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Alzheimer's Disease in the Context of an Aging Society: Challenges and Future Directions

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ABSTRACT

Alzheimer's disease (AD) remains the most prevalent form of dementia and a pressing public health concern, particularly in the context of global population aging. The pathogenesis of AD involves a multifactorial interplay of genetic, molecular, and immunological mechanisms, with amyloid-β (Aβ) and tau protein playing pivotal roles. Current pharmacological treatments provide symptomatic relief but lack disease-modifying effects. Recent advancements in anti-Aβ monoclonal antibodies such as aducanumab, lecanemab, and donanemab mark a significant shift in therapeutic strategies, although their clinical effectiveness and safety are still being carefully evaluated. Emerging therapeutic strategies, including gene therapy, tau-targeted interventions, neurostimulation techniques, and modulation of the gut microbiome, demonstrate potential but remain largely at the experimental stage, with limited or no clinical evaluation in humans to date. This review discusses the epidemiology, pathogenesis, and current as well as future directions in AD treatment.

MATERIAL AND METHODS

This article is based on a narrative review of recent research findings and clinical data related to Alzheimer's disease. It includes epidemiological statistics, clinical trial outcomes, and discusses both established pharmacological treatments and newly introduced therapies, such as monoclonal antibodies. The review also highlights emerging strategies, including gene therapies and novel therapeutic targets. Overall, it synthesizes current evidence to outline recent advances and identify areas for future research and development.

KEYWORDS

Alzheimer’s disease; amyloid-β; tau protein; monoclonal antibodies; lecanemab; donanemab; aducanumab; APOE4; gene therapy; neuroinflammation; dementia; aging population; ARIA; neurodegeneration.

INTRODUCTION

Alzheimer’s disease is the most common cause of dementia worldwide and has been recognized by the World Health Organization as a major public health priority [1]. The progressive cognitive decline associated with dementia significantly impacts daily functioning, leading not only to cognitive deficits but also to behavioral and neuropsychiatric disturbances [2]. Notably, advanced age is one of the most critical risk factors for the development of Alzheimer’s disease [3], with its prevalence doubling approximately every five years after the age of 65 [4]. Given the aging global population, this demographic trend predicts a substantial increase in disease incidence, posing a significant challenge for healthcare systems.

The aim of this paper is to provide a comprehensive overview of the current state of knowledge on the pathogenesis and epidemiology of Alzheimer’s disease, while also discussing novel diagnostic and therapeutic strategies currently under investigation. Particular attention is given to emerging approaches, such as molecular and genetic targets, neurostimulation, and modulation of the gut-brain axis, which hold promise but remain largely in preclinical or early clinical stages. This review aims to synthesize available evidence to inform future directions in both research and clinical practice.

EPIDEMIOLOGY

According to estimates published in 2018 by Alzheimer's Disease International, approximately 50 million people worldwide are affected by dementia. Projections indicate that this number could triple by 2050, primarily due to the aging global population. The highest increase in incidence is expected in low- and middle-income countries [5].

ETIOLOGY AND PATHOLOGY

Alzheimer's Disease (AD) develops as a result of a complex interplay of genetic, protein-related, and immunological factors. The key pathological processes include the accumulation of beta-amyloid (Aβ), the formation of neurofibrillary tangles (NFTs) composed of tau protein, as well as inflammatory and immune responses that ultimately lead to the progressive degeneration of neurons and their synaptic connections [1]. The predominant hypothesis explaining AD pathogenesis is the amyloid hypothesis, which postulates that the primary pathogenic event is the abnormal accumulation of Aβ, generated through the sequential cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase enzymes [6]. There are two main forms of Aβ: Aβ40 and Aβ42. Aβ42 exhibits a higher propensity for aggregation, leading to the formation of amyloid plaques, which disrupt neuronal function and induce toxic cellular changes [7]. Another feature of AD is the formation of neurofibrillary tangles (NFTs), which are intracellular aggregates of hyperphosphorylated and abnormally folded tau protein. Under physiological conditions, tau stabilizes microtubules and facilitates axonal transport. However, in AD, tau undergoes excessive phosphorylation, leading to its aggregation, loss of microtubule-stabilizing function, and eventual neuronal dysfunction. The burden of NFTs strongly correlates with the severity of cognitive decline. Genetic factors play a crucial role in AD pathogenesis, distinguishing between sporadic and familial forms of the disease. Mutations in APP, PSEN1, and PSEN2 are associated with early-onset familial AD, typically manifesting between 30 and 50 years of age [8]. In sporadic AD, the APOE gene is the most significant genetic determinant. APOE has three allelic variants: ε2, ε3, and ε4 [9]. One of the strongest genetic risk factor is the ε4 allele for late-onset AD, as it enhances amyloid deposition.

