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A Brief Review on Alzheimer's Disease

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ABSTRACT

The most devastating and progressing neurological ailment, Alzheimer's disease has no known cure. The decline in memory and cognitive ability has an impact on the person's quality of life. It is a type of dementia, representing 60-70% of case. The pathophysiology of Alzheimer's disease is still unknown because it is complicated, multifaceted disorder. However, the research identifies pathophysiological indicators (such as Amyloid beta aggregation and Phosphorylated tau aggregation) and biomarkers for illness early detection. Researchers have proposed a number of hypotheses for the onset of Alzheimer's disease, including those involving amyloid, tau, cholinergic pathways and oxidative stress. The pathophysiological causes (including hereditary aspects), diagnostic techniques and approved medication therapy plans are discussed in this review article. Additionally, several methods for developing novel treatments that treat diseases as well as the medications ongoing clinical trials were reviewed.

INTRODUCTION

The most prevalent kind of dementia in older individuals, accounting for 60–80% of cases, is Alzheimer's disease (AD). It is a fatal neurological illness that worsens over time and progresses from episodic memory issues to a gradual reduction in cognitive function overall. Alzheimer's disease cannot be cured with drugs at this time, however there are several options for managing the symptoms. Even today, the greatest unmet medical need in neurology is AD [1]. Around 50 million people were predicted to be impacted by AD worldwide in 2020. By 2050, there will be 152 million people, with this number predicted to doubling every five years[2]. Around 10% of all adults over 65 and 50% of those over 85 have AD. It ranks as the fifth most common cause of death for elderly adults. Age, genetics, and environmental variables all play a role in the complicated disease known as AD. These elements may cause AD or make it more likely to occur. There are two divisions in AD genetics. First, there is the rare autosomal dominant version known as "early-onset AD (EOAD)," and second, there is the most frequent variant known as "late-onset AD (LOAD)," which affects 90% of the population and first appears in later life [3]. Memory loss or difficulty finding things are the first symptoms of Alzheimer's disease. Language, thinking, decision-making, visuo-spatial function, attention, and orientation memory loss are among the symptoms that worsen over time[4]. The pathology of AD is complicated by the interaction of several biochemical changes, including modifications in the metabolism and deposition of amyloid precursor proteins, phosphorylation of tau (t) protein, oxidative stress, mitochondrial dysfunction, impaired energy, membrane lipid dysregulation, neurotransmitter pathway, and inflammation [5].

History

Auguste D. and Alois Alzheimer: In 1907, German psychiatrist and neuropathologist Dr. Alois Alzheimer was the first to describe a disorder that would eventually be known as Alzheimer's disease (AD). Alois Alzheimer first described the case of Auguste D, a 51-year-old woman with "a peculiar disease of the cerebral cortex" in his seminal year of 1906. Auguste had progressive memory loss, language impairment, behavioral symptoms (hallucinations, paranoia, and delusions), disorientation, and psychosocial impairment[6]. Alzheimer's biopsy of Auguste's brain after her death in 1906 found scattered cortical atrophy, "particular changes in cortical cell clusters," the accumulation of fat bodies in blood

vessels, among other conditions. Alzheimer found nerve fibre plaques and tangles, which scientists named beta amyloid plaques and neurofibrillary tau tangles in the 1980s [7].

Epidemiology

AD is a significant public health issue that has a detrimental effect on the social, economic, and health aspects of society in the US and many other countries across the world [8]. Millions of Americans suffer from Alzheimer's disease and other types of dementia. According to projections, there will be 88 million people in the United States aged 65 and older by 2050, up from 58 million in 2021, which would result in a sharp rise in the number and proportion of people living with Alzheimer's or another dementia. In 2021, 1.72 million Americans aged 65 to 74, 2.25 million Americans aged 75 to 84, and 2.27 million Americans aged 85 and above are anticipated to have Alzheimer's disease, according to newly revised statistics. Alzheimer's dementia affects 5.3% of people between the ages of 65 and 74 and 34.6% of those over the age of 85. Its prevalence increases with age. Although it is far less common and its frequency is unclear, Alzheimer's dementia can also affect people under the age of 65 [9, 10].

Types of Alzheimer disease

1) There are two forms of AD, based on when the signs and symptoms first appeared. Genetics play a role in both types.

a) Early Onset Alzheimer Disease (EOAD) or Familial AD: Patients between the ages of 40 and 60 are affected by this illness. It is a rare inherited disorder that only affects 5% of the population. Down syndrome patients are at a significant risk for AD. Early onset of Alzheimer's is characterized by a higher prevalence of plaque development, tangle formation, decrease of brain volume, and myoclonus, a type of muscular twitching and spasm.

b) Late Onset Alzheimer Disease (LOAD) or Sporadic AD: This illness is most prevalent in those over 60 and has a slower progression and memory loss. The main causes of the illness include the growth of senile plaques, neurofibrillary tangles, decreased levels of Aβ, and an increase in tau and p-tau.

