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ADVANCES IN ALZHEIMER'S DISEASE TREATMENT

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ABSTRACT

Alzheimer's disease (AD) remains one of the greatest challenges in modern medicine, serving as the leading cause of dementia in the elderly. Despite decades of research, effective causal treatment is still not available, and current therapies mainly focus on alleviating symptoms. However, in recent years, there has been significant progress in therapies targeting pathological proteins – amyloid β (Aβ) and tau – offering hope for modifying the course of the disease. In this review, we discuss the latest achievements in AD treatment, including clinical trial results involving monoclonal antibodies (lecanemab, donanemab), the role of biomarkers in early diagnosis, and the impact of non- pharmacological interventions such as diet and physical activity. Additionally, we analyze the challenges associated with anti-amyloid therapy, including side effects and limitations of current methods. We also emphasize the importance of personalized medicine and future research directions that may lead to breakthroughs in Alzheimer's disease therapy.

Materials and methods: This review was conducted systematically to identify and analyze relevant scientific literature regarding advancements in the treatment and diagnosis of Alzheimer's disease. The PubMed database was searched. Articles were searched using the following words: "Anti-amyloid therapies"; "Alzheimer's disease"; "Lekanemab"; "Donanemab"; "Alzheimer's biomarkers"; "Cerebrospinal fluid"; "CSF"; "Tau protein"; "Non- pharmacological interventions"; "Mediterranean diet"; "Dementia prevention"; "Amyloid- related imaging abnormalities"; "Disease-modifying therapies"; „traumatic brain injury".

KEYWORDS

Anti-Amyloid Therapies, Alzheimer's Disease, Lekanemab, Donanemab, Alzheimer's Biomarkers, Cerebrospinal Fluid, CSF, Tau Protein, Non-Pharmacological Interventions, Mediterranean Diet, Dementia Prevention, Amyloid- Related Imaging Abnormalities, Disease-Modifying Therapies

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of pathological proteins – amyloid plaques (Aβ) and neurofibrillary tangles (tau) – leading to neuronal loss and cognitive impairment. It is estimated that over 55 million people worldwide suffer from AD, and this number could triple by 2050, posing a tremendous burden on healthcare and social systems.

Current treatment methods, such as acetylcholinesterase inhibitors (e.g., donepezil) and memantine, only provide symptomatic relief and do not halt disease progression. However, in the last decade, there has been a breakthrough in research on therapies targeting the pathogenesis of AD, particularly in the area of anti-amyloid immunotherapy. Monoclonal antibodies, such as lecanemab and donanemab, have demonstrated in clinical trials the ability to reduce amyloid plaques and slow cognitive decline, leading to their recent regulatory approval.

Concurrently, the field of AD biomarkers is evolving, enabling early and precise diagnosis even before clinical symptoms appear. Studies of cerebrospinal fluid (CSF) and blood (e.g., measuring p-tau217, Aβ42/40) as well as amyloid and tau PET imaging are revolutionizing diagnostics, allowing for the identification of individuals at high risk of developing the disease.

In this review, we focus on the latest advancements in AD treatment, including:

1. Amyloid-targeted therapies (lecanemab, donanemab, aducanumab) and their clinical outcomes,
2. The role of biomarkers in early diagnosis and monitoring of therapy,
3. Non-pharmacological interventions (diet, exercise) in prevention and slowing disease progression,
4. Challenges and future directions, such as anti-tau therapies, anti-inflammatory drugs, and personalized medicine.

The goal of this work is to synthesize current knowledge about advancements in the treatment of AD, considering both promising therapies and the limitations of current approaches. This will facilitate a better understanding of the directions in which contemporary neurology is heading in the fight against this debilitating condition.

