IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
July 2023 Vol.:27, Issue:4

Advancements in Understanding and Managing Alzheimer's disease: A Comprehensive Review

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 30 June 2023
Accepted: 20 July 2023
Published: 30 July 2023

HUMAN JOURNALS
ijppr.humanjournals.com

Keywords: Alzheimer's disease, Amyloid-Beta plaques, Biomarkers, Immunotherapies, Lecanemab.

ABSTRACT

This review article provides a comprehensive overview of Alzheimer's disease (AD), a prevalent and challenging neurodegenerative disorder affecting the aging population worldwide. The article synthesizes recent advancements and breakthroughs in AD research, covering its pathological features, genetic and environmental factors contributing to its onset and progression, and emerging diagnostic tools and biomarkers for early detection and accurate diagnosis. It also explores a wide range of therapeutic strategies, from disease-modifying approaches to symptomatic relief, including pharmacological interventions, immunotherapies, lifestyle interventions, gene therapy, and deep brain stimulation. The importance of multidisciplinary care and the role of caregivers in supporting individuals with AD are also addressed, emphasizing the significance of psychosocial interventions and community resources. By consolidating knowledge in the field, the article aims to inspire further research into innovative approaches for prevention, early detection, and effective management of AD, ultimately aiming to alleviate the burden of this disease and provide hope for a brighter future for those affected.

INTRODUCTION

Alzheimer's disease (AD) is an increasingly prevalent neurodegenerative disorder that poses significant challenges to individuals, families, and healthcare systems worldwide. With the aging population on the rise, the impact of AD has become a major public health concern. In recent years, there has been a surge in research aimed at unraveling the complex mechanisms underlying this debilitating condition and developing effective strategies for its prevention, diagnosis, and treatment.

This review article aims to provide a comprehensive overview of the current state of knowledge regarding Alzheimer's disease. By synthesizing the latest advancements and scientific breakthroughs, we intend to offer readers an in-depth understanding of the multifaceted aspects of this condition, ranging from its pathological features to its clinical manifestations and therapeutic approaches.

The article begins by elucidating the neuropathological hallmarks of AD, including the accumulation of amyloid-beta plaques and neurofibrillary tangles, and their impact on cognitive function. We will explore the intricate interplay between genetic and environmental factors that contribute to the onset and progression of the disease, shedding light on the evolving landscape of AD etiology and risk factors.

In addition, we will delve into the emerging diagnostic tools and biomarkers that hold promise for early detection and accurate diagnosis of AD. Advances in neuroimaging techniques, cerebrospinal fluid analysis, and blood-based markers offer new avenues for identifying individuals at high risk and monitoring disease progression.

Furthermore, the article will explore the growing array of therapeutic strategies being investigated, ranging from disease-modifying approaches to symptomatic relief. We will discuss the role of pharmacological interventions, immunotherapies, lifestyle interventions, and emerging technologies such as gene therapy and deep brain stimulation, all aimed at mitigating cognitive decline and improving the quality of life for individuals with AD.

Moreover, this review will address the importance of multidisciplinary care and the role of caregivers in supporting individuals living with AD. We will highlight the crucial role of psychosocial interventions, caregiver education, and community resources in providing comprehensive care and support networks.

By consolidating the wealth of knowledge and ongoing research in the field, this review article aims to facilitate a deeper understanding of Alzheimer's disease and inspire further investigations into innovative approaches for prevention, early detection, and effective management. Ultimately, our collective efforts and advancements in understanding AD hold the potential to alleviate the burden posed by this devastating disease and offer hope for a brighter future for those affected by it.

1. Neuropathological Hallmarks of Alzheimer's disease

The "positive" lesions, such as amyloid plaques and cerebral amyloid angiopathy, tau hyperphosphorylation and neurofibrillary tangles, and glial responses, and "negative" lesions, such as neuronal and synaptic loss, are the neuropathological hallmarks of Alzheimer disease (AD).

1.1 Amyloid plaques

Beta-amyloid peptide deposits outside of cells are known as amyloid plaques, which represent a unique pathology of Alzheimer's. Based on their shape and positive or negative staining with Congo Red or Thioflavin-S, amyloid plaques are frequently divided into diffuse and dense-core categories(1). The bigger protein known as amyloid precursor protein, which is present in the lipid membrane surrounding nerve cells, is the source of beta-amyloid proteins. Every individual constitutes beta-amyloid, which the body naturally eliminates before it can endanger the brain. However, it is not eliminated in those who have Alzheimer's disease, and the beta-amyloid proteins subsequently clump or cling together to create a plaque that cannot be broken down.(2) Up to 20 years before symptoms occur, beta-amyloid protein clumps start to form in the brains of people with Alzheimer's disease. These plaques gradually start to develop in other regions of the brain that control cognitive function.

1.2 Tau Hyperphosphorylation and Neurofibrillary Tangles

Tau, a microtubule-associated protein, generally resides on the axon and performs a critical function in the brain by stabilizing and attaching to microtubules that assist transport of chemicals and nutrients from the cell body to the axon and dendrites. However, up to 20 years prior to the development of symptoms in people with Alzheimer's disease, tau is changed and forms neurofibrillary tangles within nerve cells(3). This change involves tau hyperphosphorylation, misfolding, and aggregation in addition to tau translocation to certain somatodendritic compartments. This misfolded, hyperphosphorylated tau forms intraneuronal

clumps called neurofibrillary tangles that obstruct the transport system of the neuron, impairing synaptic transmission.

Beta-amyloid plaques were shown to be associated with Alzheimer's disease, which made it possible to use amyloid PET scans to detect the disease earlier. More recently, it became possible to target and eliminate such plaques to slow down clinical decline(4).

