GENETIC AND PATHOPHYSIOLOGICAL ASPECTS OF ALZHEIMER'S DISEASE

ASPECTOS GENÉTICOS E FISIOPATOLÓGICOS DO MAL DE ALZHEIMER

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Abstract

Introduction: Alzheimer's disease (AD) is a neurodegenerative condition characterized by the progressive loss of neurons, representing the most common form of dementia among the elderly. Its incidence has been increasing worldwide. The pathology develops over several years, gradually impairing the brain's ability to compensate for neuronal damage. Objective: To review the scientific literature on AD, with a focus on its main clinical features. Methodology: A narrative literature review was conducted using the PubMed, SciELO, and Google Scholar databases. These studies were grouped into four categories: (i) clinical and epidemiological characteristics, (ii) genetic and molecular aspects, (iii) therapeutic approaches and supportive interventions, and (iv) reviews and clinical case reports. The search included the keywords "Alzheimer", "nervous tissue", "molecular diagnosis", and "Alzheimer's disease". Results: A total of 367 articles were analyzed, with 33 selected for inclusion. Among these, 15 addressed the clinical characteristics of AD, 8 focused on genetic aspects, 6 discussed current treatments and supportive therapies, and 4 presented clinical facts and curiosities. Conclusion: Current research presents multiple hypotheses regarding the onset of Alzheimer's disease. Although no clinical interventions are currently available to prevent its development, some pharmacological treatments can improve patients' quality of life. Furthermore, a healthy diet and an active lifestyle may help delay the onset of symptoms. Scientific advances in this field have been occurring rapidly.

Keywords: Alzheimer Disease; Genetics; Nervous Tissue; Molecular Diagnostic Techniques.

Resumo

Introdução: A doença de Alzheimer (DA) é uma condição neurodegenerativa caracterizada pela perda progressiva de neurônios, sendo a forma mais comum de demência em idosos. Sua incidência vem crescendo mundialmente. A patologia se desenvolve ao longo de anos, reduzindo gradualmente a capacidade do cérebro de compensar os danos neuronais. **Objetivo:** Revisar a literatura científica sobre a DA, com ênfase em suas principais características clínicas. **Metodologia:** Uma revisão narrativa da literatura foi realizada nas bases de dados PubMed, SciELO e Google Scholar. Os estudos selecionados foram organizados em quatro categorias: (i) características clínicas e epidemiológicas, (ii) aspectos genéticos e moleculares, (iii) abordagens terapêuticas e intervenções de suporte e (iv) revisões e relatos de casos clínicos. A busca incluiu os descritores "Alzheimer", "tecido nervoso", "diagnóstico molecular" e "doença de Alzheimer". **Resultados:** Foram analisados 367 artigos, dos quais 33 foram selecionados. Destes, 15 abordam as características da DA, 8 tratam de aspectos genéticos, 6 discutem tratamentos e terapias de suporte, e 4 relatam fatos clínicos e curiosidades. **Conclusão:** As pesquisas apontam diversas hipóteses sobre a origem da doença de Alzheimer. Embora ainda não existam intervenções clínicas capazes de preveni-la, há medicamentos que contribuem para a melhoria da qualidade de vida dos pacientes. Além disso, uma alimentação saudável e um estilo de vida ativo podem retardar o início dos sintomas. Os avanços científicos nessa área têm ocorrido de forma acelerada.

Palavras-chave: Doença de Alzheimer; Genética; Tecido Nervoso; Diagnóstico Molecular.

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1. Introduction

With the growth of the world population and the increase in life expectancy, Alzheimer's disease (AD) and other forms of dementia have become increasingly prevalent. In the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), these conditions are classified under the category of Major Neurocognitive Disorders (TNM) [1].

Currently, AD is the most common form of dementia worldwide, accounting for approximately 60% of all diagnosed cases. An estimated 35.6 million people are affected globally, and projections suggest that this number will double every 20 years. In Brazil, around 500,000 cases have been officially identified, although it is estimated that the real number may exceed 1.2 million,

indicating that nearly 700,000 individuals may be living with the disease without a confirmed diagnosis[2]. These numbers highlight not only the scale of the challenge but also the gaps in screening and early detection.

Alzheimer's disease was first described in 1906 by the German psychiatrist Aloysius "Alöis" Alzheimer, based on the case of Auguste Deter, a 51-year-old woman residing in a psychiatric institution. Her symptoms included cognitive impairment, disorientation, delusions, and various behavioral changes[3]. This initial clinical description laid the foundation for decades of subsequent research into the disease's neurobiological basis and clinical progression.

The symptoms of AD typically begin with mild cognitive decline due to neuronal death, often associated with aging or specific neuropathological processes. As the disease advances, affected individuals become increasingly dependent on external assistance In its early stages, AD is characterized by difficulties in forming and storing new memories, as well as reduced attention span. As the pathology progresses, cognitive and behavioral impairments become more severe, often including deficits in language, motor coordination, and executive function[4].

Although AD has been extensively studied, many aspects of its etiology, progression, and treatment remain under investigation. The complex interplay between genetic, molecular, and environmental factors continues to challenge researchers and clinicians. Therefore, understanding the clinical features and underlying mechanisms of the disease is crucial for advancing both diagnosis and therapeutic approaches.

This article presents a narrative review of the literature on Alzheimer's disease, focusing on its primary clinical manifestations, as well as current understandings of its causes, characteristics, and treatment strategies.

2. Methodology

2.1 Search strategy

This article is based on a narrative literature review, aiming to synthesize relevant knowledge on Alzheimer's disease (AD) and its clinical, genetic, and therapeutic aspects. The literature search was conducted during the first semester of 2021 using three databases: PubMed, SciELO, and Google Scholar. The search covered the period from February to October 2021. Only studies published in peer-reviewed journals were considered.

The descriptors used in the search were: *Alzheimer*, *nervous tissue*, *molecular diagnosis*, and *Alzheimer's disease*. Boolean operators (AND, OR) were employed to refine the search results, and filters were applied to include only articles published in English or Portuguese, with no restrictions on publication year to ensure a broad historical and conceptual scope.

2.2 Inclusion and exclusion criteria

Inclusion criteria were: (i) original research articles, reviews, or clinical reports that addressed clinical features, diagnosis, treatment, or genetic aspects of AD. Eligible study designs included clinical trials, observational studies, and systematic or narrative reviews; (ii) studies with clear methodological description; and (iii) publications in peer-reviewed journals. Exclusion criteria comprised: (i) editorials, letters, commentaries, or duplicated

works; (ii) articles that did not directly address AD or that focused solely on other types of dementia; and (iii) works lacking scientific rigor or proper referencing.

2.3 Study selection process

After identifying potentially relevant articles through title screening, the abstracts were analyzed to exclude those not aligned with the review's objectives. The remaining articles were read in full to allow a comprehensive evaluation of their content and relevance.