Conversely, the ε2 allele has a protective effect, reducing AD risk by approximately twofold compared to other variants. Homozygosity for the ε2 allele is associated with an exceptionally low likelihood of developing AD [3]. Microglial activation in response to amyloid deposition is now recognized as a key contributor to AD pathogenesis. Chronic neuroinflammation, mediated by microglial cells, is thought to exacerbate neuronal damage and disease progression [10].

PHARMACOLOGICAL TREATMENT OF ALZHEIMER'S DISEASE

Current pharmacological treatment for Alzheimer's disease (AD) is primarily symptomatic, aiming to improve cognitive function without altering the underlying neurodegenerative process [11]. The most widely used pharmacological agents in clinical practice include N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine, and acetylcholinesterase inhibitors (AChEIs), including rivastigmine, galantamine, and donepezil [12]. These treatments provide temporary cognitive benefits but do not prevent disease progression, highlighting the urgent need for ongoing research and the development of new drugs to enable the use of disease-modifying therapies.

ACETYLCHOLINESTERASE INHIBITORS

Acetylcholine plays a crucial role in cognitive processes, and cholinergic deficits are strongly associated with cognitive impairment and behavioral disturbances in AD [13]. Acetylcholinesterase inhibitors act by increasing acetylcholine levels in synaptic clefts through the inhibition of its enzymatic breakdown [14]. By enhancing cholinergic neurotransmission, these agents can provide symptomatic relief, particularly in patients with mild to moderate AD. However, their efficacy is limited [1].

NMDA RECEPTOR ANTAGONISTS

Excessive stimulation of NMDA receptors by glutamate, the primary excitatory neurotransmitter in the brain, has been implicated in neurodegenerative processes, contributing to neuronal damage [15]. Memantine, a NMDA receptor antagonist, regulates glutamatergic activity by reducing pathological overactivation while preserving physiological synaptic transmission [16]. This neuroprotective mechanism has led to its approval for the treatment of moderate to severe AD, where it may provide modest cognitive and functional benefits [1].

NEW PHARMACOLOGICAL STRATEGIES IN THE TREATMENT OF ALZHEIMER'S DISEASE

Intensive research is currently underway to develop therapies that could potentially modify the course of Alzheimer's disease. These efforts focus on various mechanisms and drug targets, with particular emphasis on the elimination of β-amyloid (Aβ).

BETA-AMYLOID-TARGETED THERAPIES

Aducanumab, a monoclonal antibody targeting Aβ, received approval from the U.S. Food and Drug Administration (FDA) in June 2021 [17]. Subsequent drugs with a similar mechanism of action, lacanemab and donanemab, were approved in January 2023 and July 2024, respectively. Despite promising results in reducing Aβ plaque deposition, the efficacy of these therapies has been demonstrated primarily in the early stages of the disease [18] [19]. Their use is also associated with the risk of side effects, such as amyloid-related imaging abnormalities (ARIA). ARIA includes radiological changes observed in MRI scans, including edema and effusion (ARIA-E) as well as microhemorrhages and hemosiderosis (ARIA-H). The occurrence of ARIA is particularly correlated with the presence of the APOE4 allele, which may influence both treatment risk and tolerance [20].

