetic conditions lead to vascular inflammation and damage, contributing to neurodegenerative processes.
- **Advanced glycation end products (AGEs):** These compounds, formed from high glucose levels, may promote neuronal death and increase amyloid-beta deposition (li *et al*., 2015).

iv. **Obesity:** The role of obesity in AD is complex and varies by age. Some studies suggest that:

- **Midlife obesity:** Associated with an increased risk of AD due to its inflammatory effects and metabolic dysregulation.
- **Later life obesity:** Results are mixed; some studies indicate it may even inversely correlate with dementia risk, potentially due to confounding health issues in older adults (Anstey *et al*., 2011).

v. **Dyslipidemia:** Elevated cholesterol levels are proposed as risk factors for AD. Hypercholesterolemia is linked to:

- Increased amyloid-beta deposition in the brain.
- Compromised blood-brain barrier integrity, facilitating neuroinflammation and cognitive decline (Xue Shan *et al*., 2016).

2.3 Environmental and lifestyle factors

- **Age:** The most significant non-modifiable risk factor for AD. The risk doubles every five years after age 65, with nearly one-third of individuals over 85 developing the disease (Alzheimer's association).
- **Family history:** A familial history of AD increases an individual's risk, particularly when multiple relatives are affected.
- **Cardiovascular health:** Conditions like hypertension, diabetes, and hyperlipidaemia negatively impact brain blood flow, heightening AD risk.
- **Head injury:** Repeated concussions and traumatic brain injuries have been associated with an increased risk of developing AD.
- **Lifestyle factors:** Modifiable lifestyle choices significantly influence AD risk
- **Physical inactivity:** Sedentary lifestyles correlate with higher risk.
- **Smoking:** Tobacco use is linked to increased AD risk due to its effects on vascular health and inflammation.
- **Diet:** Poor dietary habits, particularly those high in saturated fats and sugars, elevate risk. Conversely, diets rich in antioxidants and omega-3 fatty acids may offer protective benefits.

2.4 Behavioural and cognitive factors

- **Cognitive engagement:** Lifelong participation in mentally stimulating activities can enhance cognitive reserve, potentially delaying the onset of AD symptoms. Engaging in learning and problem-solving may help maintain cognitive function.
- **Social engagement:** Active participation in social and community activities supports mental health, which may reduce the risk of cognitive decline. Strong social networks are associated with better cognitive outcomes.

3. Pathophysiology associated with Alzheimer'sdisease development

Numerous hypotheses have been proposed to elucidate the pathogenesis of Alzheimer's disease (AD), but a cohesive theory remains elusive due to the disease's intricate nature. AD can be divided into two primary categories: familial Alzheimer's disease (FAD) and sporadic Alzheimer's disease (SAD). FAD constitutes 1-5% of cases and is characterised by autosomal dominant genetic mutations in the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes. This form typically manifests between the ages of 30 and 65, often leading to a rapid progression of symptoms.

In contrast, SAD, also known as late-onset AD, usually appears after the age of 65 and accounts for over 95% of cases. Its development is influenced by a complex interplay of genetic predispositions, such as the presence of the apolipoprotein E(APOE) ε4 allele, environmental factors, and various comorbidities, including cardiovascular diseases and diabetes.

3.1 The cholinergic hypothesis

The cholinergic hypothesis, introduced by Peter Davies and A. J. F. Maloney in 1976, highlights the role of acetylcholine (ACh) in Alzheimer's disease (AD). Their studies revealed reduced choline acetyltransferase activity in key brain areas, leading to lower ACh levels crucial for cognitive functions like memory and learning.

Significant loss of cholinergic neurons, especially in the nucleus basalis of Meynert, impairs cognition due to ACh's essential role in neurovascular coupling and synaptic signaling. ACh synthesis occurs through choline acetyltransferase, while its breakdown is modulated by acetylcholinesterase. The cholinergic system also supports neurogenesis and synaptic plasticity, with Aβ peptides affecting neurotransmitter release and memory (Thakur *et al*., 2018).