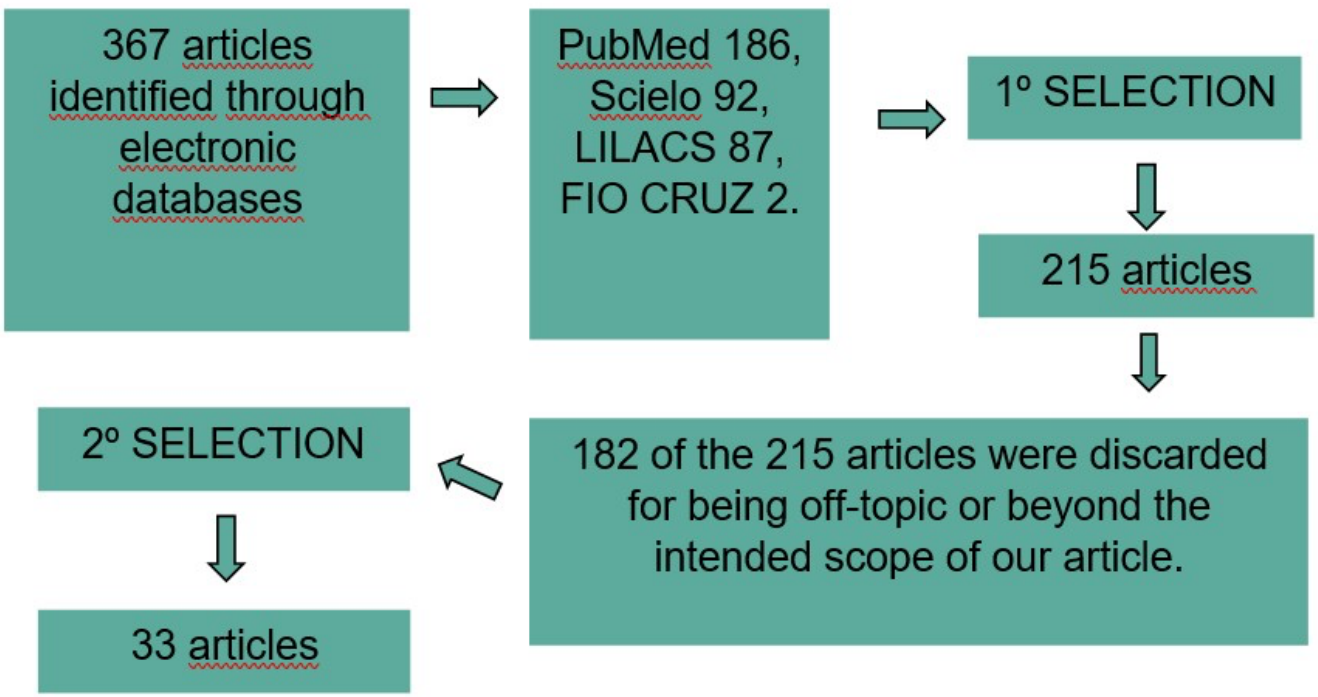
2.4 Data extraction and analysis.

Two independent reviewers conducted the screening and full-text analysis. Discrepancies were resolved by consensus. Data extraction was standardized using a structured spreadsheet to capture authorship, year, objectives, study type, and main findings. A total of 367 articles were initially retrieved, of which 33 met all criteria and were included in this review.

The selection process followed the PRISMA 2020 guidelines for reporting, and the flow of studies (identification, screening, eligibility, inclusion) is illustrated in Figure 1, with reasons for exclusion detailed at each stage. The selected studies were categorized into four thematic axes to guide the analysis and discussion: (1) clinical characteristics of AD; (2) genetic factors and pathophysiology; (3) therapeutic approaches and supportive interventions; and (4) clinical curiosities and relevant case reports.

2.5 Methodological limitations

As this is a narrative review, the process did not include a formal quality assessment of the studies included. Consequently, the synthesis may be subject to selection bias and lacks the quantitative rigor of systematic reviews or meta-analyses. Nevertheless, the inclusion of diverse study designs allowed a broad overview of clinical, genetic, and therapeutic aspects of AD.



3. Results

A total of 367 scientific articles published in Portuguese and/or English were initially identified through searches conducted between February and October 2021 in the PubMed, SciELO, and Google Scholar databases. The search utilized descriptors such as *Alzheimer's disease*, *nervous tissue*, and *molecular diagnosis*. These platforms provide broad access to peer-reviewed journals in medical and biological sciences, allowing for a comprehensive overview of literature related to Alzheimer's disease (AD).

Following the application of inclusion and exclusion criteria, 33 articles were selected for full analysis. To facilitate a structured interpretation of the findings, the selected studies were grouped into four thematic categories:

1. Clinical and epidemiological characteristics of AD
   Eleven articles examined the progression of cognitive decline in AD and its clinical manifestations. These studies also explored the correlation between clinical symptoms and caregiver burden, as well as mortality rates in Brazil and the heterogeneity of symptoms related to tau protein expression.
2. Genetic and molecular aspects
   Twelve publications focused on the molecular biology of AD, highlighting predisposing genetic factors such as the *APOE*, *BIN1*, *PSEN1*, and *CLU* genes. Several studies discussed the role of biomarkers in early diagnosis, the use of transgenic animal models, and connections with other genetic syndromes such as Down syndrome.
3. Therapeutic approaches and interventions
   Ten articles reviewed pharmacological and non-pharmacological treatments. Medications such as donepezil and memantine were examined for their effects on cognition and functionality. Other studies assessed the benefits of cognitive training and physical exercise, as well as experimental strategies like immunization with β-amyloid.
4. Reviews, theoretical contributions, and miscellaneous findings
   A subset of studies offered broader theoretical and literature reviews, with some discussing diagnostic innovations and digital health solutions. These articles contributed conceptual and integrative perspectives to the field.

Table 1 presents the full list of selected articles, organized by number, title, author(s), journal/source, and a brief description of each article's contribution to the themes above.

N°	TITLE	AUTHOR	SOURCE	ARTICLE ANALYSIS
1	Manual Diagnóstico e Estatístico de Transtornos Mentais	[1]	Review Internacional Interdisciplinar INTERthesis	It helps in the diagnosis of mental disorders such as AD.
2	Doença de Alzheimer: Estudo da mortalidade no Brasil	[2]	Cad. Saude Publica	It shows the mortality rate of AD in Brazil.
3	A doença de	[3]	Review Psiquiatria	It addresses the main

	Alzheimer: aspectos fisiopatológicos e farmacológicos		do Rio Grande do Sul	aspects of ADand possible pharmacological treatments.
4	Biomarkers for ADDiagnosis	[5]	Curr. Alzheimer Res	It teaches about the genetic biomarkers of AD.
5	Tau molecular diversity contributes to clinical heterogeneity in Alzheimer's disease.	[4]	Nature Med	It shows how the tau protein theory occurs.
6	Revisão	[6]	Quím. Nova	A review of the disease.
7	Cholinergic markers in Alzheimer disease	[7]	Jama	It shows ADand the cholinergic system.
8	Doença de Alzheimer: Hipóteses etiológicas e perspectivas de tratamento	[8]	Química Nova	It is a review about the disease.
9	ADand the basal forebrain cholinergic system: relations to β-amyloid peptides, cognition, and treatment strategies	[9]	Prog. Neurobiol	Shows what happens to the cholinergic system in relation to β-amyloid proteins in Alzheimer's disease
10	Doença de Alzheimer	[10]	Brazilian J. Psychiatry	It talks about the general aspects of Alzheimer's disease.
11	Exosomal biomarkers in Down syndrome and Alzheimer's disease	[11]	Free Radic. Biol. Med.	It shows the link between ADand Down's Syndrome.
12	Apolipoproteína E e a doença de Alzheimer	[12]	Arch. Clin. Psychiatry (São Paulo)	He talks about the allipoprotein E connection and the link to Alzheimer's disease.
13	Alterações genéticas na doença de Alzheimer	[13]	Arch. Clin. Psychiatry (São Paulo)	It shows the genetic changes that occur in Alzheimer's disease.
14	Transgenic models of Alzheimer's disease: learning from animals.	[14]	NeuroRx	It shows studies done with transgenic animals, to try to explain AD.
15	Imaging ADpathophysiology with PET	[15]	Dement. Neuropsychol.	Talk about Alzheimer's disease.
16	Genetic factors associated with	[16]	Ageing Res. Rev.	It shows the genetic factors associated with