The following section presents clinical studies regarding the three FDA-approved drugs

- Aducanumab

Clinical studies of aducanumab have shown that, while the EMERGE trial reported a 22% reduction in clinical decline, as measured by CDR-SB, in the high-dose group (10 mg/kg), the ENGAGE trial failed to replicate these results, leading to inconclusive evidence of efficacy across the studies. Nevertheless, PET imaging confirmed a dose-dependent reduction in Aβ plaques, thereby validating the biological activity of the treatment despite the inconsistent clinical benefits observed [21].

However, aducanumab is associated with a range of adverse events that warrant careful consideration in clinical decision-making. The most notable adverse events associated with aducanumab are amyloid-related imaging abnormalities (ARIA). In the high-dose group, ARIA-E (edema) occurred in up to 35% of patients, compared to approximately 2% in the placebo group. Similarly, ARIA-H (microhemorrhages) was reported in 19% of patients on high-dose therapy versus 7% in placebo. Other adverse effects such as headache, falls, dizziness, and nasopharyngitis were also more frequently observed in the treatment group compared to placebo [17].

Aducanumab received accelerated approval from the U.S. Food and Drug Administration (FDA) in June 2021, based on its ability to reduce brain amyloid-β plaques, despite no conclusive evidence of cognitive benefit at the time of approval [22]. In contrast, the European Medicines Agency (EMA) rejected marketing authorization in December 2021, citing uncertainties in efficacy and concerns about safety (EMA, 2021) [23]. A confirmatory phase 4 trial (ENVISION) is currently ongoing to verify clinical benefit and is expected to be completed in 2026 [24]. It is also worth noting that in January 2024, Biogen and Eisai announced their decision to discontinue the commercial availability of aducanumab (Aduhelm), citing limited demand and a strategic shift toward more promising therapies, such as lecanemab [25].

- Lacanemab

Another FDA-approved drug is lecanemab. In the large, randomized phase III clinical trial Clarity AD involving lecanemab administered at a dose of 10 mg/kg every two weeks, statistically significant reductions in cognitive function scores were observed [26]. The average

baseline score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) scale was approximately 3.2 in both the lecanemab and placebo groups, indicating an early stage of Alzheimer's disease. After 18 months of treatment, the adjusted mean change was 1.21 in the lecanemab group and 1.66 in the placebo group, resulting in a difference of 0.45 points in favor of lecanemab (95% confidence interval [CI]: 0.23–0.67; P<0.001). This indicates a 27% slowing of disease progression in the lecanemab group compared to placebo. For the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog14), the average baseline scores were 24.45 in the lecanemab group and 24.37 in the placebo group. After 18 months, the adjusted mean change was 4.14 in the lecanemab group and 5.58 in the placebo group, resulting in a difference of 1.44 points in favor of lecanemab (95% CI: 0.61–2.27; P<0.001) [18]. These results suggest that lecanemab treatment led to less cognitive decline compared to placebo, both in global assessments (CDR-SB) and cognitive-specific measures (ADAS-Cog14).

The study also analyzed the incidence of amyloid-related imaging abnormalities (ARIA), including edema (ARIA-E) and microhemorrhages (ARIA-H), in patients treated with lecanemab compared to placebo. ARIA-E (edema): In the lecanemab group, 8.9% of patients with one or no copies of the ApoE4 gene experienced ARIA-E, compared to 12.6% in the entire study population. In the placebo group, the incidence of ARIA-E was 1.3% in the same genotypic subgroup. ARIA-H (microhemorrhages): In the lecanemab group, 12.9% of patients with one or no copies of ApoE4 experienced ARIA-H, compared to 16.9% in the entire study population. In the placebo group, the incidence of ARIA-H was 6.8% in the same genotypic subgroup [18].