1.3 Cerebral amyloid angiopathy

Cerebral amyloid angiopathy, which is characterized by beta-amyloid deposits in the tunica media of leptomeningeal arteries, cortical capillaries, tiny arterioles, and medium-sized arteries in the posterior parts of the brain, is another neuropathological hallmark of Alzheimer's disease. Nearly every brain of an Alzheimer's patient has some degree of cerebral amyloid angiopathy(5), which is frequently mild. Vascular wall thinning in those with severe cerebral amyloid angiopathy may eventually result in lobar hemorrhage.

1.4 Glial responses

The number of glial cells in the brain is typically 10 to 1 greater than the number of neurons. They can take many different forms, such as microglia and astrocytes. The interaction between glial cells and neurons is essential for brain function. Since glia is closely related to all types of neuropathological events, they are essential for both the normal and dysfunctional functioning of the central nervous system. Thus, glial responses are necessary for the development and outcome of neurocognitive and neurodegenerative illnesses, including Alzheimer's.

Beta-amyloid plaques are one of the trash, debris, and protein buildup that is consumed by microglia in healthy brains(6). However, microglia cells do not effectively remove poisons and debris from the brain in people with Alzheimer's disease. Similarly to this, in people with Alzheimer's disease, astrocytes are not signaled to remove and eliminate the remaining plaque buildup and cellular debris.

1.5 Negative lesions associated with Alzheimer's disease

Negative lesions such as losses of neurons and synapses are neuropathological indicators of Alzheimer's disease. In people with Alzheimer's disease, damaged and dying neurons spread across the brain(7), disrupting connections between neural networks and perhaps shrinking certain brain regions.

For the brain to work properly, synapses must grow and shrink dynamically. However, the mechanics of neural plasticity are disturbed in Alzheimer's patients, which ultimately leads to a net loss of synapses(8). Early pathological signs of Alzheimer's disease include synaptic loss, which is thought to be caused by beta-amyloid and tau pathology.

2. Cognitive decline

Cognitive decline is a common characteristic of Alzheimer's disease (AD), primarily recognized as memory impairment. Although the specific cause of AD is unknown, the cognitive deficiencies that characterize the condition are linked to unique neuropathological abnormalities in the limbic and cortical systems, which are crucial for language, learning, memory, and visuospatial processing. The extent of cognitive dysfunction depends on the distribution of neuropathological changes in the cerebral cortex and limbic system(9), affecting learning, memory, language, and visuospatial skills. Similar symptoms are seen in related disorders such as Lewy body dementia (LBD) and Parkinson's disease dementia (PDD), as they share some pathological features. Vascular dementia (VaD) shows varying cognitive deficits, with some functions severely impaired and others relatively spared. Cholinesterase (ChE) inhibitors, used to raise acetylcholine levels in the brain, are licensed for treating AD symptoms and have shown benefits in related dementias. Various physiological measures, like regional cerebral blood flow and cerebrospinal fluid levels of ChE enzymes, act as markers for the clinical efficacy of ChE inhibitors. However, cognitive assessment remains the primary measure of efficacy in clinical studies. Large-scale trials have demonstrated the effectiveness of ChE inhibitors in treating cognitive impairments associated with AD. Ongoing studies aim to compare symptomatic efficacy and effects on disease progression between different dementia types(10).

3. Epidemiology

Alzheimer's disease (AD) is a major public health concern with a significant impact on individuals, families, and healthcare systems worldwide. The epidemiology of AD reveals a rising trend in prevalence and incidence as the global population ages. The estimated prevalence of AD varies across regions, but it is consistently higher in older age groups. Currently, approximately 50 million people are living with AD globally, and this number is projected to triple by 2050(11).

Advanced age is the most significant risk factor, with the risk doubling approximately every five years after the age of 65. Genetic factors also play a role, particularly the APOE ε4 allele, which increases the risk of late-onset AD(12). Lifestyle factors such as low educational attainment, sedentary behavior, unhealthy diet, smoking, and cardiovascular risk factors have been linked to an increased risk of AD(13). There have also been reports of racial differences in AD prevalence. In comparison to older Caucasians, older African Americans and Hispanics have a higher prevalence of AD. This is partly due to poorer educational attainment and a higher frequency of cardiovascular comorbidities, while other genetic and environmental factors are also likely to be important(14–16). The prevalence of AD is influenced by gender. Women make up over two-thirds of all AD patients. According to ADAMS, 16% of women and only 11% of males live with dementia after the age of 71. While it is true that women generally live longer than men, this does not fully account for the disparity. Additionally, it's likely that social, hormonal, and genetic factors—such as the fact that women in their 70s and 80s have lower educational and vocational performance than men—have a substantial impact(17).

According to systematic review estimates from 2010, the frequency in China rose with age, from 0.2% in those aged 55–59 to 48.2% in people aged 95–99. After adjusting for age, the duration of the research, and area (urban vs. rural), a different study carried out in China discovered that women were similarly twice as likely to suffer AD dementia than men (prevalence ratio, 2.37, 95% CI 1.90, 2.96, p 0.0001)(18).