	longevity: a review of recent findings			longevity and correlates with AD.
17	High-speed apolipoprotein E genotyping and apolipoprotein B3500 mutation detection using real-time fluorescence PCR and melting curves.	[17]	Clin. Chem.	Talk about Alipoprotein E.
18	Linguagem e memória na doença de Alzheimer em fase moderada.	[18]	Review CEFAC	It shows the phases of AD and what each one affects in the patient's brain.
19	Sintomas neuropsiquiátricos na doença de Alzheimer: frequência, correlação e ansiedade do cuidador.	[19]	Review Bras. Geriatr. e Gerontol.	It reports on the characteristic symptoms of the disease, and their correlation with the caregiver.
20	Long-term donepezil treatment in 565 patients with AD(AD2000): randomised double-blind trial.	[20]	Lancet (London, England)	It shows the risks and benefits of treatment with the drug donepezil.
21	Diagnóstico diferencial das demências.	[21]	Arch. Clin. Psychiatry (São Paulo)	Talk about the diagnosis of dementias.
22	Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system-too little activation is bad, too much is even worse.	[22]	Neuropharmacology	He talks about the drug memantine for the treatment of Alzheimer's disease.
23	Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging.	[23]	Am. J. Psychiatry	Talk about memory.
24	Tratamento	[24]	Review Hosp. Univ.	Talk about

	farmacológico da doença de Alzheimer		Pedro Ernesto	pharmacological treatments of AD.
25	Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse	[25]	Nature	It shows immunization tests for AD.
26	Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease	[26]	J. Neurol. Neurosurg. Psychiatry	It talks about the treatment and its effects.
27	Eficácia do treinamento cognitivo associado ao exercício físico em indivíduos com doença de Alzheimer: uma metanálise.	[27]	Research Society and development	Shows the benefits of cognitive training associated with exercise for treatment in Alzheimer's patients.
28	Doença de Alzheimer	[28]	Centro de estimulação para idosos- CEI	It talks about the general aspects of the disease.
29	Early diagnosis and treatment of Alzheimer	[29]	Hong Kong Med J	It shows the diagnoses and treatments for the disease.
30	Oportunidad em la salud digital: uma respuesta al control de las demencias	[30]	Review méd. Chile	It talks about the control of dementias.
31	Combined association of Presenilin-1 and Apolipoprotein E polymorphisms with maternal meiosis II error in Down syndrome births.	[31]	Human and Medical Genetics	It shows the combination of drugs.
32	The combined risk effect among BIN1 , CLU , and APOE genes in Alzheimer ' s disease.	[32]	Human and Medical Genetics	It talks about the genes related to Alzheimer's.
33	Comparative transcriptome analysis of the hippocampus from sleep-deprived and Alzheimer ' s	[33]	Cellular, Molecular and Developmental Genetics	It is an analysis of the disease.

disease mice.

4. Discussion

HOW AD AFFECTS THE NERVOUS SYSTEM

Alzheimer's disease (AD) induces a progressive deterioration of the central nervous system, primarily through synaptic loss and neuronal death in regions essential for higher cognitive functions, including the cerebral cortex, entorhinal cortex, ventral striatum, and hippocampus. These neuroanatomical changes are not random but follow a relatively stereotyped pattern that reflects the spread of underlying molecular pathologies. Histopathological findings in AD brains – such as β-amyloid (Aβ) plaques, tau-based neurofibrillary tangles (NFTs), and chronic neuroinflammation – constitute the foundation upon which several competing etiopathogenic hypotheses have been formulated [29,30].

The most widely discussed model is the *amyloid cascade hypothesis*, which proposes that the abnormal proteolytic cleavage of amyloid precursor protein (APP) triggers a series of events leading to the aggregation and deposition of Aβ peptides. These peptides form extracellular senile plaques, which are believed to be neurotoxic, promoting oxidative stress, synaptic dysfunction, and ultimately, neuronal apoptosis[6,29,30]. While this hypothesis is supported by genetic and biochemical evidence – particularly in familial forms of AD – it fails to fully account for the poor correlation between amyloid load and clinical severity, especially in sporadic cases.

A complementary but distinct line of explanation is the *cholinergic hypothesis*, which attributes cognitive decline primarily to the degeneration of cholinergic neurons and deficits in acetylcholine-mediated neurotransmission. The identification of markedly reduced levels of choline acetyltransferase and acetylcholinesterase in the brains of AD patients supports this view [7,9]. This framework has served as the pharmacological basis for the use of cholinesterase inhibitors. However, critics argue that this hypothesis, while useful for symptomatic treatment, does not address the upstream pathological drivers of AD.

Some researchers attempt to reconcile these hypotheses by suggesting that amyloid pathology may induce cholinergic dysfunction secondarily, implying a cascade of interdependent mechanisms rather than isolated pathways[3]. Moreover, neuroinflammation, oxidative stress, and tau pathology – once seen as consequences – are now recognized as possible co-factors or even initiators of neuronal degeneration.

Thus, although both the amyloid and cholinergic models have provided valuable insights, neither fully explains the clinical and biological complexity of AD. Contemporary perspectives increasingly advocate for *multifactorial models*, which incorporate genetic predispositions, protein misfolding, neurotransmitter deficits, and glial activation into a more integrated understanding of AD neuropathogenesis.

GENETIC ASPECTS OF ALZHEIMER'S DISEASE

The etiology of Alzheimer's disease (AD) encompasses a multifactorial interplay between genetic predisposition and environmental exposures. While external agents—such as infectious pathogens, neurotoxic compounds, and factors that destabilize the cytoskeleton—may contribute to cellular damage, increasing evidence underscores the central role of inherited genetic variants in modulating individual susceptibility to AD[10]. Importantly, heritability in AD is autosomal and not sex-linked, indicating that both males and females are equally vulnerable to its genetic influences.

One of the most compelling associations between genetics and AD is observed in individuals with Down syndrome (trisomy 21). The presence of an extra copy of chromosome 21 leads to overexpression of the *amyloid precursor protein* (APP) gene, which is located on this chromosome. As a consequence, individuals with trisomy 21 tend to exhibit early accumulation of β-amyloid (Aβ) and a markedly increased risk of developing early-onset AD pathology[11]. This association provides strong empirical support for the hypothesis that APP overexpression plays a pivotal pathogenic role.

Beyond APP, several other genes have been consistently implicated in familial and sporadic forms of AD. Mutations in *presenilin 1* (PSEN1) and *presenilin 2* (PSEN2) – which encode proteins involved in the γ-secretase complex responsible for APP cleavage – are associated with early-onset, autosomal dominant AD. These mutations typically increase the production of the neurotoxic Aβ42 isoform, reinforcing the amyloidogenic model of disease [12]. Their penetrance and predictability make them reliable biomarkers for familial AD, although they represent a minority of cases.