Lecanemab received full FDA approval in July 2023, becoming the first amyloid beta-directed antibody with such approval [27]. The European Medicines Agency (EMA) has issued a positive opinion for Leqembi (lecanemab), developed by Eisai, for the treatment of early-stage Alzheimer's disease, following its initial rejection in July 2024. Previously approved in the United States, Japan, China, South Korea, and Israel, the drug aims to slow symptom progression in patients with mild cognitive impairment or mild dementia. After re-evaluating the evidence, the EMA recommended its approval on November 14, 2024, with a restricted indication for adults with early Alzheimer's who carry one or no copies of the Apolipoprotein E4 (ApoE4) gene and present amyloid-beta plaques. It is important to emphasize that the risk

of amyloid-related imaging abnormalities (ARIA) was higher in patients carrying two copies of the ApoE4 gene. Therefore, it is strongly recommended that ApoE4 genotyping be conducted prior to starting lecanemab treatment to assess individual risk and potential treatment benefits [28].

- Donanemab

The final drug under discussion is donanemab, and its results from the phase III *TRAILBLAZER-ALZ 2* trial. In the phase III *TRAILBLAZER-ALZ 2* trial, which assessed the efficacy and safety of donanemab in the treatment of early-stage Alzheimer's disease, donanemab demonstrated significant results in slowing disease progression and improving cognitive function measures compared to placebo. Integrated Alzheimer's Disease Rating Scale (iADRS): In the population with low to moderate tau levels, after 76 weeks of treatment, the donanemab group showed a mean change of -6.02 points, while the placebo group changed by -9.27 points. The difference was 3.25 points (95% CI: 1.88–4.62; $P<0.001$), corresponding to a 35.1% slowing of disease progression in the donanemab group compared to placebo. Clinical Dementia Rating–Sum of Boxes (CDR-SB): In the same population, the change was 1.20 points in the donanemab group and 1.88 points in the placebo group. The difference was -0.67 points (95% CI: -0.95 to -0.40; $P<0.001$), indicating a 36.0% slowing of disease progression in the donanemab-treated patients. Patients treated with donanemab had a 38.6% lower risk of progressing to the next stage of the disease compared to those in the placebo group (HR=0.61; $P<0.001$).

However, this drug is also associated with adverse events. Infusion-related reactions: 8.7% of participants in the donanemab group experienced infusion-related reactions, compared to 0.5% in the placebo group. Serious reactions occurred in 0.4% of patients treated with donanemab. Amyloid-related imaging abnormalities (ARIA): ARIA-E (edema): Occurred in 24.0% of participants in the donanemab group (6.1% of cases were symptomatic), compared to 0.5% in the placebo group. ARIA-H (hemorrhages): Observed in 31.4% of participants in the donanemab group, compared to 13.6% in the placebo group [29][30].

Donanemab, marketed under the trade name Kisunla, was approved by the U.S. Food and Drug Administration (FDA) in July 2024 for the treatment of early-stage Alzheimer's disease. In contrast, the European Medicines Agency (EMA) issued a negative opinion regarding the

approval of donanemab for market authorization in the European Union in March 2025, determining that the potential risks associated with the drug outweigh its benefits [31][32].

Other monoclonal antibodies targeting Aβ, such as gantenerumab and solanezumab, are currently undergoing clinical trials, whereas research on bapineuzumab was discontinued due to unsatisfactory clinical outcomes [33]. Alternative therapeutic strategies are also being explored, including vaccines that induce an active immune response against Aβ, which are currently in clinical trial phases [34]. Beyond monoclonal antibody-based therapies, another class of potential drugs includes BACE1 and BACE2 inhibitors, which function by blocking β-secretase activity, thereby preventing Aβ production. Verubecestat and other BACE inhibitors failed in phase III trials due to lack of clinical benefit and potential worsening of cognitive decline, leading to the discontinuation of their development [3].