New Anti-Amyloid Drugs in the Treatment of Alzheimer's Disease

In recent years, there has been a significant breakthrough in the development of therapies targeting the pathological protein amyloid-β (Aβ) in Alzheimer's disease (AD), revolutionizing the approach to treating this condition. Monoclonal antibodies directed against Aβ, such as lecanemab, donanemab, and aducanumab, have become the first approved disease-modifying therapies (DMTs), offering real hope for slowing the progression of AD [1]. The CLARITY-AD study, published in 2023 in the New England Journal of Medicine, demonstrated that lecanemab leads to a 27% reduction in the rate of cognitive decline in patients with early-stage AD, measured using the CDR-SB (Clinical Dementia Rating-Sum of Boxes) scale [2]. This effect correlated with a significant reduction in brain amyloid burden, confirmed by PET imaging, where the average reduction was 59.1 centiles on the SUVR (Standardized Uptake Value Ratio) scale after 18 months of therapy [3]. Similar results were observed for donanemab, which in the TRAILBLAZER-ALZ study showed a 32% slowing of disease progression on the iADRS (Integrated Alzheimer's Disease Rating Scale) [4]. Importantly, donanemab demonstrated particularly strong efficacy in removing mature amyloid plaques, with 84% of patients reaching an amyloid level considered negative in PET imaging after completing therapy [5].

The mechanisms of action of these monoclonal antibodies differ significantly. While aducanumab and lecanemab primarily bind to soluble oligomers and Aβ fibrils, donanemab specifically recognizes a modified form of Aβ (N3pG-Aβ) present in mature amyloid plaques [6]. These differences translate into varying efficacy and safety profiles for each drug. In the case of lecanemab, the incidence of amyloid-related imaging abnormalities (ARIA), including edema (ARIA-E) and microhemorrhages (ARIA-H), is 12.6% and 8.9%, respectively [7]. In comparison, donanemab is associated with a higher risk of ARIA (24% for ARIA-E and 19% for ARIA-H), particularly in APOE4 allele carriers [8]. Aducanumab, the first approved anti-Aβ antibody, has the highest rate of adverse effects (35% ARIA-E), which, combined with controversies regarding its efficacy, has significantly limited its use in clinical practice [9].

Despite promising results, anti-amyloid therapies have significant limitations. First, they are effective only in the early stages of AD, which necessitates precise biomarker diagnostics before initiating treatment [10]. Second, the high cost of therapy (approximately $26,500 per year for lecanemab) poses challenges for healthcare systems [11]. Third, the requirement for regular monitoring through magnetic resonance imaging to detect ARIA significantly increases the burden for both patients and medical facilities [12]. Additionally, the observed clinical effects, while statistically significant, remain moderate in terms of clinical relevance, highlighting the need for further refinement of these therapies [13].

Currently, intensive research is underway to optimize anti-amyloid therapies. New generations of antibodies, such as remternetug, are in clinical trials and may have a better safety profile [14]. Concurrently, studies are being conducted on oral Aβ aggregation inhibitors, such as ALZ-801, which may serve as an alternative to intravenous therapies [15]. An important direction of research is also the search for predictive biomarkers of treatment response, which would allow for better selection of patients who would benefit most from therapy [16].

Conclusions from the table:

1. Lecanemab has the best safety profile among approved drugs.
2. Donanemab exhibits the strongest efficacy in amyloid removal but comes with a higher risk of ARIA.
3. Aducanumab is rarely used due to controversies regarding its efficacy.

In summary, the new anti-amyloid drugs represent a breakthrough in the treatment of AD, confirming the validity of the amyloid hypothesis. However, their optimal use in clinical practice requires addressing numerous challenges, including improving the availability of biomarker diagnostics, reducing therapy costs, and better understanding the long-term effects of treatment [17]. Further development of this class of drugs, combined with therapies targeting other aspects of AD pathogenesis, may lead to more effective therapeutic strategies in the future [18].

Table 1. Comparison of Anti-Amyloid Drugs in Alzheimer's Disease: Lecanemab, Donanemab, and Aducanumab