In contrast, the *apolipoprotein E* (APOE) gene, particularly its ε4 allele, has been identified as the most significant genetic risk factor for late-onset AD. While not directly causal, APOE ε4 influences several pathogenic processes, including Aβ aggregation and clearance, tau phosphorylation, synaptic function, and neuroinflammation. Importantly, the presence of the APOE ε4 allele does not guarantee disease development, highlighting the complex interaction between genetic risk and modifiable environmental or epigenetic factors.

Despite the strong associations between these genes and AD, their individual predictive power remains limited, particularly in isolation. This reinforces the current consensus that AD cannot be explained by single-gene mutations in most cases. Rather, it is the cumulative effect of multiple low-penetrance variants – interacting with aging, lifestyle, and comorbidities – that shapes disease vulnerability and trajectory.

Recent advances in genomics, including genome-wide association studies (GWAS) and polygenic risk scoring, are expanding the landscape of AD genetics beyond the classical APP-PSEN-APOE axis. These tools have identified additional loci of interest and may contribute to future efforts at personalized risk assessment, although clinical translation remains an ongoing challenge.

In summary, while genetic mutations in

APP, PSEN1, PSEN2, and APOE provide valuable insights into AD pathogenesis, they represent only part of a broader and more intricate network of biological mechanisms. A more integrative approach – linking genetic data with molecular, clinical, and environmental information – is essential for advancing predictive diagnostics and targeted interventions.

ApoE GENE

Among the various genetic markers associated with Alzheimer's disease (AD), the *apolipoprotein E* (APOE) gene stands out as the most significant risk factor for late-onset forms of the disease. Located on chromosome 19, the APOE gene encodes a glycoprotein involved in lipid metabolism, neuronal repair, and synaptic plasticity. Although the gene exists in three major allelic forms - ε2, ε3, and ε4 – it is the ε4 allele that has been consistently associated with increased AD risk [12,13].

Individuals carrying one copy of the ε4 allele have a two- to threefold increased risk of developing AD, while homozygous ε4 carriers may experience up to a twelvefold increase in risk, alongside an earlier disease onset. In contrast, the ε2 allele appears to confer a modest protective effect, though its mechanisms remain poorly understood. Importantly, the presence of ε4 is neither necessary nor sufficient for disease development, which underscores the non-deterministic nature of its influence and the complexity of AD pathogenesis.

The pathological effects of APOE ε4 extend beyond its role in lipid transport. This allele has been implicated in several biological pathways that contribute to AD progression: (i) it reduces Aβ clearance and promotes its aggregation into toxic oligomers and plaques; (ii) it exacerbates tau hyperphosphorylation and tangle formation; (iii) it impairs synaptic function and neuronal resilience; and (iv) it modulates inflammatory responses through interactions with astrocytes and microglia. These multifaceted actions suggest that APOE ε4 plays both upstream and downstream roles in the neurodegenerative cascade.

Despite the robust associations established in epidemiological and molecular studies, the clinical utility of APOE genotyping remains controversial. While it can aid in risk stratification and research recruitment, its predictive power in isolation is limited and may contribute to anxiety or false security in asymptomatic individuals. For this reason, the inclusion of APOE testing in routine clinical practice is still debated, and when performed, it must be accompanied by adequate genetic counseling and ethical safeguards.

Furthermore, recent studies have questioned the adequacy of framing APOE ε4 purely as a risk allele, calling attention to the gene's context-dependent effects. For example, its impact may vary by sex, age, ethnicity, and the presence of comorbidities such as cardiovascular disease or diabetes. These findings point to a need for more nuanced interpretations of APOE-associated risk, integrated with polygenic models and personalized assessments of lifestyle and environmental exposures.

In summary, while APOE ε4 remains a cornerstone of AD genetic research, its role is better understood as part of a broader, systemic imbalance involving

protein aggregation, metabolic dysregulation, and immune dysfunction. As precision medicine advances, APOE may transition from being merely a genetic marker to a therapeutic target—particularly in strategies aimed at modulating lipid metabolism, enhancing Aβ clearance, or reducing neuroinflammation.

AMYLOID PLAQUE:

Amyloid-β (Aβ) plaques have long been recognized as a central histopathological hallmark of Alzheimer's disease (AD). These extracellular aggregates, composed primarily of insoluble Aβ peptides derived from the aberrant proteolytic cleavage of amyloid precursor protein (APP), accumulate in brain parenchyma and cerebral vasculature, disrupting neuronal communication and initiating inflammatory cascades[6,13].

The formation of these plaques is most prominently explained by the *amyloidogenic pathway*, wherein APP undergoes sequential cleavage by β- and γ-secretases, producing Aβ40 and the more aggregation-prone Aβ42 isoform. It is this latter species that is most closely linked to neurotoxicity due to its propensity to form soluble oligomers—considered more damaging than the plaques themselves—through mechanisms involving oxidative stress, membrane disruption, and synaptic impairment[8,14].

While the *amyloid cascade hypothesis* has dominated the field for decades, its limitations have become increasingly evident. The weak correlation between amyloid burden and clinical severity, particularly in older adults who exhibit high plaque load without cognitive decline, challenges the notion of a direct causal relationship. Moreover, therapeutic strategies aimed at reducing Aβ accumulation – such as monoclonal antibodies or β-secretase inhibitors—have largely failed to produce significant cognitive improvements in clinical trials, prompting reevaluation of Aβ as a primary driver versus a downstream epiphenomenon.

One alternative perspective posits that amyloid pathology may act as a *permissive factor*, setting the stage for other pathological events – such as tau hyperphosphorylation, mitochondrial dysfunction, and neuroinflammation – to exert their full neurodegenerative effects. In this view, the clinical manifestation of AD arises not from the presence of plaques per se, but from the convergence of multiple, synergistic insults to neuronal integrity.

Moreover, findings from *transgenic animal models* overexpressing mutant human APP support a nuanced interpretation. Although these models reliably develop amyloid plaques and cognitive deficits, they often fail to recapitulate the full spectrum of human AD pathology, particularly tau pathology and significant neuron loss. This discrepancy further reinforces the notion that amyloid accumulation, while necessary for disease initiation in some cases, is insufficient on its own to account for disease progression [14].

Finally, recent work has highlighted the *role of the brain's immune system*, particularly microglial cells, in responding to amyloid deposits. Microglial activation appears to play a dual role—initially protective but eventually becoming maladaptive, promoting chronic inflammation and

synaptic loss. This shift from a “clearing” to a “toxic” phenotype aligns with emerging models that view AD as a disorder of failed resolution of neuroinflammation, with amyloid as a persistent trigger.

In light of these complexities, amyloid plaques should be viewed not as the singular cause of AD, but as part of a multifactorial network of pathophysiological events. Therapeutic strategies may benefit more from targeting Aβ within this broader context – emphasizing early intervention, modulation of the immune response, and combination approaches that address tau pathology, synaptic dysfunction, and metabolic resilience.

MOLECULAR DIAGNOSIS OF ALZHEIMER'S DISEASE

The advancement of molecular diagnostics has profoundly influenced the early detection and characterization of Alzheimer’s disease (AD), particularly in cases with genetic predisposition. However, while genetic screening and sequencing technologies have improved substantially, the interpretation of their results remains a challenge due to the complexity and heterogeneity of the disease.

A common starting point in molecular diagnosis is the analysis of *single nucleotide polymorphisms (SNPs)* in genes known to be associated with AD, such as *APP*, *PSEN1*, *PSEN2*, and *APOE*. Among these, the *APOE* ε4 allele remains the most robust and widely studied genetic risk marker for late-onset AD. Polymorphisms in this gene are mapped on the long arm of chromosome 19 and have been linked to increased amyloid deposition and reduced Aβ clearance [15,16]. However, the presence of this allele is neither necessary nor sufficient for the development of AD, which underscores the disease’s multifactorial nature.