ANTI-TAU THERAPIES

Contemporary clinical research also includes therapeutic strategies targeting tau protein, whose hyperphosphorylation and aggregation play a key role in the pathogenesis of Alzheimer's disease. One of the approaches involves the use of protein kinase inhibitors aimed at limiting abnormal post-translational modifications of tau. Compounds such as saracatinib, salsalate, and nilotinib were initially investigated for their potential in reducing tau pathology. However, subsequent studies failed to demonstrate consistent clinical benefit in Alzheimer's disease, and they are no longer in active development for this indication [35][36]. Tideglusib failed to show clinical efficacy in phase II trials and is no longer being actively pursued as a treatment for Alzheimer's disease. Alternative therapeutic approaches include microtubule stabilization and inhibition of tau aggregation; however, current research has not provided convincing evidence of the effectiveness of these strategies. In the field of immunotherapy, studies are being conducted on the use of monoclonal antibodies targeting tau as well as active immunization

utilizing vaccines containing synthetic tau peptides [37]. Despite significant interest in tau-targeted therapies, no such treatment has been approved for clinical use to date. While several monoclonal antibodies and small molecules targeting tau phosphorylation, aggregation, or propagation are under investigation, most remain in early to mid-stage clinical trials, and conclusive evidence of clinical efficacy is currently lacking.

TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors exhibit neuroprotective effects by modulating the activity of immune system cells, including macrophages, microglia, and mast cells in the central nervous system. One of the main compounds under investigation is masitinib. A phase II/III trial suggested that masitinib may slow cognitive decline in mild-to-moderate AD, but larger confirmatory studies are necessary to establish its efficacy and safety[38].

GENE THERAPIES

Gene therapy in Alzheimer's disease is based on the modification of gene expression using viral vectors, such as recombinant adeno-associated viruses (rAAVs), to protect neurons and slow neurodegenerative processes. Potential therapeutic strategies include:

- *Neuroprotection and Neuron Regeneration***:** Therapy using nerve growth factor (NGF) can stimulate neuron regeneration and extend their functionality. Studies have shown that exogenous NGF can induce axon growth and persist in the brain for up to a decade.
- *Modulation of β-amyloid Metabolism:* Transfer of the PGC1-alpha gene reduces β-amyloid accumulation through regulation of metabolic pathways, which contributes to improved cognitive functions and protects neurons from degeneration.
- *Modification of the APOE4 Allele:* Preclinical research explores the possibility of using CRISPR-Cas9 to modify APOE4 to APOE3, but this remains theoretical and has not reached clinical trial stages.

Among the gene therapies under investigation in the context of Alzheimer's disease, vector-based therapies such as AAV2-NGF, PGC1-alpha transfer, and APOE4 gene editing techniques stand out [39]. To date, no gene therapies have been approved for Alzheimer's disease, and

most remain at the preclinical or early-phase clinical stage. However, their potential opens up new perspectives for future treatment strategies. Further research is essential in the quest to develop effective treatments for this debilitating condition.

OTHER THERAPEUTIC APPROACHES

In addition to monoclonal antibodies and gene therapies, alternative treatment methods are being investigated, including:

- MODULATION OF THE GUT MICROBIOME:

There is an increasing body of evidence suggesting that the gut microbiome may play a role in the development of Alzheimer's disease (AD). Research in this area includes probiotic and prebiotic therapies as well as dietary modifications. Disruptions in the balance of the microbiota (dysbiosis) may impact the immune homeostasis of the brain via the gut-brain axis, potentially contributing to the pathogenesis of neurodegenerative diseases, including dementia and Alzheimer's disease [40]. Current studies are focused on bacterial-secreted proteins, such as Pext from Lactobacillus acidophilus and HM14 from Bifidobacterium longum, which have demonstrated the ability to modulate immune responses [41]. While certain bacterial-derived proteins have demonstrated immunomodulatory effects in animal models, clinical relevance in humans remains to be determined.

- NEUROSTIMULATION

The potential application of neurostimulation techniques in Alzheimer’s disease (AD) is currently under investigation. While these methods are well-established in the treatment of Parkinson’s disease, tremor, and dystonia, their use in AD remains experimental [42].

Brain stimulation techniques can be broadly categorized into two main groups:

- **Non-invasive Brain Stimulation (NIBS)**
    - Transcranial Magnetic Stimulation (TMS): Utilizes magnetic pulses to modulate neuronal activity in targeted cortical regions. Preliminary studies suggest TMS

may enhance cognitive functions, particularly via stimulation of the dorsolateral prefrontal cortex.