In studies conducted in the USA, Europe, Japan, and China, the incidence of clinically confirmed AD dementia ranges from 2.0 to 16.8 new cases of AD per 1000 person-years. The large variance in incidence may be partially explained by changes in the age ranges of the study populations that were included, the demographics of the countries analyzed the study periods, and the operational diagnosis of AD dementia. For instance, a meta-analysis looking into the prevalence of clinical Alzheimer's disease in Europe found that prevalence increased with age (cases of clinical AD per 1000 person-years: 65-74 years, 3.4; 75-84 years, 13.8; C 85 years, 35.8)(19–22). (Ref. Table No. 1)

Table 1 Prevalence of clinical AD dementia

Author, year	Country (year)	Population	Patients with AD dementia, %	Patients with AD dementia, n
Fiest 2016 (20)	Multicountry	Aged C 60 years	Period prevalence 3.04% (95% CI 1.56, 5.91), Point prevalence 4.02% (95% CI 2.91, 5.56)	NR
Takizawa 2015 (21)	France (2009)	Aged C 60 years	3.0%	NR
	Italy (2000)	Aged C 64 years	4.2%	
	Spain (2009)	Aged C 75 years	6.4%	
	UK (NR)	NR	4.9%	
	USA (2001)	Aged C 70 years	6.8%	
Niu 2017 (18)	Europe[b]	Varied	5.1%	NR
Ciu 2020 (20)	China (2019)	Aged C 60 years	3.8% (95% CI 2.14, 5.47)[c]	NR
Chan 2013 (22)	China (2010)[d]	Aged C 55 years	55–59 years: 0.2%	5.69 million
			60–64 years: 0.6%	
			65–69 years: 1.3%	
			70–74 years: 2.7%	
			75–79 years: 5.5%	
			80–84 years: 10.4%	
			85–89 years: 18.5%	
			90–94 years: 30.9%	
Zhao 2020 (23)	China[e]	NR	95–99 years: 48.2% 4.0% (95% CI 3.0, 4.0)[e]	NR
Brookmeyer 2018 (24)	USA (2017)	NR	NR	6.08 million[f]

4. Pathophysiology

The buildup of aberrant neuritic plaques and neurofibrillary tangles is a hallmark of Alzheimer`s disease.

Plaques are tiny lesions that are spherical in shape and include an extracellular amyloid beta-peptide core around by increased axonal terminals. Amyloid aggregates that cause neuronal toxicity are caused by an increase in beta-amyloid levels. Beta-amyloid favors abnormal APP breakdown over the production of aggregated fibrillary amyloid protein. In Alzheimer`s disease, amyloid buildup surrounds meningeal, cerebral, and grey matter arteries.

In neurons, a protein called tau forms fibrillary intracytoplasmic formations known as neurofibrillary tangles. Tau is hyperphosphorylated in Alzheimer`s disease and forms tau clumps because of extracellular beta-amyloid aggregation(25,26).

It's important to note that the stages can vary from person to person, and not all individuals with Alzheimer's will experience every stage. Here are the typical stages of Alzheimer's disease:

1. Stage 1: Preclinical Alzheimer's disease

This stage occurs before any noticeable symptoms manifest. In this early phase, the person may have abnormal levels of certain proteins in their brain, such as amyloid beta and tau, which are considered hallmarks of Alzheimer's disease. However, they do not show any evident cognitive or memory issues, and their daily activities are not affected. At this point, the disease can only be detected through research or specialized medical tests.

2. Stage 2: Mild Cognitive Impairment (MCI)

During this stage, mild cognitive decline becomes noticeable. The individual may experience lapses in memory, have trouble finding the right words, or misplace items more frequently. These cognitive changes might be apparent to the person themselves or their close family and friends, but they do not interfere significantly with daily life or independence. It's worth noting that not everyone with MCI will progress to Alzheimer's disease.

3. Stage 3: Mild Alzheimer's disease

In this stage, the symptoms become more evident and can affect the person's ability to function independently. Memory deficits worsen, and they may start to forget recent events,

faces, or conversations. Difficulty with problem-solving, planning, and organization might also become apparent. Individuals may experience challenges with work, social activities, and other complex tasks. Behavioral changes, such as irritability or apathy, can begin to emerge.

4. Stage 4: Moderate Alzheimer's disease

As the disease progresses, the symptoms become more severe. Memory loss and cognitive impairment become much more pronounced. Individuals may struggle to recall significant personal details, have difficulty with basic arithmetic, and may not recognize close family members or friends. Performing everyday tasks, such as dressing or cooking, becomes challenging without assistance. Behavioral changes might include agitation, delusions, and wandering.

5. Stage 5: Moderately severe Alzheimer's disease

At this stage, individuals require substantial assistance with daily activities. They may lose the ability to dress appropriately or maintain personal hygiene. Their speech might become more limited, and they may struggle to express themselves clearly. Personality changes can be quite noticeable, and they may experience anxiety or restlessness.

6. Stage 6: Severe Alzheimer's disease

In the severe stage, individuals lose the ability to communicate coherently and may no longer recognize their own family members. They require constant supervision and assistance with all activities of daily living. Motor skills decline, and they may have difficulty walking or sitting without support. Incontinence becomes a significant issue, and they are vulnerable to various infections due to a weakened immune system.

7. Stage 7: Very severe Alzheimer's disease

This final stage is characterized by a severe decline in physical and cognitive function. Individuals lose the ability to speak, make meaningful connections, or respond to their environment. They become bedridden and require 24/7 care. As the disease progresses, they may also lose the ability to swallow, leading to complications such as pneumonia. Ultimately, Alzheimer's disease can be fatal, often due to these secondary conditions.

5. Biomarkers

AD-specific antemortem biomarkers used in the context of careful clinical characterization has aided to establish levels of certainty for an AD pathology that was impossible when the only means of verification of the underlying pathology was at autopsy. In addition, the use of these biomarkers has enhanced our knowledge of AD. Combining amyloid and tau biomarkers with non-specific biomarkers of neurodegeneration was at the foundation of the research framework for AD proposed in 2018. The A-T-N approach is intended to classify individuals in the AD spectrum. Diagnostic algorithms are being developed to provide recommendations on the most meaningful combination and to order these biomarkers according to the specific clinical situation.