High-throughput sequencing platforms – such as whole-exome or targeted panel sequencing – enable the detection of pathogenic variants across the *APP*, *APOE*, *PSEN1*, and *PSEN2* genes. Once sequencing is complete, data are processed through bioinformatics pipelines, aligned to reference genomes, and analyzed using curated variant databases. Variants are then classified according to their pathogenic potential. In certain protocols, follow-up *polymerase chain reaction (PCR)* amplification is performed to validate detected mutations and improve analytical sensitivity [17].

Despite the technical rigor of these methods, their *clinical interpretability is limited*. The pathogenicity of many variants remains uncertain, especially in polygenic or sporadic cases. Additionally, molecular diagnosis cannot provide a definitive confirmation of AD in isolation; it must be interpreted in combination with clinical, neuropsychological, and neuroimaging findings [31,33]. This integrative approach is essential not only for accurate diagnosis but also to avoid misclassification in patients who may present similar symptoms due to other neurodegenerative conditions.

Moreover, ethical concerns arise in the context of predictive testing, particularly in asymptomatic individuals or those with a family history of AD. The psychological burden of learning one’s genetic risk, coupled with the current

lack of curative interventions, complicates the justification for routine population screening. Genetic counseling is therefore an indispensable component of the diagnostic process, ensuring that individuals receive support in understanding and contextualizing the results.

Another important consideration is the distinction between early- and late-onset AD. Variants in *APP*, *PSEN1*, and *PSEN2* are most often linked to early-onset familial forms and confer high penetrance. In contrast, *APOE* is primarily associated with late-onset cases and serves more as a susceptibility marker than a determinant of disease onset. Consequently, the presence of *PSEN1* or *PSEN2* mutations may warrant proactive clinical surveillance, while *APOE* status is better used for risk stratification in conjunction with lifestyle and biomarker assessments.

Recent research is expanding the field of molecular diagnostics through the inclusion of *polygenic risk scores (PRS) and epigenetic biomarkers*, which aim to capture the cumulative effect of multiple low-impact genetic variants and environmental influences. Although these approaches are still in development, they hold promise for personalizing prevention strategies and therapeutic decision-making.

In summary, while molecular diagnostics provide essential tools for investigating the genetic underpinnings of Alzheimer's disease, they must be employed judiciously and within a comprehensive diagnostic framework. Their greatest value lies not in providing certainty, but in contributing to a probabilistic understanding of risk, informing early interventions, and shaping personalized medicine initiatives.

CLINICAL STAGING OF AD

The clinical progression of Alzheimer's disease (AD) is commonly described in three major stages—early (or mild), moderate, and advanced (or severe)—which reflect the gradual decline in cognitive, behavioral, and functional capacities. Although this tripartite division is widely accepted and useful for clinical orientation, it presents several limitations when critically examined in light of recent evidence.

In the *early stage*, patients typically experience subtle but persistent memory lapses, especially in the domain of short-term episodic memory, along with mild impairments in language, attention, and executive functioning. Personality changes, such as increased irritability or apathy, may also appear. Importantly, individuals in this phase often retain awareness of their deficits and may actively attempt to mask or rationalize them [18]. Because of the compensatory mechanisms still available at this stage, early symptoms are frequently misattributed to normal aging, resulting in underdiagnosis or delayed intervention.

The *moderate stage* marks a clear progression in symptom severity. Language becomes fragmented, spatial and temporal disorientation intensifies, and behavioral symptoms—such as agitation, aggression, or hallucinations—often emerge. The individual begins to lose autonomy in activities of daily living, such as dressing, managing finances, or preparing meals [19]. At this stage, caregiver burden significantly increases, and the need for structured support becomes evident. Notably, the moderate

phase also exhibits great heterogeneity: some patients may show accelerated deterioration, while others decline more slowly depending on comorbidities, cognitive reserve, and psychosocial factors.

In the *advanced stage*, the person with AD is fully dependent on others for basic self-care and hygiene. Communication is profoundly impaired, and recognition of loved ones may be lost. Physical decline is marked, often accompanied by rigidity, immobility, dysphagia, and susceptibility to infections, pressure ulcers, and malnutrition [18]. In many cases, the syndrome of "immobilization" leads to complications that become the direct cause of death. These motor and systemic features are sometimes neglected in the literature, which continues to emphasize cognitive deficits as the central manifestation of AD, thereby underrepresenting the broader scope of disability.

Despite the utility of this linear staging framework, current research challenges its adequacy in capturing the full spectrum of AD presentations. Patients may fluctuate between stages, present with atypical symptoms (e.g., primary progressive aphasia or posterior cortical atrophy), or experience overlapping phases that defy neat categorization. Moreover, the staging model does not account for *biomarker profiles*, such as levels of cerebrospinal fluid (CSF) tau and Aβ or PET imaging findings, which often precede clinical symptoms by years.

In response, newer models – such as the A/T/N classification system (Amyloid/Tau/Neurodegeneration) – have been proposed to complement traditional clinical staging by incorporating biological markers. While promising for research and precision medicine, these systems are not yet fully integrated into routine clinical practice, particularly in resource-limited settings.

Ultimately, the staging of AD must be understood not only as a diagnostic tool but also as a framework for planning care, guiding therapeutic interventions, and supporting caregivers. Multidisciplinary assessment – including neuropsychological, neurological, and functional evaluations – is essential for refining the staging process and tailoring patient-centered approaches.

TREATMENT STRATEGIES

Current treatment approaches for Alzheimer's disease (AD) remain largely palliative, aiming to mitigate symptoms and maintain quality of life, rather than altering the underlying disease process. This limitation reflects the complex and multifactorial nature of AD, which involves diverse pathological pathways including amyloid and tau deposition, neuroinflammation, oxidative stress, and synaptic dysfunction.

Pharmacological interventions are centered on two main classes of drugs: cholinesterase inhibitors (ChEIs) and NMDA receptor antagonists. ChEIs – such as donepezil, rivastigmine, and galantamine – function by inhibiting the breakdown of acetylcholine, a neurotransmitter crucial for memory and learning. These drugs have shown moderate efficacy in improving cognitive function and delaying institutionalization in patients with mild to moderate AD [20,21].

Memantine, an NMDA receptor antagonist, is indicated for moderate to severe stages of AD. It acts by modulating glutamatergic

neurotransmission and preventing excitotoxicity—a process implicated in neuronal death [22] Although it is often prescribed in combination with ChEIs, the additive benefit remains modest, and clinical outcomes are variable across individuals.

Historically, tacrine was the first ChEI approved for AD, but its clinical use was discontinued due to poor tolerability and a high incidence of hepatotoxicity [6] This illustrates an important challenge in AD pharmacotherapy: the balance between efficacy and adverse effects, especially in elderly populations with multiple comorbidities and polypharmacy.

From a critical standpoint, these therapeutic classes offer limited innovation and have remained largely unchanged for over two decades. Numerous drug candidates targeting amyloid production and aggregation have failed in advanced clinical trials, prompting a reexamination of the amyloid hypothesis as a therapeutic foundation [8]. These failures suggest that intervening at symptomatic stages may be too late, and that earlier, possibly preclinical, interventions are required—ideally guided by biomarker-based risk stratification.