- Transcranial Direct Current Stimulation (tDCS): Involves applying low-intensity electrical currents to the scalp to modulate neuronal excitability. Early results indicate potential benefits in memory and executive functioning in AD patients.

- **Invasive Brain Stimulation**
  - Deep Brain Stimulation (DBS): Requires surgical implantation of electrodes in specific brain structures to directly influence neuronal activity. In AD, regions such as the nucleus basalis of Meynert and fornix have been targeted.
  - Vagus Nerve Stimulation (VNS): Involves implantation of a device to stimulate the vagus nerve, which may indirectly affect brain function. Although primarily used in epilepsy and depression, VNS shows potential in cognitive modulation in AD [43].

A pilot study conducted in 2017 investigated the effect of fornix-targeted DBS on brain structure in AD patients. The study included six patients with mild AD who received DBS and a matched control group of 25 AD patients without DBS. Structural MRI was used to assess changes in the volume of brain structures (e.g., hippocampus, fornix, mammillary bodies) over a 12-month period. These volumetric changes were correlated with hippocampal glucose metabolism (a proxy for neuronal activity). Notably, two patients demonstrated an increase in hippocampal volume, with one maintaining hippocampal volume over three years post-diagnosis—a rare phenomenon in AD. Moreover, the hippocampal atrophy rate was significantly slower in the DBS group compared to controls. None of the control patients exhibited bilateral hippocampal enlargement. These findings, despite the small sample size, suggest DBS may mitigate neurodegeneration in AD [42].

Another randomized controlled study evaluated the effect of age on the clinical response to DBS. A total of 42 patients with mild AD were randomly assigned to receive either active DBS (n=21) or sham stimulation (n=21), with all participants undergoing identical surgical procedures. Patients were followed for 12 months. Among patients aged ≥65 years, those receiving active DBS exhibited slower cognitive decline compared to the non-stimulated control group. In contrast, patients <65 years experienced greater cognitive deterioration with

active DBS relative to controls. These results suggest age may be a critical determinant of DBS efficacy in AD, underscoring the need for age-stratified approaches in future trials and therapeutic strategies [44].

Both invasive and non-invasive brain stimulation techniques show potential in alleviating cognitive symptoms in Alzheimer's disease. However, the current evidence is primarily derived from small-scale experimental studies. Due to the limited number of studies and inconsistent findings, further large-scale, methodologically rigorous clinical trials are warranted to better establish their efficacy and safety profiles.

DISCUSSION

The growing prevalence of Alzheimer's disease, largely driven by demographic shifts, underscores the urgent need for effective prevention and treatment strategies. Although current pharmacological agents offer only symptomatic relief, the development and approval of monoclonal antibodies targeting Aβ deposition—such as aducanumab, lecanemab, and donanemab—mark a significant advancement. However, these treatments are associated with considerable risks, especially in individuals carrying the APOE4 allele, and show the greatest efficacy in early stages of the disease. The mixed outcomes of clinical trials further highlight the need for robust confirmatory studies. Additionally, alternative strategies including anti-tau therapies, gene modification techniques, and gut-brain axis interventions are in experimental phases, reflecting the complex and multifactorial nature of AD. Future therapeutic success will likely depend on precision medicine approaches that integrate genetic profiling, early diagnosis, and combination therapies tailored to individual patient profiles.

CONCLUSION

Alzheimer's disease remains a formidable challenge in aging societies worldwide, with its incidence expected to rise dramatically in coming decades. While symptomatic treatments remain the mainstay of clinical management, the advent of disease-modifying monoclonal antibodies represents a breakthrough, albeit with limitations related to efficacy, safety, and genetic considerations. Novel therapeutic avenues such as tau-targeting therapies, gene editing,

microbiome modulation and neurostimulation techniques are under development, indicating a multipronged approach is essential for effective long-term management of AD.

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