3.2 The amyloid cascade theory

The amyloid cascade hypothesis, a widely recognized model for the development of Alzheimer's disease (AD), suggests that the accumulation of amyloid-beta (Aβ) peptides in the brain is the key event that initiates the disease. This buildup occurs due to an imbalance between the production and removal of Aβ, which in turn sets off a series of harmful processes, such as the development of neurofibrillary tangles (NFTs) and neurodegeneration. Aβ peptides, composed of 36 to 43 amino acids, are produced through the proteolytic breakdown of amyloid precursor protein (APP), a protein essential for brain function. The APP gene is located on chromosome 21, which explains the higher risk of early-onset AD in individuals with trisomy 21 (Down syndrome) or APP gene duplications. The overproduction of APP is thought to increase Aβ levels in the brain, leading to the formation of plaques.

APP processing occurs through two main pathways: the non-amyloidogenic pathway, mediated by α-secretase, and the amyloidogenic pathway, mediated by β-and γ-secretases. In the non-amyloidogenic pathway, α-secretase cleaves APP to produce a soluble fragment, sAPPα, which may have neuroprotective effects and contribute to neuronal plasticity and survival.

Conversely, in the amyloidogenic pathway, β-secretase (mainly the BACE1 enzyme) cleaves APP to generate a soluble fragment, sAPPβ, which is associated with neuronal death. This fragment is further cleaved by a γ-secretase complex, comprising presenilin 1 or 2, nicastrin, APH-1, and PEN-2, resulting in Aβ peptides, predominantly Aβ40 and Aβ42. Under physiological conditions, there exists a balance between the amyloidogenic and non-amyloidogenic pathways, with the latter being preferentially favoured (Gupta *et al*., 2016; Zhang*et al*., 2011; Zhang *et al*., 2012).

3.3 Tau hyperphosphorylation

Tau hyperphosphorylation is a key pathological feature of Alzheimer's disease (AD), characterized by the formation of neurofibrillary tangles comprised of aggregated Tau protein. Tau, a phosphoprotein primarily found in axons, plays a critical role in stabilizing and assembling microtubules, which are essential for axonal transport and the maintenance of dendritic structure. In addition to its presence in axons, Tau is also located in somatodendritic compartments and glial cells. The biological activity of Tau is tightly regulated by post-translational modifications, with phosphorylation being the most significant. In AD, Tau undergoes abnormal hyperphosphorylation at multiple sites, which diminishes its affinity for microtubules. This loss of affinity promotes Tau aggregation, leading to the formation of neurofibrillary tangles. The aggregation of Tau disrupts microtubule assembly and impairs axonal transport, severely affecting neuronal function.As a consequence of hyperphosphorylation, synaptic integrity deteriorates, resulting in neuronal dysfunction and cell death. This process is a critical contributor to the cognitive decline observed in AD patients (Kanaan *et al*., 2015; Mondragón Rodríguez*et al.,* 2014).

3.4 Oxidative stress in Alzheimer'sdisease

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the body's antioxidant defences. This excess of oxidants can lead to damage to lipids, proteins, and nucleic acids, significantly impacting neuronal health.

Oxidative stress is significantly implicated in the pathogenesis of neurodegenerative diseases, particularly Alzheimer's disease (AD). The following mechanisms illustrate its impact:

i. **Direct damage:** Reactive species can directly disrupt cellular functions, leading to neuronal cell death. Oxidative modifications of lipids (lipid peroxidation), proteins (protein carbonylation), and nucleic acids (DNA oxidation) contribute to cellular injury and apoptosis.

ii. **Signallingdisruption:** Hydrogen peroxide (H_2O_2) serves as a second messenger in various signaling pathways. Elevated levels can impair redox signalling, affecting key processes like

a. **Mitochondrial function:** H_2O_2 can lead to mitochondrial dysfunction, which further exacerbates ROS production.

b. **Inflammation:** Oxidative stress promotes inflammatory responses, which are critical in the progression of AD.

c. **Autophagy:** Impaired autophagy can result in the accumulation of damaged proteins and organelles, further fueling neurodegeneration.

iii. **Cognitive decline:** The cumulative effect of oxidative damage in neurons contributes to cognitive decline observed in AD patients. Mitochondrial dysfunction and inflammation can lead to synaptic loss and neurodegeneration, hallmark features of Alzheimer's pathology (Aamir and Meher Unnisa, 2023; Forman and Zhang, 2021; Mondragón Rodríguez *et al*., 2014).

3.5 Neuroinflammation hypothesis in Alzheimer's disease

The neuroinflammation hypothesis posits that chronic inflammation in the brain plays a pivotal role in the pathogenesis of Alzheimer's disease. According to Balducci and Forloni (2018), microglias are integral to maintaining homeostasis in the brain, responding to injury and clearing amyloid-beta plaques. However, in AD, microglial activation becomes dysregulated, leading to a state of chronic inflammation. This sustained inflammatory response not only fails to resolve the toxic buildup of amyloid plaques but also exacerbates neuronal damage and promotes neurodegeneration.