Parameter	Lecanemab (Leqembi®)	Donanemab	Aducanumab (Aduhelm®)
Mechanism of Action	Monoclonal IgG1 antibody binding soluble Aβ oligomers	Monoclonal IgG1 antibody binding N3pG-Aβ (mature plaques)	Monoclonal IgG1 antibody binding Aβ aggregates
Clinical Trials	CLARITY-AD (2023)	TRAILBLAZER-ALZ (2021)	EMERGE/ENGAGE (2020)
Efficacy	27% slowing of progression (CDR-SB) over 18 months	32% slowing of progression (iADRS) over 18 months	Not significant (only in EMERGE subset)
Reduction of Amyloid (PET)	59.1 centiles on the SUVR scale after 18 months	84% of patients reached amyloid negativity	22% reduction in SUVR
Dosage	10 mg/kg biweekly (IV)	700 mg q4 weeks (IV) - possibility to pause for amyloid clearance	10 mg/kg q4 weeks (IV)
ARIA Frequency	12.6% (ARIA-E), 8.9% (ARIA-H)	24% (ARIA-E), 19% (ARIA-H)	35% (ARIA-E)
Risk Factors for ARIA	APOE4 carriers (higher risk)	APOE4 carriers (2× higher risk)	APOE4 carriers (risk >30%)
Approval	FDA (2023), EMA (2024)	FDA (2023), EMA (two opinions)	FDA (2021), withdrawn by UE (2022)
Annual Cost (USD)	~26,500	~28,200 (estimated)	~28,000 (currently rarely used)
Target Population	Early AD (MCI or mild dementia) + confirmed amyloid	Early AD + high amyloid levels	Early AD (controversial indications)
Monitoring Requirements	MRI for ARIA monitoring	High ARIA risk, early diagnosis required	Low efficacy, regulatory controversies

Biomarkers in the Early Diagnosis of Alzheimer's Disease

Early and accurate diagnosis of Alzheimer's disease (AD) presents a key challenge in modern neurology, especially concerning new disease-modifying therapies that are effective only in the early stages [19]. Traditional diagnostic criteria based on clinical symptoms often allow for the diagnosis of AD only in advanced stages of neurodegeneration, when therapeutic intervention may be less effective. In response to this limitation, there has been a rapid development of biomarkers over the past decade that enable the identification of pathological changes long before clinical symptoms appear [27]. Currently, biomarker diagnostics focus on three main areas: amyloid pathology (Aβ), tau protein changes, and neurodegeneration, as reflected in the revised NIA-AA criteria from 2018 and 2023 [19].

The most established biomarkers are those related to cerebrospinal fluid (CSF), including decreased levels of Aβ42 and elevated concentrations of phosphorylated tau (p-tau181, p- tau217) [21,23]. While these methods are invasive, they remain the gold standard in AD diagnostics, offering sensitivity and specificity exceeding 90% [21]. However, a breakthrough in recent years has been the development of blood tests assessing these same biomarkers, significantly increasing the availability of screening studies [20]. Particularly promising is the blood biomarker p-tau217, whose diagnostic accuracy approaches that of CSF studies, as confirmed by numerous studies [20,21,25]. Concurrently, the technology for ultrasensitive immunoassays (e.g., Simoa) is being developed, allowing for the detection of abnormal levels of Aβ42/40 and neurofilament light chains (NfL)—markers of neurodegeneration—even at the preclinical stage [24,28].

Molecular imaging using amyloid PET (e.g., florbetapir, flutemetamol) and tau PET (e.g., flortaucipir) constitutes another pillar of diagnostics, enabling the visualization of pathological changes in vivo [22,29]. Studies have shown that tau PET not only confirms the diagnosis but also correlates with disease severity and predicts the rate of progression [22,29]. Despite its high effectiveness, a limitation remains the high cost and limited availability of this technique [30]. In response, efforts are underway to develop more affordable

alternatives, including PET imaging targeting neuroinflammation (e.g., TSPO- PET) and the application of artificial intelligence in the analysis of routine MRI scans [30].

Currently, the greatest hopes are placed on the integration of various biomarkers into so- called diagnostic panels, which could not only confirm AD but also differentiate it from other tauopathies or neurodegenerative diseases [26,27]. An example is the combination of measuring p-tau217 in blood with the assessment of Aβ in CSF or PET, which, according to studies, increases diagnostic accuracy to 96% [21,25]. At the same time, new research directions are emerging concerning biomarkers, such as synaptic proteins (e.g., neurogranin), markers of blood-brain barrier damage, or analyses of the gut microbiome, which may revolutionize diagnostics in the future [27].

Despite these advancements, standardization of measurement methods between centers and the development of affordable solutions for widespread use remain challenges. However, the dynamic progress in the field suggests that in the coming years, we can expect the implementation of blood tests with sensitivity comparable to CSF in routine clinical practice, which would radically change the approach to early diagnosis and monitoring of AD therapy [2,9]. Combined with new treatment methods, biomarkers lay the foundation for personalized medicine, where intervention occurs at a stage when it has the potential to significantly modify the natural course of the disease [19,27].