In parallel, non-pharmacological interventions are gaining recognition as essential components of comprehensive care. These include cognitive stimulation, physical activity, nutritional strategies, and caregiver education [3]. While their mechanisms are not fully understood, such interventions have been associated with slower cognitive decline and improved mood and functional capacity. Importantly, they are low-risk and adaptable to different stages of the disease, making them suitable for integrated care plans.

Recent research advocates for multimodal treatment strategies, combining pharmacological, behavioral, and social interventions tailored to the individual's clinical profile. This approach aligns with the principles of precision medicine and recognizes the heterogeneity of AD in both symptomatology and progression. In this context, the rigid application of pharmacological protocols without psychosocial support is increasingly seen as insufficient and ethically questionable.

In sum, the current therapeutic landscape for AD remains constrained by the absence of disease-modifying agents and the late-stage diagnosis of most patients. While symptomatic treatments can provide meaningful benefits, they do not alter the trajectory of neurodegeneration. The future of AD treatment lies in the development of personalized, biomarker-driven, and stage-specific interventions – ideally initiated before the onset of irreversible brain damage.

CHOLINESTERASE INHIBITORS (I-ChE)

Cholinesterase inhibitors (I-ChE) constitute the pharmacological cornerstone in the symptomatic treatment of mild to moderate Alzheimer's disease (AD). These drugs act by inhibiting the enzyme acetylcholinesterase, thereby increasing the availability of acetylcholine (ACh) at synapses and enhancing cholinergic transmission—a neurotransmission pathway known to be severely compromised in AD due to the degeneration of basal forebrain cholinergic neurons.

Among the most commonly prescribed reversible inhibitors are *donepezil, galantamine,* and *rivastigmine*, which differ in pharmacokinetic profiles but share a similar mechanism of action. Clinical trials and meta-analyses have demonstrated that these drugs produce modest improvements in cognition, activities of daily living, and global clinical impression scales, particularly during the early and intermediate stages of the disease [21]. However, it is important to recognize that their impact on long-term disease progression is minimal, as they do not influence the underlying neurodegenerative mechanisms.

Therapeutic effects typically become clinically evident within 12 to 18 weeks of initiation, though individual responses vary. Notably, the benefit of I-ChE tends to plateau over time, with gradual loss of efficacy as the disease advances and cholinergic neurons continue to degenerate. This raises questions about the optimal duration of treatment and the criteria for discontinuation, which remain poorly defined in clinical guidelines.

Gastrointestinal side effects – such as nausea, vomiting, diarrhea, and abdominal discomfort – are among the most frequently reported adverse events and often limit tolerability, especially in frail elderly patients. Although generally considered safe, careful patient selection and monitoring are necessary to avoid complications, particularly in those with pre-existing gastrointestinal, cardiac, or hepatic conditions.

Critically, while I-ChEs have been widely adopted in clinical practice, their use has also been the subject of debate. Some authors argue that the modest cognitive gains do not always translate into meaningful functional or quality-of-life improvements, particularly when adverse effects are present. Furthermore, the expectation of benefit often leads to prolonged prescriptions without regular reassessment of therapeutic goals or efficacy, a practice that may burden both patients and healthcare systems.

In summary, cholinesterase inhibitors offer a limited but clinically relevant symptomatic benefit in AD management. Their role should be understood within a broader therapeutic context that includes non-pharmacological interventions and ongoing functional evaluation. The decision to initiate or maintain treatment must be individualized, guided by clear therapeutic objectives, patient and caregiver preferences, and regular assessment of risks and benefits.

TACRINE

Tacrine (1,2,3,4-tetrahydro-9-aminoacridine) was the first cholinesterase inhibitor approved for the treatment of Alzheimer's disease (AD), marking an important milestone in the pharmacological management of neurodegenerative dementias. Introduced in the early 1990s, tacrine offered initial optimism as a prototype of symptomatic therapy targeting the cholinergic deficits characteristic of AD. Its mechanism of action—reversible inhibition of both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE)—was associated with transient improvements in cognitive performance, particularly in attention and memory domains.

However, despite its historical significance, tacrine's clinical use was

rapidly limited due to *significant hepatotoxicity*, necessitating frequent liver function monitoring, as well as a *short half-life* that required multiple daily doses. These pharmacological limitations contributed to poor adherence and a narrow therapeutic window. Reports of elevated liver transaminases and the potential for irreversible liver damage led regulatory agencies and prescribers to abandon its use in favor of better-tolerated alternatives such as donepezil and galantamine [6].

From a critical perspective, the case of tacrine illustrates the challenges inherent in early drug development for AD: promising mechanisms of action may be undermined by unfavorable pharmacokinetics, low tolerability, or inadequate long-term efficacy. Moreover, tacrine's trajectory underscores the importance of post-marketing surveillance and pharmacovigilance in detecting adverse effects not fully evident in pre-approval trials.

Its rapid obsolescence also shifted the focus of clinical research toward the development of second-generation ChEIs with improved safety profiles, longer half-lives, and more selective enzyme targeting. In this sense, tacrine served not only as a therapeutic pioneer but also as a regulatory lesson in balancing innovation with patient safety.

Although tacrine is no longer in clinical use, it retains academic relevance as a reference compound in preclinical studies exploring cholinergic modulation. Additionally, its pharmacological scaffold has inspired the synthesis of hybrid molecules with dual activity on AChE and other targets, demonstrating its ongoing influence on medicinal chemistry research.

DONEPEZILLA, RIVASTIGMINE, AND GALANTAMINE

Donepezil, rivastigmine, and galantamine represent the second generation of cholinesterase inhibitors (ChEIs) and are currently among the most widely prescribed pharmacological agents for the symptomatic management of mild to moderate Alzheimer's disease (AD). These drugs share a common mechanism of action—prolonging the availability of acetylcholine (ACh) in the synaptic cleft by inhibiting acetylcholinesterase (AChE)—but differ in pharmacological profile, selectivity, and tolerability.

Donepezil is a selective, reversible AChE inhibitor with a long half-life that allows for once-daily administration. *Rivastigmine* inhibits both AChE and butyrylcholinesterase (BChE), and is available in oral and transdermal formulations. *Galantamine* not only inhibits AChE but also acts as an allosteric modulator of nicotinic receptors, potentially enhancing endogenous ACh release.

These agents have demonstrated statistically significant, though clinically modest, effects on cognitive function, behavioral symptoms, and activities of daily living. Their therapeutic effects are generally observed after 12 to 18 weeks of continuous use and are most pronounced during the early stages of the disease [8].

Dosing typically ranges from 5 to 10 mg/day for donepezil, with titration depending on the patient's response and tolerability. Despite their broad use, these drugs do not modify the underlying

neurodegenerative process and offer only symptomatic relief.

Adverse effects are relatively common and primarily gastrointestinal—nausea, vomiting, diarrhea, and abdominal discomfort. Rivastigmine's transdermal patch was developed in part to mitigate such effects and improve adherence. Additional side effects, such as weight loss, bradycardia, and insomnia, may occur, particularly in frail elderly populations or those with preexisting cardiovascular conditions.

Critically, the widespread use of these agents has raised questions regarding their long-term clinical relevance. While they may temporarily stabilize cognitive decline, the overall impact on disease progression and patient autonomy remains limited. Furthermore, the absence of regular reassessment protocols in clinical practice can lead to prolonged use beyond the point of efficacy, potentially exposing patients to adverse effects without therapeutic benefit.