5.1 ***Imaging Biomarkers*** The initial imaging modalities used to diagnose individuals with cognitive impairment were CT, FDG-PET, and MRI, but their lack of specificity or sensitivity for Alzheimer's disease made them challenging to incorporate into a conceptual model. The emergence of A-PET imaging in 2004 defined the roles of FDG-PET and MRI as neurodegenerative markers, while CT was superseded for research purposes by MRI. The 2011 National Institute of Ageing - Alzheimer's Association criteria established a diagnostic paradigm based on amyloid and neurodegeneration biomarker profiles to characterize the connection with Alzheimer's disease in people throughout the cognitive spectrum(27,28).

In the initial evaluation of a person with suspected cognitive impairment, a structural MRI or CT is required. MRI is frequently used as a first step to rule out other causes of cognitive impairment and assess macroscopic brain atrophy as a reflection of tissue loss. Hippocampal atrophy(29), which is related to Alzheimer's disease, can also occur in people with cognitive impairment due to hippocampal sclerosis, frontotemporal lobar degeneration, or cerebrovascular illness, as well as in people who don't have cognitive impairment(30).

FDG-PET imaging has revealed a pattern of temporal-parietal and hippocampal hypometabolism that precedes volume loss in the same areas and is very typical of Alzheimer's disease. FDG-PET may be especially beneficial after A-PET imaging in those with raised A for staging, short-term prediction, and differentiating between AD variations, as well as in people without elevated A on PET scans for the diagnosis of non-AD illnesses(31,32).

Quantitative A-PET imaging offers data on the extent and location of amyloid accumulation, allowing for the staging and monitoring of A accumulation and the detection of A in the earliest stages of AD. Longitudinal A-PET investigations show a very low rate of A accumulation, with a lag period of 10-20 years between the commencement of accumulation and the onset of symptomatic cognitive impairment(33,34).

The introduction of tau-PET into clinical research has changed the A-PET acceptable use criteria and the formulation of tau-PET appropriate use criteria. Tau-PET abnormalities are highly predictive of later cognitive impairment in both asymptomatic and symptomatic people and sensitive to the regional spread of tauopathy over time(35,36).

5.2 ***CSF Biomarkers*** Decreases in A42 and increases in phosphorylated tau are widely accepted CSF biomarkers for Alzheimer's disease (AD). These biomarkers are recognized for their diagnostic value and are used clinically in Europe and the US(37). Normalization using CSF A40 or p-tau levels have shown greater diagnostic efficacy than A42 alone. p-tau181 is a specific biomarker for tau pathology, while t-tau is a general marker of neurodegeneration. Both p-tau181 and t-tau have minimal value in illness severity staging(38).

New CSF biomarkers, such as neurogranin, SNAP25, and SYT1, are on the verge of acceptance, but their specificities for AD have not yet been established. Non-AD biomarkers, such as cerebrovascular pathology, -synuclein, and TDP43, can be useful in developing diagnostic frameworks for other neurodegenerative illnesses and identifying co-occurrence in people with aberrant AD biomarkers(39).

5.3 ***Blood-based biomarkers*** for Alzheimer's disease are quickly developing, but their effect sizes and other statistics for distinguishing AD or MCI from controls are smaller than those for CSF biomarkers, and additional research is needed to properly grasp the relationships with more validated CSF and PET biomarkers. The development of blood-based biomarkers for A42, p-tau181, p-tau217, and the neurofilament light chain will considerably increase the ability to include or exclude AD as an etiology(40). Based on a mass spectroscopy assay, one blood-based assay measuring the A42/A40 ratio was approved in the United States and the European Union in 2020. With an area under the curve value of 0.88 (95% CI 0.82-0.93), this assay closely corresponds with A-PET status. Blood-based biomarkers should still be regarded as screening tools rather than diagnostic biomarkers(41).

6. Therapeutic approaches

The amyloid hypothesis suggests that the accumulation of amyloid-beta protein in the brain plays a critical role in the development of Alzheimer's disease. Therapies aimed at reducing the production or enhancing the clearance of amyloid-beta are being explored. These approaches include monoclonal antibodies that target amyloid-beta, beta-secretase (BACE) inhibitors that reduce the production of amyloid-beta, and gamma-secretase modulators that alter the production of specific forms of amyloid-beta.

7. Disease-modifying approaches

Without relying on specific ideas about the etiology of the disease, one AD therapeutic option is to shield or repair the neurons that are damaged by the disease process. Treatments for neurotrophic factor offer such a method. However, focusing on certain targets within a fictitious disease cascade may result in disease modification that is more successful. Two key disease mechanism-based theories(42), which have been researched for more than ten years, are predicated on the idea that tau and amyloid-(A) play a role in the pathogenesis of AD. Senile plaques, one of the main pathogenic aspects of AD, are primarily made up of AD. The primary component of neurofibrillary tangles, another defining AD pathology, is tau(43).

7.1 Amyloid Beta (Aβ) targeting

In theory, finding tiny molecules that can enter the brain and disrupt Aβ-Aβ peptide connections would seem appealing. The identification of nucleation and deposition inhibitors has been studied and assayed using a variety of test methods during the past ten years. Only a small number of aggregation inhibitors, though, have entered clinical trials(44).

The most direct approach in anti-amyloid therapy is reduction of Aβ42 production. Aβ is generated proteolytically from a large precursor molecule, APP, by the sequential action of two proteases, β-secretase and γ-secretase. A third protease, α-secretase, which competes with β-secretase for the APP substrate, can preclude the production of Aβ by cleaving the peptide in two. This outline immediately points to three strategies to reduce Aβ: inhibition of β-secretase, inhibition of γ-secretase and stimulation of α-secretase.

7.1.1 α secretase stimulation:

Early research has shown that cell-surface receptors can trigger the α -secretase pathway, which reduces the amount of APP substrate that is available for Aβ production(45)

However, it must be kept in mind that more APP enters the α than the β-secretase route, thus the desired decrease in Aβ requires a significant alteration in the metabolism of both APP and a number of other membrane proteins that are substrates for α-secretase. There are no documented negative effects of this strategy(46).