Complementing this perspective, von Bernhardi *et al*. (2015) discuss how microglial dysregulation is a hallmark of brain ageing and neurodegeneration. They describe the transition of microglia from a protective to a neurotoxic phenotype in the context of AD. This shift is characterized by the release of pro-inflammatory cytokines and reactive oxygen species, which further contribute to neuronal loss and cognitive decline. Notably, interactions between microglia and tau protein in the later stages of AD may lead to increased tau phosphorylation and exosomal tau secretion, promoting the spread of tau pathology. Additionally, exaggerated microglial activation can trigger the complement cascade, resulting in aberrant synapse pruning, which further exacerbates AD pathology.

3.6 Metal ion hypothesis in Alzheimer's disease

The metal ion hypothesis posits that dysregulation of metal ions particularly transition metals like aluminium (Al), copper (Cu), zinc (Zn), and iron (Fe), contributes to the pathogenesis of Alzheimer's disease (AD). This hypothesis is based on observations that these metals can influence the aggregation of amyloid-beta (Aβ) plaques and neurofibrillary tangles, key features of AD.

Key transition metals involved

1. **Aluminium (Al)**

- **Role:** Aluminium is a ubiquitous metal found in various environmental sources, including food, water and pharmaceuticals.
- **Pathological effects:** While the exact role of aluminium in AD remains controversial; studies suggest that high levels of aluminium exposure may correlate with increased risk of neurodegeneration. Aluminium can accumulate in the brain and potentially disrupt cellular processes, induce oxidative stress, and promote the aggregation of Aβ. Some research indicates that aluminium may facilitate neuroinflammation and contribute to cognitive decline.

2. **Copper (Cu)**

- **Role:** Copper is essential for enzymatic processes, including neurotransmitter synthesis and antioxidant defence.
- **Pathological effects:** In AD, copper binds to Aβ peptides, promoting their aggregation into toxic oligomers and fibrils. Elevated copper levels can also enhance the production of reactive oxygen species (ROS), leading to oxidative stress and neuronal damage.

3. **Zinc (Zn)**

- **Role:** Zinc is crucial for neuronal function, synaptic transmission, and plasticity.
- **Pathological effects:** Zinc is found in high concentrations in amyloid plaques and influences Aβ aggregation. Excess zinc can induce conformational changes in Aβ, promoting aggregation and neurotoxicity, while also disrupting neuronal signaling.

4. **Iron (Fe)**

- **Role:** Iron is vital for oxygen transport and energy metabolism.
- **Pathological effects:** Iron accumulation in the brain is associated with oxidative stress and neuroinflammation in AD. Elevated iron can catalyze free radical formation, leading to cellular damage. Additionally, iron facilitates Aβ aggregation and neurofibrillary tangle formation (Chen *et al*., 2023; Babiæ Leko *et al*., 2023).