Non-Pharmacological Strategies in the Prevention and Therapy of Alzheimer's Disease.

In light of the limitations of current pharmacological therapies for Alzheimer's disease (AD), increasing attention is being paid to non-pharmacological interventions that can influence modifiable risk factors and slow disease progression [31]. Epidemiological studies indicate that up to 40% of dementia cases may be associated with modifiable risk factors such as lifestyle, diet, and physical activity [32]. This chapter presents the current state of knowledge regarding the most effective non-pharmacological strategies in the prevention and support of AD treatment.

Diet and nutrients play a crucial role in preventing neurodegeneration. A meta-analysis of 18 studies from 2022 showed that strict adherence to a specific diet is associated with a 33% reduction in the risk of developing mild cognitive impairment (MCI) and AD [33]. The mechanisms behind this effect include reducing inflammation, improving endothelial function, and increasing neurogenesis [34]. Among specific nutrients, omega-3 fatty acids (DHA), flavonoids (found in berries and green tea), and B vitamins, especially in individuals with hyperhomocysteinemia, are particularly promising [35]. The FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) demonstrated that combining a Mediterranean diet with DHA and vitamin B12 supplementation leads to significant improvements in cognitive function in individuals at elevated risk of dementia [36].

Physical activity is another key element in the prevention of AD. A meta-analysis of 36 randomized controlled trials found that among older adults, regular physical activity (150 minutes per week) improved cognitive test scores by an average of 0.5 standard deviations compared to the control group [37]. Cognitive training and intellectual stimulation show particular effectiveness in building cognitive reserve. In the digital age, computer-based training programs are gaining popularity, although their effectiveness in preventing AD requires further research [38].

Metabolic interventions focus on controlling cardiovascular risk factors. The SPRINT- MIND study showed that intensive blood pressure control (target <120 mmHg) is associated with a 19% reduction in the risk of MCI and probable dementia [39]. Similarly, proper glycemic control in individuals with type 2 diabetes may reduce the risk of dementia by as much as 30% [40]. In recent years, particular attention has also been given to the relationship between sleep disorders and the pathogenesis of AD. Studies indicate that sleep apnea therapy (CPAP) may reduce β-amyloid accumulation and improve cognitive functions [41].

Combined therapies appear particularly promising. The FINGER study, the first randomized controlled trial evaluating a multidisciplinary intervention, showed a 25% improvement in overall cognitive functions in the intervention group (diet, exercise, cognitive training, and risk factor control) compared to the control group [42]. These results confirm the need for a holistic approach to AD prevention that integrates various therapeutic modalities [43].

Despite promising results, the implementation of non-pharmacological strategies in clinical practice faces numerous challenges, including a lack of standardization in protocols and difficulties in long- term adherence [44]. Further research is needed to determine the optimal combinations of interventions and their impact on different stages of the disease. Nevertheless, current scientific evidence clearly indicates that lifestyle modification is a crucial element of a comprehensive approach to the prevention and therapy of Alzheimer's disease [45].

Challenges and Future Directions in Alzheimer's Disease Therapy

Challenges in drug development primarily include difficulties in designing effective disease- modifying therapies (DMT). Although monoclonal antibodies targeting beta-amyloid (Aβ), such as lekanemab and donanemab, have shown some efficacy in reducing pathological changes, their impact on cognitive functions remains moderate [46]. Furthermore, the occurrence of adverse effects, such as amyloid-related imaging abnormalities (ARIA), significantly limits the population of patients who may benefit from these therapies [47]. Another challenge is the heterogeneity of AD, which likely requires a personalized approach to treatment that takes into account different subtypes of the disease [48].

Innovative therapeutic directions focus on several promising areas. Therapies targeting tau protein, such as monoclonal antibodies (e.g., zagotenemab) or tau aggregation inhibitors, are currently in clinical trials [49]. Other promising approaches include modulation of the immune system (e.g., through microglia stimulation), gene therapy (including the use of CRISPR/Cas9 for editing AD-related genes), and the application of stem cells [50]. Special attention is also being given to research on anti-inflammatory and neuroprotective compounds, such as NLRP3 inhibitors (e.g., inzomelod) and modulators of glucose metabolism in the brain [51].