In this context, ChEI therapy should be framed not as a default treatment, but as part of a broader, individualized care plan that includes non-pharmacological strategies and caregiver support. The decision to initiate, continue, or discontinue treatment must be based on a thorough evaluation of clinical response, side effects, and patient-centered outcomes.

In summary, donepezil, rivastigmine, and galantamine provide symptomatic benefit in AD and remain first-line options for early-stage management. However, their limitations—especially regarding long-term efficacy and tolerability – underscore the need for more effective, disease-modifying therapies and a shift toward precision-based, integrative treatment models.

MEMANTINE

Memantine is the only non-cholinergic pharmacological agent currently approved for the treatment of moderate to severe stages of Alzheimer's disease (AD). Unlike cholinesterase inhibitors, which aim to enhance deficient cholinergic transmission, memantine targets the *glutamatergic system* – a key neurotransmission pathway involved in learning and memory but also in excitotoxicity, a process implicated in neurodegeneration.

Memantine acts as a *low-affinity, uncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors*, selectively blocking pathological overactivation of glutamate signaling without disrupting normal physiological transmission. This mechanism is thought to confer neuroprotective effects by reducing calcium influx and subsequent neuronal damage [22].

Clinical trials have shown that memantine provides modest but significant improvements in cognition, behavior, and daily functioning in patients with moderate to severe AD. When used as monotherapy or in combination with cholinesterase inhibitors, it may also delay institutionalization and reduce caregiver burden. However, these benefits must be interpreted with caution, as effect sizes are small and highly variable across individuals.

Tolerability is one of memantine's strengths of mine. Compared to cholinesterase inhibitors, it is associated

with a lower incidence of gastrointestinal side effects. The most common adverse reactions include dizziness, headache, confusion, and constipation—generally mild and transient. This favorable safety profile makes memantine particularly suitable for use in frail elderly populations and those who cannot tolerate cholinesterase inhibitors.

From a critical standpoint, however, memantine shares the same limitation as other currently available drugs: it *does not modify disease progression*. Its therapeutic role is restricted to symptomatic relief in more advanced stages, and its prescription is often based more on clinical tradition than on solid long-term outcome data. Moreover, real-world studies suggest that the benefits observed in randomized trials may be attenuated in typical care settings, especially when comorbidities and polypharmacy complicate treatment adherence.

Recent efforts to enhance memantine's efficacy have included exploration of combination therapies, early intervention, and individualized dosing strategies based on pharmacogenomics. However, results remain preliminary, and memantine continues to serve primarily as an *adjunct therapy* in advanced disease management.

In conclusion, memantine occupies a distinct and important position within the pharmacological armamentarium for AD, offering a complementary mechanism of action and a well-tolerated profile. Yet its limited efficacy reinforces the broader need for disease-modifying agents and a paradigm shift toward early, personalized, and multifactorial interventions in Alzheimer's care.

SUPPORTIVE THERAPIES

ANTIDEPRESSANTS

Neuropsychiatric symptoms are prevalent across all stages of Alzheimer's disease (AD), with *depression, agitation, anxiety, hallucinations, and delusions* affecting approximately 60% of patients[23]. These symptoms not only exacerbate cognitive and functional decline but also significantly increase caregiver burden and the risk of institutionalization. As a result, the use of *antidepressants* has become a common pharmacological strategy in the broader management of AD.

Among the antidepressants most frequently prescribed are *selective serotonin reuptake inhibitors (SSRIs)* such as sertraline and fluoxetine. These medications are generally favored for their relatively favorable safety profile, especially compared to older classes such as tricyclic antidepressants, which are contraindicated in many elderly patients due to anticholinergic effects and cardiovascular risks.

Despite their widespread use, however, the *evidence supporting the efficacy of antidepressants in AD remains inconclusive*. While some studies have reported modest improvements in depressive symptoms, particularly in the early and moderate stages of the disease, randomized controlled trials and meta-analyses have shown mixed results. In some cases, placebo effects are comparable to those of pharmacological interventions, raising concerns about overprescription and limited clinical impact.

Furthermore, the *diagnosis of depression in the context of AD is itself a clinical challenge*. Overlapping symptoms—such as apathy, fatigue, and cognitive impairment—can obscure accurate assessment, leading to potential misdiagnosis and inappropriate treatment. This highlights the importance of using validated neuropsychiatric instruments tailored for dementia populations, and involving multidisciplinary teams in diagnostic and therapeutic decision-making.

In addition to uncertain efficacy, antidepressant treatment carries potential risks. Adverse effects such as gastrointestinal disturbances, hyponatremia, insomnia, and increased risk of falls and fractures must be carefully weighed, particularly in frail or polymedicated elderly individuals. Moreover, *antidepressants may interact with cognitive-enhancing medications,* complicating pharmacological regimens and increasing the need for clinical vigilance.

Given these considerations, many experts advocate for a *stepwise approach* to managing depression and related behavioral symptoms in AD. Non-pharmacological interventions—such as structured routines, physical activity, music therapy, and caregiver education—should be prioritized as first-line strategies. Pharmacological treatment should be reserved for moderate to severe symptoms that cause significant distress or risk, and always accompanied by careful monitoring and regular reassessment.

In conclusion, while antidepressants remain an important tool in the management of behavioral and psychological symptoms of dementia, their use should be cautious, individualized, and grounded in comprehensive clinical evaluation. Optimizing mental health care in AD demands not only judicious use of medications but also broader investment in psychosocial support systems for both patients and caregivers.

ANTIOXIDANTS

Oxidative stress is a well-documented component of Alzheimer's disease (AD) pathophysiology, contributing to neuronal damage through the accumulation of reactive oxygen species (ROS) and impairment of mitochondrial function. This recognition has led to increasing interest in the potential *neuroprotective role of antioxidants*, particularly in the early stages of AD, where oxidative damage may precede significant neuronal loss [24].

Among the most studied antioxidants in the context of AD are *vitamin E (α-tocopherol) and selegiline*, a monoamine oxidase B inhibitor with antioxidant properties. These agents are hypothesized to counteract free radical–induced cellular injury, stabilize neuronal membranes, and reduce inflammatory responses. Clinical trials have yielded mixed results: while some studies have shown that high-dose vitamin E may modestly delay functional decline in patients with mild to moderate AD, others have failed to demonstrate significant cognitive or behavioral benefits.

Moreover, concerns have been raised regarding the *safety of long-term antioxidant supplementation,* particularly at high doses. For example, excessive vitamin E intake has been

associated with an increased risk of hemorrhagic stroke and all-cause mortality in some populations. These findings underscore the need for cautious interpretation of early therapeutic enthusiasm and reinforce the importance of individualized treatment planning.

Despite these limitations, antioxidants continue to be used as *adjunctive therapies*, often as part of broader dietary or nutraceutical approaches to cognitive health. They are commonly included in over-the-counter supplements marketed for memory support, although many such products lack rigorous clinical evaluation. The disconnect between biochemical plausibility and clinical efficacy highlights a persistent challenge in translating antioxidant research into meaningful therapeutic strategies.

Recent advances have shifted the focus toward *targeted antioxidant strategies*, such as mitochondria-directed compounds and multifunctional molecules that combine antioxidant, anti-inflammatory, and metal-chelating properties. While promising, these approaches remain largely experimental and have not yet produced consistent clinical benefits in large-scale trials.