4. Staging of Alzheimer's disease continuum

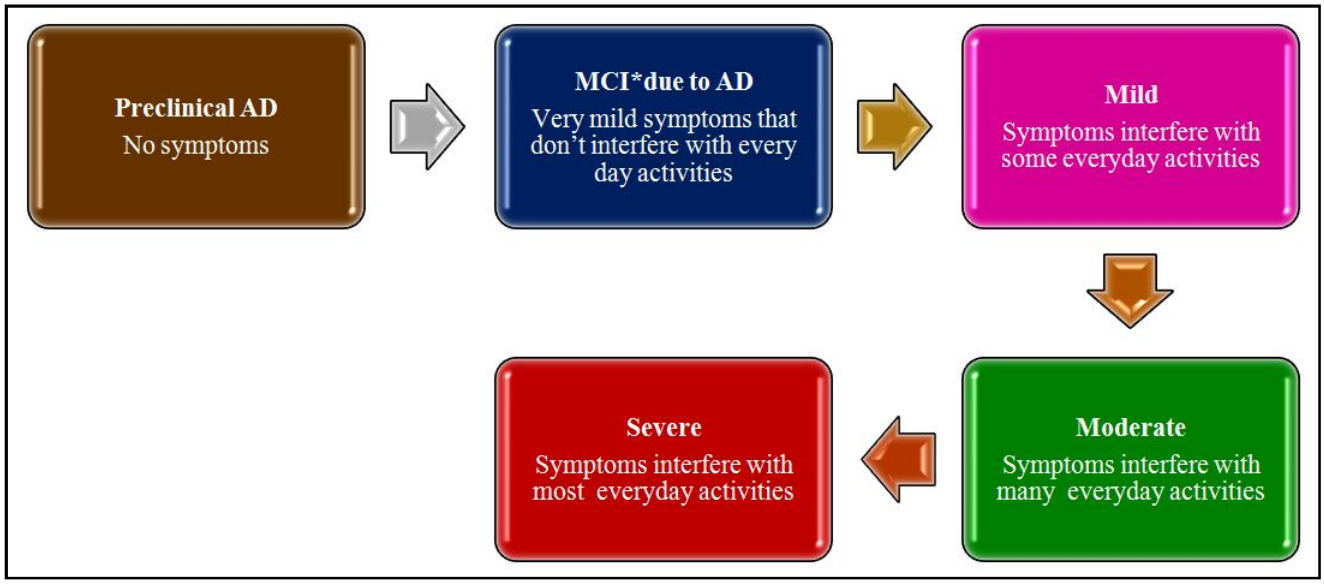

Figure 1: Staging of Alzheimer's disease continuum. Source:Alzheimer's Association (2020).

The Alzheimer's disease continuum is divided into stages that reflect the progression of the disease:

i. **Preclinical Alzheimer's:** No visible symptoms, but brain changes like amyloid plaques and tau tangles begin years before cognitive decline.

ii. **Mild cognitive impairment (MCI):** Early memory and cognitive issues appear, but they do not yet interfere with daily life. Some individuals progress to Alzheimer's.

iii. **Mild Alzheimer's disease:** Noticeable memory loss and confusion emerge, impacting daily tasks such as managing finances or remembering recent events.

iv. **Moderate Alzheimer's disease**: Individuals face significant cognitive decline, making daily activities challenging. Symptoms include substantial memory loss, confusion about time and place, difficulty recognizing loved ones, and language problems. Behavioral changes, such as anxiety and mood swings, may occur, necessitating assistance with personal care.

v. **Severe Alzheimer's disease**: In this final stage, cognitive and physical abilities decline markedly. Individuals lose the ability to communicate and recognize family members, requiring full-time care. They may also experience mobility and swallowing issues, increasing their vulnerability to infections and other health complications (Figure 1).

5. Neuroimaging techniques for AD diagnosis

Neuroimaging techniques play a crucial role in the diagnosis and assessment of Alzheimer's disease. They provide valuable insights into brain structure, function, and biochemical changes associated with the disease.

i. **Magnetic resonance imaging (MRI):** Neuroimagingespecially MRI is essential in diagnosing Alzheimer's disease (AD) employing sophisticated techniques. MRI is based on the use of radio waves and magnetic fields to create good explanations and clear images of the structures of the brain. sMRI is especially useful for studying AD since it enables the identification of outcome quantitative indices, such as brain volumes, in addition to monitoring pathophysiologic changes in the living human brain. MRI systems differ in the magnitude of the magnetic field; the average varies from 1. 5 ranged from the high-performance 1. 5 Tesla (1. 5T) scanners to the slightly lower 3 Tesla (3T) ones.

The 3T scanners give a high signal-to-noise ratio, and higher resolution in space and time than 1. 5T scanners. Also, Functional Magnetic Resonance Imaging (fMRI) helps in the mapping of the brain and records the brain's function and functioning.

ii. **Positron emission tomography (PET):** Is an imaging technique that employs radiotracers to evaluate brain activity by measuring glucose metabolism and the presence of amyloid plaques. This method provides valuable information on various cognitive functions such as working memory, recollection, thought processes, auditory processing, and visual perception, thus offering insights into overall brain activity and health.

iii. **Computed tomography (CT):** Scans are a medical imaging method that utilizes X-rays to produce detailed cross-sectional images of the body. While CT scans can assist in the early diagnosis of Alzheimer's disease by revealing structural changes in the brain, they are generally less sensitive compared to other imaging techniques, such as MRI or PET, in detecting subtle early-stage abnormalities associated with the disease..