The development of biomarkers and diagnostics remains crucial for progress in Alzheimer's disease (AD) therapy. Currently, there are intensive efforts underway to improve non- invasive methods for disease detection, including blood tests based on ultra-sensitive technologies that detect pathological forms of tau and Aβ [52]. Concurrently, the technology of digital biomarkers is being developed, utilizing artificial intelligence to analyze patterns of speech, movement, and usage of electronic devices, which may allow for the early detection of subtle cognitive changes [53]. An important direction is also the personalization of diagnostics through the integration of data from various sources, including genetics, neuroimaging, and body fluid studies [54].

Systemic and ethical challenges associated with new AD therapies are equally significant. The high costs of treatment (e.g., lekanemab - approximately $26,500 per year) raise questions about the availability and cost-effectiveness of these therapies within healthcare systems [55]. Furthermore, the development of early diagnostic methods creates important ethical dilemmas regarding informing patients about the risk of developing AD when effective treatments are not yet available [56]. These issues require extensive discussion involving clinicians, patients, families, and policymakers [57].

Future research directions will likely focus on several key areas. An important avenue is the search for new therapeutic targets, such as synaptic proteins, mitochondria, or the gut microbiome, which may play a significant role in the pathogenesis of AD [58].

In summary, although the challenges in treating AD are significant, the current period can be considered a breakthrough time in research on this disease [59]. The combination of new pharmacological therapies, advanced diagnostic methods, and holistic non-pharmacological approaches offers hope for significant progress in the fight against AD in the coming decade [60]. However, it will be crucial to ensure that these advancements are accessible to all patients, regardless of their socioeconomic status or geographical location [61].

Conclusions

Alzheimer's disease (AD) remains one of the most significant public health challenges in aging societies; however, recent years have brought groundbreaking discoveries that fundamentally change therapeutic prospects. This review has demonstrated that the contemporary approach to AD treatment is evolving from solely symptomatic interventions towards a comprehensive strategy that includes early biomarker diagnostics, targeted disease-modifying therapies, and preventive non-pharmacological interventions.

The most important achievement of the past decade is undoubtedly the development and approval of the first therapies targeting the pathological amyloid-beta protein, particularly lecanemab and donanemab. Data from phase III clinical trials unequivocally confirm that these monoclonal antibodies can significantly reduce amyloid burden in the brain and moderately slow the progression of cognitive deficits in the early stages of the disease. At the same time, the development of non-invasive blood biomarkers, particularly those based on phosphorylated tau (p-tau217, p-tau181), has created the opportunity for early identification of individuals at high risk of developing AD, which is crucial for the optimal use of new therapies.

Concurrently, research on non-pharmacological intervention strategies, such as the groundbreaking FINGER study, has provided compelling evidence that multidisciplinary programs involving dietary modification, increased physical activity, cognitive training, and control of cardiovascular risk factors can significantly improve cognitive functions in at-risk individuals. This preventive approach appears particularly promising in the context of the long, multiyear preclinical phase of AD.

Despite these significant advancements, this work has also highlighted important challenges that need to be addressed. These include the limited effectiveness of current therapies in advanced stages of the disease, the high cost of modern drugs and biomarker diagnostics, the risk of adverse effects associated with anti-amyloid therapies, and the need for a better understanding of AD heterogeneity. There is an urgent need to develop therapies targeting other aspects of pathogenesis, particularly tau protein and neuroinflammatory processes.

The future of AD treatment will likely involve personalized, multifaceted therapeutic strategies that combine:

- Early diagnostics using sensitive blood biomarkers and molecular imaging,
- Targeted pharmacological therapies tailored to the individual patient's pathological profile,
- Comprehensive non-pharmacological interventions addressing modifiable risk factors,
- Advanced methods for monitoring treatment response utilizing digital biomarkers.

Recent years have brought a definitive breakthrough in our approach to AD, transforming it from an inevitably progressive neurodegenerative disorder into a disease with a potentially modifiable course. However, fully realizing this potential will require further intensive research, investment in healthcare systems, and multidisciplinary collaboration among scientists, clinicians, and policymakers. Despite the remaining challenges, the current period can be regarded as one of unprecedented hope for millions of patients affected by Alzheimer's disease and their families.

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