In the context of M1 muscarinic receptor agonists, which may theoretically serve as cognitive enhancers and may possibly have an impact on disease progression if they have a significant effect on brain Aβ production, α-secretase stimulation has been thoroughly studied. Small research found that giving M1 agonists to AD patients reduced the amount of A42 in their CSF fluid. The question of whether M1-specific agonists can be produced without activating other muscarinic receptors and resulting in negative side effects will be crucial to answer(47).

7.1.2 ¥ - secretase inhibition:

The main focus of worldwide efforts in anti-amyloid therapy has been directed toward inhibiting the production of Aβ42 using secretase inhibitors. This approach, similar to protease inhibitors developed for angiotensin-converting enzyme and HIV protease, was recognized early on to hold significant potential even before the identification of β- and γ-secretase.

Since 1992, it has been evident that cells naturally expressing β- and γ-secretase enzymes secrete substantial amounts of Aβ when genetically modified to overexpress APP(48). To find compounds that reduce Aβ production without causing toxicity, numerous companies screened vast collections of compounds using large-scale assays.

However, this screening approach mainly identified inhibitors of the γ-secretase pathway, which potently blocked the production of all Aβ isoforms. Through medicinal chemistry programs, drug-like molecules were developed, showing the ability to reduce both plasma and soluble brain Aβ levels in mice shortly after a single administration(49,50). Bristol-Myers Squibb announced the initiation of Phase II clinical trials for the first γ-secretase inhibitor in 2001.

Information on the results of this trial remains unpublished, and other companies have been tight-lipped about the development status of their γ-secretase-inhibitor programs. An exception is Lilly, which recently published data from a 6-week Phase II trial of a functional γ-secretase inhibitor, demonstrating a significant decrease in plasma Aβ concentration at a

well-tolerated dose during the short trial, but no such reduction was observed in cerebrospinal fluid(51).

While progress was made in understanding the biology of γ-secretase, it remains an unusual transmembrane protease complex composed of at least four proteins—presenilin, nicastrin, anterior pharynx (APH1), and presenilin enhancer 2 (PEN2). Despite the successful production of observable γ-secretase activity in yeast through overexpression of these proteins, reconstitution from purified components and the active site structure remain elusive(52).

Identifying the γ-secretase components and utilizing gene-targeted models led to significant advancements, identifying several γ-secretase substrates beyond APP, such as NOTCH1, DELTA1, JAG2, ERBB4, and others. Studies indicated the essential role of γ-secretase cleavage of NOTCH1 during embryonic development, with subsequent analyses showing the effects of γ-secretase inhibitors on thymocyte differentiation, known to be NOTCH1-dependent(53).

A new development emerged in 2001, revealing that certain NSAIDs, when present in very high concentrations, can modulate γ-secretase cleavage, reducing Aβ42 production while increasing the production of a smaller, less aggregation-prone isoform called amyloid-β. Interestingly, this effect did not block Notch cleavage at the 49 positions of Aβ, suggesting direct modulation of γ-secretase or its substrate by these NSAIDs, independent of their known targets COX1 and COX2. The mechanism behind this phenomenon remains to be fully understood(54). As of now, the generation of therapeutically useful potent γ-secretase inhibitors remains uncertain.

7.1.3 β secretase inhibition: However, with the discovery of presenilin as a potential component of γ-secretase and concerns over the inhibition of Notch cleavage, the focus of interest shifted back to the other protease involved, β-secretase. This enzyme, now a subject of numerous studies seeking a molecular target in the amyloid pathway, was identified in 1999 as beta-site APP-cleaving enzyme 1 (BACE1), a transmembrane aspartic protease along with its homolog BACE2(55), forming a new branch of the pepsin family. While the physiological role of BACE2 and its substrates remains unknown, it does not appear to play a significant role in APP processing and thus is not considered a drug target for Alzheimer's disease (AD).

BACE1, being a type I transmembrane protein, cleaves APP at the active site on the luminal side of the membrane. Studies in tissue culture and animal models indicated that β-secretase is expressed in all tissues, with higher levels observed in neurons of the brain. Recent publications reported increased β-secretase activity in sporadic AD(56,57), but its role in the pathogenic cascade remains to be fully established.

To assess potential side effects of pharmacological β-secretase inhibition, BACE1 knockout mice were analyzed, prompted by the lethal phenotype observed in presenilin-knockout mice and concerns about toxicity related to γ-secretase inhibitors. The knockout mice showed a deficiency in Aβ production, validating BACE1 as β-secretase and revealing the absence of compensatory mechanisms for β-secretase cleavage in mice. Detailed analyses of the knockout mice demonstrated normal gross morphology, anatomy, tissue histology, hematology, and clinical chemistry. Gene expression profiling and phenotypic assessment of older BACE1-knockout mice(58) also did not show any global compensatory changes in neural gene expression, with no structural alterations observed in any organ, including neural tissues.

Initial behavioral analysis of BACE1-knockout mice showed no obvious deficits in basal neurological and physiological functions, but they exhibited a timid and less exploratory behavior associated with increased serotonin turnover in the hippocampus, suggesting a possible role of BACE1 in neurotransmitter turnover or release. Further studies on the behavior of BACE1-knockout mice are needed to fully understand the more subtle cognitive and behavioural consequences of β-secretase ablation(59).

Overall, the absence of Aβ production and distinct pathology in BACE1-knockout mice provides encouraging prospects for β-secretase drug development, particularly when compared to the challenges faced in γ-secretase inhibition. Nevertheless, the development of inhibitors for β-secretase is proving to be challenging, partly due to the large active site revealed by X-ray crystal structures(60).