iv. **Diffusion tensor imaging (DTI):** It is a sophisticated MRI method that looks at water molecular flow in the brain. It is especially valuable for the identification of pathological diffusion measures characteristic of AD. Because DTI provides a measure of the white matter's integrity and the alterations in neural connectivity, it assists in identifying alterations in the brain structure that characterise AD.

v. **Single photon emission computed tomography (SPECT):** Is a nuclear imaging technique that employs gamma-ray tracers to assess brain blood flow and metabolic activity. In the context of Alzheimer's disease (AD), SPECT imaging is utilised to monitor these physiological parameters, providing insights into the disease's progression and early detection. Additionally, diffusion tensor imaging (DTI) has been incorporated into clinical guidelines as a biomarker to aid in the early identification and tracking of AD (Mohammed *et al.,* 2024).

6. Treatments

Symptomatic cognition-enhancing agents for Alzheimer's disease

6.1 Cholinesterase inhibitors

Cholinesterase inhibitors are the mainstay of pharmacological treatment for AD. They work by increasing the availability of acetylcholine (ACh), a neurotransmitter critical for learning and memory.

i. Tacrine

- **Mechanism:** Tacrine was the first acetylcholinesterase (AChE) inhibitor approved in 1993. It reversibly inhibits AChE, leading to increased levels of ACh in the brain. This stimulation enhances both muscarinic and nicotinic receptors, which can improve glucose metabolism in neuronal tissues.
- **Efficacy:** Studies have shown that tacrine can improve cognitive performance and help with atypical behaviours in patients with mild to moderate AD.
- **Limitations:** Despite its initial promise, tacrine's clinical use is limited due to significant hepatotoxicity, peripheral side effects, and elevated serum levels of liver enzymes, making it less favourable in practice (Parums 2024).

ii. Donepezil

- **Mechanism:** Approved in 1996, donepezil is a second-generation AChE inhibitor. It decreases the breakdown of ACh in synaptic clefts, prolonging its action and thereby enhancing cognitive function in AD patients.
- **Pharmacokinetics:** Donepezil undergoes significant hepatic metabolism, and its active metabolite is a 6-oxo derivative. Its high lipid solubility allows it to effectively cross the blood-brain barrier and bind to AChE in the cerebral cortex.
- **Side effects:** Common side effects include gastrointestinal disturbances, such as nausea, vomiting, and diarrhoea, as well as fatigue and muscle cramps (Parums, D.V., 2024).

iii. Rivastigmine

- **Mechanism:** Approved by the FDA in 2000, rivastigmine inhibits both AChE and butyrylcholinesterase (BChE). It is available in both oral and transdermal forms and enhances cognitive function by stimulating both parasympathetic and cholinergic systems in the central nervous system.
- **Pathophysiological impact:** Research indicates rivastigmine may influence the processing of amyloid precursor protein (APP) by promoting á-secretase activity, potentially impacting AD pathology (Vicente-Zurdo *et al*., 2022; Gayke *et al*., 2022).
- **Advantages:** Its unique carbamate structure is critical for its therapeutic effects, encouraging the development of similar compounds.

iv. Galantamine

- **Mechanism:** Introduced in 2001, galantamine is a selective, reversible, and competitive AChE inhibitor that also stimulates nicotinic receptors. This dual action enhances ACh effects, contributing to improved cognitive function in patients with mild to moderate AD.
- **Oxidative stress:** Galantamine may also counteract the oxidative effects of amyloid-beta (Aβ) peptides, which are implicated in AD.
- **Pharmacokinetics:** It has a short half-life of approximately 7 h, with about 90% bioavailability when taken orally. While clinical trials have shown improvements in memory and emotional status, its rate of effectiveness is slower compared to other agents.

6.2 NMDA receptor antagonist

1. Memantine

- **Mechanism:** Memantine, launched in March 2003, is the only drug specifically indicated for moderate to severe AD. It acts as a voltage-dependent, moderate-affinity, non-competitive antagonist at NMDA receptors, which are critical for neuronal function and are often dysregulated in AD.
- **Efficacy:** By selectively modulating NMDA receptors, memantine improves nerve impulse transmission and reduces calcium influx into neurons, mitigating excitotoxicity.
- **Safety profile:** Clinical trials indicate that memantine does not cause significant liver side effects, making it a suitable option for combination therapy.

- **Combination therapy:** In 2014, the FDA approved a formulation combining memantine and donepezil, which demonstrated enhanced therapeutic efficacy compared to either agent alone (Parums, 2024).