In summary, while oxidative stress is a relevant pathological mechanism in AD, antioxidant therapies have yet to prove effective as stand-alone treatments. Their clinical utility may lie in *supportive roles*, particularly in combination with lifestyle modifications, dietary interventions, and pharmacological treatments that address multiple dimensions of disease progression. Future research should focus on identifying subpopulations most likely to benefit and optimize delivery mechanisms that enhance bioavailability and target specificity.

IMMUNOTHERAPY

Immunotherapy has emerged as one of the most promising – and controversial – strategies for addressing the underlying neuropathology of Alzheimer's disease (AD). Unlike symptomatic treatments, immunotherapeutic approaches aim to *modify the disease process* by targeting the accumulation of amyloid-β (Aβ) plaques, a key pathological hallmark of AD. Both *active (vaccination-based) and passive (antibody-based)* immunotherapies have been explored, with varying degrees of success and safety concerns [21,25].

Early preclinical studies in transgenic mouse models demonstrated that immunization with Aβ-derived antigens could reduce plaque burden and prevent cognitive decline. These findings generated considerable enthusiasm and led to the first human clinical trials. However, one of the most notable early efforts – *the AN1792 vaccine trial* – was halted during Phase II due to the development of *aseptic meningoencephalitis* in approximately 6% of participants. Although postmortem analysis showed reduced amyloid pathology in some treated individuals, the risks associated with immune activation in the central nervous system raised major safety concerns [25,26].

Subsequent strategies have focused on *passive immunization*, involving the administration of monoclonal antibodies that selectively bind Aβ peptides to promote their clearance. Agents such as aducanumab, lecanemab, and donanemab have progressed through clinical trials with mixed outcomes. While some have shown evidence of reduced

amyloid burden on PET imaging, the *clinical benefits remain modest and inconsistently reproducible*, often limited to slowing cognitive decline by a few months. Moreover, risks such *as amyloid-related imaging abnormalities (ARIA)* – including cerebral edema and microhemorrhages—persist as significant barriers to widespread use.

From a critical standpoint, immunotherapy trials underscore a recurring challenge in AD research: *disconnects between biomarker effects and clinically meaningful outcomes*. Reduction in plaque load does not consistently translate into functional improvements, suggesting that amyloid removal alone may be insufficient once downstream neurodegeneration and tau pathology are established.

There is growing consensus that *early intervention* – ideally during the preclinical phase of AD – is essential to maximize the therapeutic potential of immunotherapy. This shift has placed greater emphasis on early biomarker-based diagnosis, including CSF and blood assays and amyloid PET imaging, to identify individuals at risk before the onset of irreversible damage.

In conclusion, while immunotherapy represents a critical advance in the pursuit of disease-modifying treatments for AD, its clinical application remains constrained by *limited efficacy, safety concerns, and the complexity of timing*. Continued research is needed to refine antibody specificity, improve delivery mechanisms, and integrate anti-amyloid approaches with complementary strategies targeting tau, neuroinflammation, and synaptic preservation.

COGNITIVE THERAPY

Cognitive therapy has emerged as a valuable non-pharmacological intervention in the management of Alzheimer's disease (AD), particularly in the early stages when residual cognitive functions can still be meaningfully engaged. Grounded in the principles of neuroplasticity, cognitive therapy aims to stimulate memory, language, executive function, and attention through structured activities that promote *mental engagement and functional autonomy* [27].

Unlike pharmacological treatments, which often offer only modest symptomatic relief, cognitive therapy focuses on *maintaining and optimizing remaining abilities*, delaying functional decline, and enhancing quality of life. Evidence from controlled trials and meta-analyses suggests that cognitive training may improve specific domains – such as working memory and verbal fluency – and has a positive impact on patients' emotional well-being and social participation [28].

Importantly, cognitive therapy is not a monolithic intervention; it encompasses a range of strategies, including *cognitive stimulation therapy (CST), reminiscence therapy, reality orientation, and task-based training*. These approaches can be tailored to the individual's cognitive profile, disease stage, and personal preferences, making them adaptable and person-centered.

Despite its benefits, cognitive therapy is not without limitations. The *heterogeneity in methodology, session frequency, and outcome measures* across studies complicates the interpretation of its efficacy. Moreover,

the long-term sustainability of cognitive gains remains uncertain, with some improvements diminishing after the intervention ceases unless followed by continued engagement and caregiver support.

Another critical issue is *access and equity*. While cognitive therapy is recommended in clinical guidelines, its implementation is uneven, particularly in low-resource settings where trained professionals and structured programs are scarce. Additionally, caregiver involvement is often essential for effective participation, which can place additional demands on already overburdened families.

Recent research has begun to explore *multimodal interventions* that integrate cognitive therapy with physical exercise, music therapy, digital tools, and pharmacological treatments, reflecting the multifactorial nature of AD. These combined approaches appear to offer synergistic benefits and align with current trends in personalized and integrative dementia care.

In conclusion, cognitive therapy holds significant promise as part of a holistic management strategy for AD. While not curative, it contributes meaningfully to patient well-being, functional maintenance, and caregiver resilience. To realize its full potential, future efforts must focus on improving standardization, expanding access, and embedding cognitive interventions within multidisciplinary care pathways.

5. Conclusion

Alzheimer's disease (AD) remains the most prevalent form of dementia among the elderly, currently affecting approximately 500,000 individuals in Brazil and an estimated 35.6 million worldwide. Despite extensive research efforts, the precise etiology of AD remains elusive. Multiple hypotheses—ranging from the amyloid cascade to tau pathology and cholinergic dysfunction—have been proposed, and it is increasingly likely that a multifactorial model will be necessary to fully explain the disease's onset and progression.

Currently, no clinical intervention is capable of preventing or curing AD. Available treatments provide only symptomatic relief and do not halt the underlying neurodegeneration. Nevertheless, accumulating evidence supports the role of *healthy lifestyle behaviors* – including physical activity, cognitive engagement, and a balanced diet – in *delaying disease onset* and maintaining functional independence for longer periods. In this context, public health strategies that promote preventive measures across the lifespan are of paramount importance.

Genetic testing may offer insights into individual susceptibility, especially for those with a family history of AD. However, the *clinical utility and ethical implications* of genetic screening remain debated, particularly in the absence of effective preventive therapies. For some, genetic knowledge may foster proactive health decisions; for others, it may induce unnecessary anxiety, especially when actionable options are limited. As such, genetic counseling must accompany any form of testing to ensure informed and supported decision-making.

While the *development of disease-modifying therapies* continues to accelerate, especially in the fields of immunotherapy, monoclonal antibodies, and precision medicine, the clinical

impact of these innovations remains modest and often restricted to specific subpopulations. More inclusive, longitudinal, and translational studies are needed to bridge the gap between molecular findings and real-world outcomes.

It is also important to acknowledge the *limitations of the present review*. As a narrative synthesis, the selection and interpretation of studies are subject to potential bias, and the scope of analysis may not capture the full heterogeneity of the AD research landscape. Future reviews could benefit from systematic methodologies and meta-analytical approaches to more rigorously evaluate the effectiveness of emerging interventions.

In sum, while advances in AD research are encouraging and offer hope for improved quality of life, the absence of a definitive cure calls for *a balanced perspective*, grounded in scientific rigor, ethical reflection, and an ongoing commitment to interdisciplinary collaboration.

6. Conflict of Interest Statement

The authors declare that there is no conflict of interest in the development and writing of this work.

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