8. Role of pharmacological intervention

Patients with concomitant depression or anxiety may benefit from the use of pharmacological interventions. Treating depression and anxiety in persons with MCI or dementia due to AD differs from the treatment of the general population as drugs with an anti-cholinergic pharmacology should be avoided and lower doses of psychoactive drugs should be used.

Antidepressants such as citalopram or sertraline may be effective for both anxiety and depression and can be used safely in patients with cognitive impairment(61).

Comorbid sleep disorders, such as obstructive sleep apnoea, should be treated using oral appliances or nasal devices that create expiratory positive airway pressure; patients with dementia may have difficulty adapting to sleeping with a mask. Because people with dementia have trouble explaining their pain, treating pain in those with cognitive impairment can be difficult. There are also strict restrictions on the use of drugs other than acetaminophen and NSAIDs because many potent analgesics may result in drowsiness or impaired attention(62).

Only three cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—and the NMDA receptor antagonist memantine are available as pharmacological treatments for AD. While donepezil is exclusively licensed in the USA for severe dementia, cholinesterase inhibitors are approved in the USA and Europe for mild to moderate dementia caused by AD but not for people with MCI. A minority of people may experience nausea, vomiting, loose stools, or appetite loss when using cholinesterase inhibitors. Muscle cramps, headaches, and unpleasant dreams are less typical side effects. Memantine is only approved in the USA for moderate to severe dementia caused by AD, and its effects are likewise rather subdued. Memantine has a few negligible side effects(63). On the underlying biology of AD, neither memantine nor cholinesterase inhibitors have any appreciable effects.

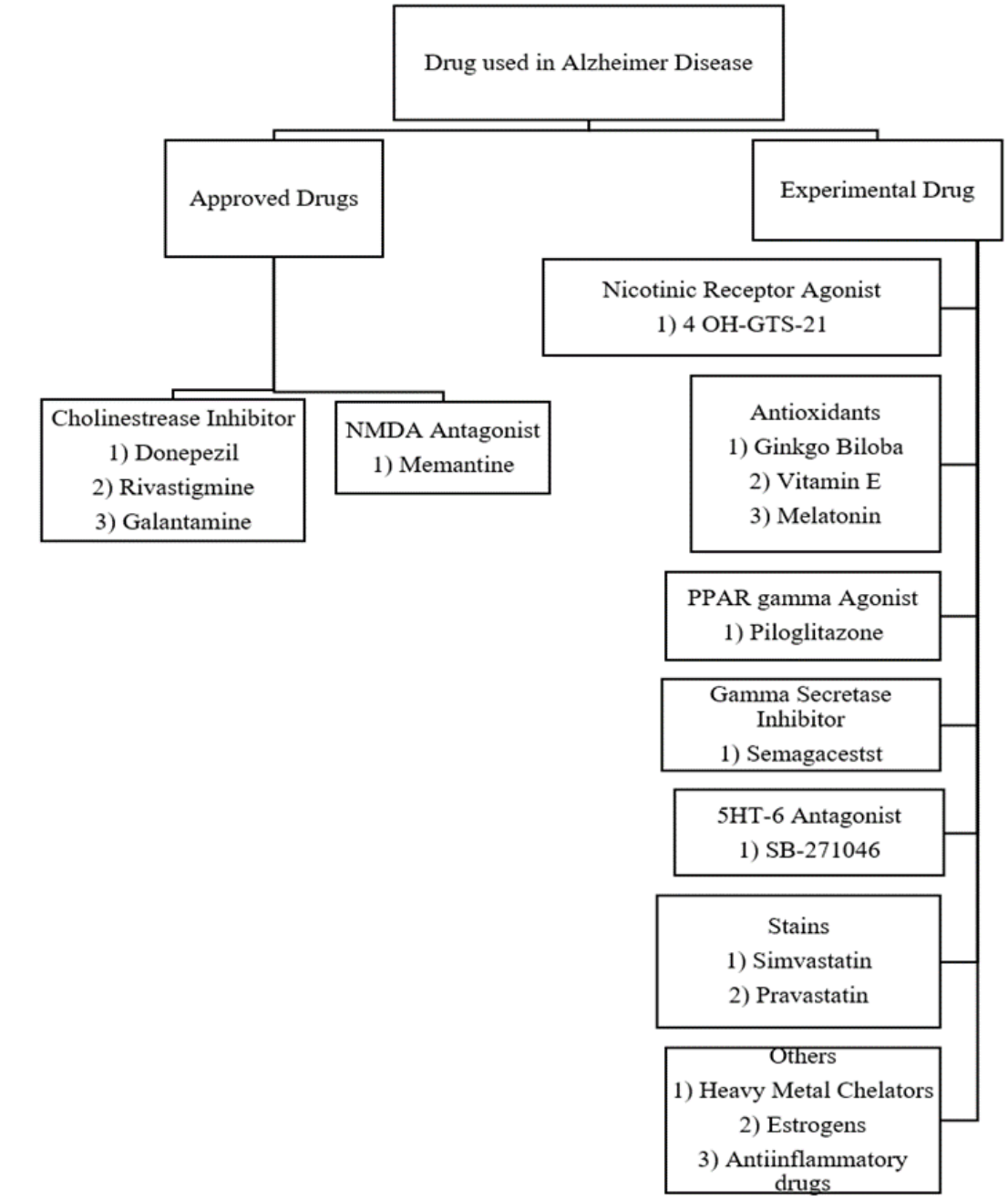

Figure no. 1

Aducanumab and lecanemab are experimental drugs targeting amyloid-beta plaques in Alzheimer's disease. Aducanumab, developed by Biogen, has shown positive effects on cognitive outcomes in phase III trials and received FDA accelerated approval. Lecanemab, developed by Eisai and Biogen, has also demonstrated a significant reduction in plaques and cognitive decline in phase II trials, with further investigations ongoing. Both drugs hold potential as disease-modifying therapies, but further research is needed to fully understand

their efficacy and safety. These advancements offer hope for individuals with AD and their families in slowing down the progression of this devastating disease(64,65).