7. Emerging strategies for managing Alzheimer's disease

7.1 Amyloid protein-targeted immunotherapy

Amyloid protein-targeted immunotherapy is an innovative approach aimed at leveraging the body's immune system to selectively recognize and clear pathological amyloid proteins, which play a crucial role in neurodegenerative diseases, most notably Alzheimer's disease.

7.1.1 Mechanism of action of amyloid protein-targeted immunotherapy

In amyloid-targeted immunotherapy, monoclonal antibodies are the primary therapeutic agents. These synthetic antibodies are engineered to specifically recognize and bind to beta-amyloid protein fragments, targeting them for clearance from the brain. The immunotherapy works by:

i. **Neutralizing soluble amyloid:** Monoclonal antibodies can bind to soluble forms of amyloid-beta (Aβ) before they aggregate into plaques. This reduces the formation of new amyloid deposits, potentially preventing further neurotoxicity.

ii. **Promoting plaque clearance:** By binding to insoluble amyloid-beta plaques already deposited in brain tissue, antibodies facilitate their removal. The microglial cells, the brain's resident immune cells, can then recognize and engulf these antibody-bound plaques, aiding in their clearance through a process called phagocytosis.

iii. **Altering amyloid aggregation:** Some antibodies alter the conformation of amyloid-beta fragments, preventing their aggregation into toxic forms. This reduces the fibrillization process, which leads to the formation of neurotoxic amyloid plaques.

7.2 Clinical success and challenges of monoclonal antibodies

7.2.1 Aducanumab: Controversies and approval

Monoclonal antibodies for Alzheimer's disease treatment have shown promise in various stages of clinical trials. Aducanumab, a monoclonal antibody developed by Biogen, is a prominent example that targets amyloid-beta plaques. Approved by the U.S. Food and Drug Administration (FDA) in 2021, aducanumab has demonstrated plaque reduction in the brains of Alzheimer's patients, offering potential disease-modifying benefits. Aducanumab received accelerated approval from the U.S. FDA for the treatment of mild Alzheimer's disease. However, its approval has been met with significant criticism due to inconsistent trial results and reliance on amyloid reduction as a primary endpoint without clear evidence of corresponding clinical benefits. This reliance raises concerns about the validity of using amyloid clearance as a surrogate marker for meaningful cognitive improvement.

A study by Bomasang-Layno *et al.* (2021) on aducanumab showed a significant reduction in amyloid-beta plaque levels following treatment. This study was crucial in highlighting that amyloid plaque clearance correlates with slower cognitive decline in patients with early Alzheimer's disease. Although, this offers hope, the study also underlined the need for careful monitoring of side effects, especially amyloid-related imaging abnormalities (ARIA), which include brain swelling and microhemorrhages. As a result, aducanumab is no longer indicated for clinical use in the USA and has not received approval in Europe. This decision came after debates regarding its overall clinical efficacy in improving cognitive outcomes, despite evidence of amyloid plaque reduction. Biogen, the drug's manufacturer, announced plans to discontinue the commercialization of aducanumab and shift its resources towards other Alzheimer's disease initiatives, such as advancing new therapies that could provide more robust clinical benefits. It is important to note that this decision was not driven by concerns over aducanumab's safety or efficacy but rather by strategic reallocation of resources in light of mixed feedback regarding its long-term benefits. Nevertheless, the ENVISION trial, a phase 3b/4 study, is currently underway to further evaluate the clinical benefits of aducanumab in patients with early-stage Alzheimer's disease. The goal of this trial is to provide additional data on its efficacy, especially in a well-defined subset of patients with early symptoms. This study may offer more conclusive evidence regarding aducanumab's potential as a disease-modifying treatment, potentially influencing future decisions on its clinical use (Alexander and Karlawish, 2021; Moghavem *et al.,* 2021; Hershey and Tarawneh, 2021; Cummings and Salloway, 2022).

7.2.2 Lecanemab: A promising treatment for Alzheimer's disease

Lecanemab, a humanized IgG1 monoclonal antibody, represents a significant development in the treatment of Alzheimer's disease (AD). It was approved by the U.S. FDA on January 6, 2023, for early-stage AD patients. Unlike earlier antibodies that primarily target insoluble amyloid-beta (Aβ) plaques, lecanemab binds with high affinity to soluble aggregated forms of Aβ protofibrils, which are considered more neurotoxic than monomers or insoluble fibrils. This selective targeting of protofibrils may contribute to lecanemab's ability to reduce amyloid levels with potentially fewer side effects, particularly the amyloid-related imaging abnormalities (ARIA) that have been a concern in previous antibody therapies (Söderberg *et al.,* 2022).

7.2.2.1 Mechanism of action

Lecanemab binds preferentially to protofibrils, the soluble precursors of large amyloid plaques, which are thought to be more neurotoxic than fully formed plaques. By neutralizing these toxic protofibrils, lecanemab aims to intervene in the amyloid cascade at an earlier stage. This approach contrasts with drugs like aducanumab, which targets highly aggregated, insoluble Aβ forms. The distinct mechanism is hypothesized to contribute to lecanemab's lower incidence of ARIA, a condition that includes brain swelling and microhemorrhages.

7.2.2.2 Clinical trials and efficacy: Phase 2b trial

In a phase 2b trial with 854 participants with early Alzheimer's disease, lecanemab's results were initially underwhelming. At the 12-month mark, there was no statistically significant difference between the lecanemab and placebo groups in terms of changes in the composite cognitive scores. However, by 18 months, a clear dose- and time-dependent effect on amyloid clearance was observed. Participants receiving the optimal dose of 10 mg/kg intravenously every two weeks showed a reduction in clinical decline on certain measures, alongside a marked decrease in amyloid burden. The trial also revealed a 9.9% incidence of ARIA with oedema (ARIA-E), with less than 3% of participants experiencing symptoms.

7.2.2.3 Phase 3 trial (Clarity AD)

The pivotal phase III clarity AD trial involved 1,795 participants with early-stage Alzheimer's disease. Over an 18-month treatment period, lecanemab demonstrated significant amyloid clearance and modest cognitive improvements compared to placebo. The mean amyloid level in the treatment group was reduced to 22.99 centiloids, falling below the threshold for amyloid positivity (approximately 30 centiloids). Cognitive and functional decline, as measured by standardized assessments, was also slowed, albeit to a minor degree. In addition to reducing amyloid burden, lecanemab treatment was associated with decreased markers of tau pathologyand neuroinflammation, which are central to Alzheimer's disease progression. However, levels of neurofilament light (NfL), a marker of neurodegeneration that changes more slowly, were not significantly affected over the study period (Van Dyck *et al.,* 2023; Honig *et al.,* 2023).

7.3 Donanemab: A targeted approach to Alzheimer's disease treatment

Donanemab, an immunoglobulin G1 monoclonal antibody, specifically targets an epitope unique to mature amyloid plaques in the brain. In July 2024, the U.S. FDA approved donanemab for the treatment of adults with early symptomatic Alzheimer's disease who have confirmed amyloid pathology. The approval comes with a boxed warning regarding the risk of amyloid-related imaging abnormalities (ARIA), a common side effect associated with amyloid-targeting therapies (Fda.gov/drugs; Mintun *et al.,* 2021).

7.3.1 Mechanism of action and clinical efficacy

Donanemab's mechanism involves the targeted clearance of amyloid plaques, particularly focusing on the unique structure of mature plaques. This specificity allows for effective intervention in the amyloid cascade, a hallmark of Alzheimer's disease pathology.

7.3.2 Phase 1 trials

Initial phase 1 trials demonstrated that donanemab facilitates rapid clearance of amyloid plaque loads, as evidenced by [18F] florbetapir positron emission tomography (PET) scans. These scans showed significant reductions in amyloid deposits, indicating Donanemab's efficacy in targeting and clearing these neurotoxic aggregates.

7.3.3 Trailblazer-ALZ trial Trailblazer-ALZ trial

The Trailblazer-ALZ trial, a double-blind, phase 2, placebo-controlled study, further assessed the safety and efficacy of donanemab in early symptomatic Alzheimer's patients with intermediate tau levels and elevated amyloid confirmed *via* PET scans. The results were promising, indicating a 32% reductionin the progression of Alzheimer's disease compared to the placebo group after 76 weeks, measured by the integrated Alzheimer's Disease Rating Scale (iADRS).This clinical improvement was accompanied by a remarkable 85% reduction in amyloid plaques among participants receiving donanemab. By the end of the trial period, 68% of participants achieved an amyloid-negative status, indicating effective plaque clearance of Alzheimer's (Navitsky *et al.,* 2018; Schcherbinin *et al.,* 2022).