Frightening hallucinations, delusions leading to socially disruptive behavior, or physically aggressive behavior always require pharmacological intervention. Pimavanserin may be the only drug specifically indicated for the treatment of behaviors collectively known as agitation: frightening hallucinations and delusions, physically aggressive behavior, and other socially disruptive behaviors. Atypical antipsychotics, such as quetiapine, are generally the mainstay of treatment for agitation in people with dementia(66). Drug-induced parkinsonism in dementia is an unacceptable consequence of attempts to control agitation. (Ref. Fig No. 1)

9. Immunotherapy for Alzheimer's disease

The significant attention towards anti-amyloid immunotherapy for Alzheimer's disease (AD) followed Elan Corporation's groundbreaking publication(67). The study revealed a reduction in amyloid pathology in a transgenic mouse model of AD after vaccination with aggregated Aβ42, without causing noticeable damage to the neuropil. The authors proposed that Aβ42 immunization triggers a specific immune response that effectively clears Aβ, leading to a marked reduction in pathology in both young and old animals. Subsequent studies using different transgenic mouse models also replicated the reduction in amyloid pathology(68).

Previous research had demonstrated the resolution of peripheral light chain-associated amyloid deposits through antibody-mediated methods. However, in the Aβ vaccination experiments, it was challenging to determine the direct effects of injected Aβ aggregates, the role of the adjuvant, or the involvement of a T-cell response. The Elan group reported that administering mouse antibodies against human Aβ directly to a mouse amyloid model replicated the effects of vaccination on the amyloid burden. However, when mouse splenocytes were examined in vitro, there was no evidence of a T-cell proliferative response to Aβ, indicating that a T-cell response might not be necessary for reducing amyloid plaques.

Furthermore, investigations showed that the animals had no abnormal leakage at the blood–brain barrier (BBB), and there was no extensive BBB damage, even in older mice with substantial amyloid burden, in a different transgenic model. The efficacy of amyloid reduction through passive immunization was also observed in a different APP transgenic model called the APP23 mouse, originally developed by Novartis(69). However, treatment with an anti-Aβ antibody in this model led to a twofold increase in haemosiderin-positive

cells (a marker of microbleeds) compared to the baseline, as this mouse model of cerebral amyloid angiopathy is prone to spontaneous hemorrhagic strokes(70).

10. Lifestyle Intervention

Lifestyle intervention has emerged as a promising approach to prevent or delay the onset of Alzheimer's disease (AD). Research suggests that certain lifestyle factors, including physical activity, a healthy diet, mental stimulation, quality sleep, stress management, heart health, social engagement, and avoiding smoking and excessive alcohol, play a crucial role in reducing the risk of AD. By implementing these lifestyle changes early and maintaining them over time, individuals can promote brain health and potentially lower their risk of developing AD. While lifestyle intervention cannot guarantee immunity against AD, it offers a proactive and accessible strategy to support cognitive function and overall well-being(71). Consultation with healthcare professionals can help tailor these lifestyle changes to individual needs and circumstances.

11. Emerging technologies for diagnosing AD

Emerging technologies are transforming Alzheimer's disease (AD) diagnosis by leveraging advancements in imaging, biomarker analysis, and artificial intelligence. These include neuroimaging techniques like PET and MRI, which visualize AD-related brain changes, and CSF analysis, which identifies abnormal proteins. Blood-based biomarkers, retinal imaging, wearable devices, AI, and smartphone apps offer less invasive and accessible approaches for early AD detection and monitoring. However, rigorous clinical validation is crucial before integrating these tools into routine clinical practice. Their adoption could enable early and accurate AD diagnosis, leading to improved management and treatment for those impacted by this devastating disease(72).

12. Gene therapy for diagnosing AD

Target protein	Function AD	Vector	Site of expression	Effect
NGF	Neurotrophic, synaptic plasticity	MLV (Ex vivo)	B.F. (Fibroblasts)	No acceleration of AB deposition
		MLV (Ex vivo)	N.B. (Fibroblasts)	Trophic effect on cholinergic neurons and cognitive improvements
		MLV (Ex vivo)	Rostral-caudal Ch4 (Fibroblasts)	Protection against brain atrophy
		MLV (Ex vivo)	B.F.	Protection against age-related degeneration of cholinergic innervations
		MLV (Ex vivo)	Fimbria-fornix (Fibroblasts)	Restorative after lesions
		MLV (Ex vivo)	N.B.M. (Fibroblasts)	Clinical trial. Trophic effect on cholinergic neurons and cognitive improvements
		rAAV	Intraseptal/Medial septum	Protection of lesion-induced degeneration
		rAAV	B.F.	Cholinergic trophic effect and amelioration of memory function
		rAAV-2	Septum	Neurotrophic, increased synaptic activity
BDNF	Neurotrophic, synaptic plasticity	Lentivirus	Entorhinal cortex	Neurotrophic, cognitive improvements
Neprilysin (membrane-bound form)	AB degradation, neuroprotection	rAAV	Hippocampus, dentate gyrus	Reduced soluble AB and AB burden
(membrane-bound		Lentivirus	F.C. and	Reduced AB burden

form)			Hippocampus	
(membrane-bound form)		HSV	Hippocampus	Reduced AB burden
(membrane-bound form)		Lentivirus (Ex vivo)	Hippocampus (Fibroblasts)	Neuroprotection by cleaved NPY and reduced AB burden
(secreted form)		Lentivirus	Hippocampus	Reduced AB burden, and behavioral improvement
(membrane-bound form)		Lentivirus	F.C. and Hippocampus	Reduced soluble AB, reduced AB burden, and improved memory function
(membrane-bound form)		Lentivirus (Ex vivo)	Blood system (bone marrow cells)	Reduced AB burden
(membrane-bound form)		rAAV-8	Hind limb muscle	Reduced AB burden
ECE	AB degradation	rAAV-5	Hippocampus, Cortex	Reduced AB burden
Cathepsin B	AB degradation	Lentivirus	Hippocampus	Reduced AB burden
APOE2	Lipoprotein metabolism, AB burden	Lentivirus	Hippocampus	Reduced AB levels, and reduced AB burden
BACE1	AB generation	Lentivirus (siRNA)	Hippocampus	Reduced soluble AB. and reduced Ap burden
APP	AB generation	HSV (siRNA)	Hippocampus	Reduced AB burden