7.4 Impact on tau and clinical decline

A post-hoc analysis of the Trailblazer-ALZ trial results suggested that greater amyloid plaque clearance correlated with slower progression observed in tau PET scans. This finding is particularly significant as tau pathology is closely associated with cognitive decline in Alzheimer's disease. The analysis indicated that the clinical benefits of donanemab were more pronounced among carriers of the apolipoprotein E ε4 (APOE ε4) allele, a genetic variant that increases the risk of developing Alzheimer's (Navitsky *et al.,* 2018; Schcherbinin *et al.,* 2022).

7.5 Implications of monoclonal antibody research in Alzheimer's disease treatment

The research outcomes surrounding monoclonal antibodies such as aducanumab, lecanemab, anddonanemab carry significant implications for the treatment landscape of Alzheimer's disease (AD). These therapies highlight the necessity for personalized medical strategies tailored to the unique genetic and clinical profiles of individual patients. This individualized approach is crucial for optimizing treatment efficacy and improving patient outcomes.

7.6 Personalized medicine and patient selection

The evolving data on monoclonal antibodies underscore the importance of refining patient selection criteria. Identifying which patients are most likely to benefit from specific treatments based on biomarkers, genetic predispositions, and clinical stages of AD can enhance the effectiveness of these therapies. Moreover, optimizing dosing schedules and exploring combination therapies could further improve treatment responses.

By leveraging insights gained from previous studies, researchers can better navigate these challenges, potentially leading to significant advancements in AD management and moving closer to the development of impactful disease-modifying therapies.

7.7 Challenges in clinical translation

Despite the promise of these monoclonal antibodies, translating research findings into routine clinical practice presents notable challenges:

i. **Cost of treatment:** The high cost associated with monoclonal antibody therapies raises concerns about accessibility and affordability for patients. This financial burden can limit the widespread adoption of these treatments, especially in healthcare systems with constrained budgets.

ii. **Logistical complexities:** The requirement for intravenous infusion complicates treatment administration. This necessitates specialised healthcare infrastructure and trained personnel, which may not be readily available in all settings, particularly in rural or underserved areas.

iii. **Multifactorial nature of AD:** Alzheimer's disease is influenced by a complex interplay of genetic, environmental, and lifestyle factors. Addressing these contributing elements necessitates a comprehensive, multidisciplinary approach that goes beyond monoclonal antibodies alone. Integrating lifestyle modifications, cognitive therapies, and supportive care can enhance overall treatment strategies.

7.8 The promise of passive immunization

Among the innovative approaches in AD research, passive immunization stands out as a dynamic domain. This strategy, which involves administering antibodies to help clear amyloid plaques and

other toxic proteins, offers considerable potential as a disease-modifying treatment. Passive immunization may provide immediate therapeutic benefits while researchers continue to explore and refine active immunization strategies and other modalities (Zhang *et al*., 2021).

8. Conclusion

Unraveling Alzheimer's disease (AD) reveals a complex interplay of mechanisms, including amyloid-beta (Aβ) plaque accumulation and neurofibrillary tangles formed by hyperphosphorylated tau protein. These pathological features contribute to neuronal dysfunction, neuroinflammation, and cognitive decline. While the amyloid hypothesis has been foundational in understanding AD, it faces challenges due to mixed outcomes in clinical trials targeting Aβ. Alternative hypotheses, including the cholinergic and tau hypotheses, underscore the multifaceted nature of the disease and the need for comprehensive treatment approaches.Recent advancements in therapeutic strategies, particularly the development of monoclonal antibodies such as Aducanumab, Lecanemab, and Donanemab, offer promising prospects for managing AD by targeting Aβ plaques. However, their use raises safety concerns, particularly regarding amyloid-related imaging abnormalities (ARIA), highlighting the importance of careful patient selection.

Future research should prioritize identifying reliable biomarkers for early detection, developing strategies to mitigate adverse effects, and exploring combination therapies to enhance treatment efficacy. A multidisciplinary approach that integrates emerging nonpharmacological interventions such as cognitive training and lifestyle modifications; alongside pharmacological treatments is essential. By adopting precision medicine strategies that tailor therapies to individual profiles, we can move closer to more effective and safer interventions. Addressing these challenges and knowledge gaps will be crucial for improving outcomes and enhancing the quality of life for patients and their families as we advance our understanding of Alzheimer's disease.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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