Refer: Nilsson P, Iwata N, Muramatsu SI, Tjernberg LO, Winblad B, Saido TC. Gene therapy in Alzheimer's disease–potential for disease modification. Journal of cellular and molecular medicine. 2010 Apr;14(4):741-57.

13. Deep brain stimulation

Deep brain stimulation (DBS) is a neurosurgical technique showing promise as a potential treatment for Alzheimer's disease (AD) and related dementias. It involves implanting electrodes into specific brain regions to deliver electrical stimulation, aiming to enhance memory and cognitive function affected by AD-related neurodegeneration. Targeting brain regions like the fornix and nucleus basalis of Meynert, DBS aims to modulate neural activity and promote cognitive improvement. While research is ongoing, DBS has shown mixed results in clinical trials, and its mechanisms of action and long-term effects require further study. DBS is considered an invasive procedure, and careful consideration of potential risks and benefits is essential. While not a cure for AD, DBS offers a potential adjunctive therapy for cognitive decline, warranting further investigation and refinement(73).

14. Role of caregivers in supporting patients living with AD

Social support and care in the community play a crucial role in enhancing the quality of life for individuals with Alzheimer's disease (AD). Family support, joining support groups, community programs, memory care facilities, home care services, education and training, respite care, and community engagement all contribute to a supportive environment for those living with AD and provide much-needed assistance and relief for caregivers. By fostering understanding and compassion, the community can help individuals with AD lead meaningful lives while navigating the challenges of the disease(74).

15. Future prospects

In recent years, our understanding of Alzheimer's disease (AD) has significantly improved, but it remains incomplete. Next-generation genetic studies have identified crucial pathways in AD pathogenesis, leading to the discovery of novel drug targets. A more sophisticated view of the preclinical phase now considers b-amyloid, tau, and inflammation as part of the cellular phase of AD progression. However, challenges in target engagement and patient selection have complicated some clinical trials, particularly in later-stage AD patients, where amyloid may not be the most appropriate target(75). Ongoing trials have shown promising preliminary results in earlier-stage AD patients with aducanumab, reducing the amyloid burden and delaying disease progression. Other studies are investigating strategies to clear amyloid or prevent its pathological forms using BACE or c-secretase inhibitors/modulators during the preclinical phase. Studies in familial AD cohorts are identifying at-risk individuals

through genetic screening, and alternative targets like tau pathology are gaining interest in various clinical trials(76).

Affordability and equitable access to disease-modifying therapies are crucial considerations. Accurate identification of at-risk individuals for disease prevention is essential, and the development of specific biomarkers using PET, CSF, and blood has provided valuable insights into AD pathways. Long-term follow-up will enable the creation of risk models and biomarkers for early or mid-life interventions(77). In the future, personalized risk scores combining genetic data and health measures could guide targeted treatments based on an individual's disease stage. Such advances offer hope for more effective and individualized AD prevention and management.

Result and discussion

This comprehensive review article successfully provides an in-depth overview of Alzheimer's disease, covering its pathological features, clinical manifestations, and therapeutic approaches. By synthesizing the latest advancements and scientific breakthroughs, the article offers readers a deep understanding of the multifaceted aspects of this neurodegenerative disorder. It sheds light on the intricate interplay between genetic and environmental factors contributing to AD's onset and progression and explores promising emerging diagnostic tools and biomarkers for early detection and accurate diagnosis. Additionally, the article delves into the growing array of therapeutic strategies, ranging from disease-modifying approaches to symptomatic relief, including pharmacological interventions, immunotherapies, lifestyle interventions, and emerging technologies like gene therapy and deep brain stimulation. The importance of multidisciplinary care and the crucial role of caregivers in supporting individuals with AD are also highlighted, emphasizing the significance of psychosocial interventions and community resources. Overall, this review article successfully fulfils its aim of facilitating a deeper understanding of Alzheimer's disease and inspiring further investigations into innovative approaches for prevention, early detection, and effective management, offering hope for a brighter future for those affected by this devastating disease.

CONCLUSION

In conclusion, Alzheimer's disease is a pressing global health concern due to its increasing prevalence and the challenges it poses to individuals, families, and healthcare systems. The surge in research efforts aimed at unraveling the complex mechanisms underlying AD and developing effective strategies for prevention, diagnosis, and treatment is promising. This review article provides a comprehensive overview of the current state of knowledge, covering the neuropathological hallmarks of the disease, the interplay of genetic and environmental factors, and emerging diagnostic tools and biomarkers for early detection. The exploration of therapeutic strategies, from disease-modifying approaches to symptomatic relief, offers hope for improving the quality of life for those affected by AD. Additionally, the emphasis on multidisciplinary care, caregiver support, and psychosocial interventions highlights the importance of comprehensive care networks. By consolidating research findings and inspiring further investigations, we aim to deepen our understanding of AD and pave the way for innovative approaches to prevention and management, ultimately aiming to alleviate the burden of this devastating disease and bring hope for a brighter future for those impacted by it.

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