2) Based on their severity or state of disease, it is classified as 3 types viz,

a) Mild Alzheimer’s disease

b) Moderate Alzheimer's disease

c) Severe Alzheimer's disease[11,12].

Neuropathological changes in AD

Three major categories can be used to describe the neuropathological alterations in AD that offer information about the development of the illness and its symptoms.

- Positive lesions, also known as lesions associated with accumulation, are observed in the brain tissue of AD patients and are characterised by the accumulation of neurofibrillary tangles, amyloid plaques, neuropil threads, dystrophic neurites, and other deposits.
- Negative lesions (loss-related lesions) are characterised by significant atrophy from synaptic, neuropil, and neuronal loss.
- As a result of neuroinflammation, oxidative stress, and damage to cholinergic neurons, inflammation and plasticity (associated to reactive processes that cause neurodegeneration) occur [13, 14].

Senile plaques and neurofibrillary tangles are also important markers of AD. Although these two are not specific to AD and can be detected in other human neurodegenerative illnesses as well as in clinically normal people; they are the key neuropathological hallmarks of AD [15].

Senile plaques:

Senile plaques are extracellularly deposits of beta-amyloid peptide (Aβ) with different morphological forms such as neuritic, dense-cored, diffuse, classic and compact type plaques. Transmembrane amyloid precursor protein (APP) is converted into beta amyloid peptide (Aβ) through the proteolytic cleavage of enzymes such as β-secretase and α-secretase [16]. These enzymes break down APP into a number of amino acid fragments, in which Aβ40 and Aβ42 are directly involved in AD pathogenesis. These particular Aβ42 monomers join together with insoluble fibrils to form Aβ plaques, which are toxic to neurons [2].The formation of these thicker amyloid plaques causes microglial activation, reactive astrocytosis, cytokine production, and damage to axons and dendrites in the hippocampus, amygdala, and cerebral cortex. Cognitive deficits, synaptic and neuronal loss, and general brain atrophy are the final effects of these structural changes [17, 4].

Neurofibrillary Tangles (NFT)

NFT are abnormal filaments of hyperphosphorylated tau that twist around one another to form paired helical filaments (PHF) and accumulate in the cytoplasm of neuroperikaryotic cells, axons, and dendrites, where they lead to the loss of cytoskeletal microtubules and proteins associated with tubulin [17]. The hyperphosphorylated tau protein is a prominent component of NFTs in AD patients, and its evolution can be seen in the NFT's morphological stages, which comprises of

i. Pre-tangle phase NFTs, in which phosphorylated tau proteins accumulate in the somatodendritic compartment without the formation of PHF.

ii. Mature NFTs: Filament aggregation of tau protein and relocation of the nucleus to the peripheral part of soma.

iii. Extracellular tangles (ghost NFTs stage) are the result of neuronal death brought on by an abundance of filamentous tau protein that is partially proteolytically resistant [18].

Synaptic loss:

Memory impairment is typically seen in the early stages of AD and is caused by damage in the synaptic areas of the neocortex and limbic system. Axonal dystrophy, loss of dendritic spines, oxidative stress, mitochondrial damage, and other processes are minor fractions of the mechanisms causing synaptic loss [19].

Hypothesis of Alzheimer disease

Although Alzheimer's disease has been around for more than a century, its fundamental pathological aetiology is still not fully known, and there is no treatment that prompts a natural cure. Many theories are put up for the pathophysiology of AD given our existing knowledge. The most popular among these are the oxidative theory, cholinergic hypothesis, mitochondrial cascade hypothesis, tau hypothesis, and amyloid cascade hypothesis [20].

1. Amyloid beta hypothesis

The most widely used and researched of the aforementioned theories is the amyloid cascade theory. According to some experts, the hallmark of AD pathophysiology is the presence of amyloid plaques [2]. The non-amyloidogenic and amyloidogenic pathways are thought to be involved in the cleavage of APP. Alpha(α)-secretase and gamma(γ)-secretase are responsible

for cleaving the APP in the non-amyloidogenic route, producing soluble non-toxic peptides. The beta (β)-secretase and gamma (γ)-secretases in the amyloidogenic pathway cleave the Aβ40 and Aβ42 amino acid peptides, respectively, into two major insoluble Aβ forms that are toxic and prone to producing fibrils, which cause neurodegeneration [21].

This theory attributes a cascade of sequence starting from the changes in Aβ metabolism that includes increase in total Aβ production, increase in the Aβ42/ Aβ40 ratio, reduced Aβ degradation/clearance. Following this, A42 deposits begin to oligomerize and diffuse, which has a mild negative impact on synaptic function and triggers inflammatory reactions (including activation of microglia and astrocytes) and the development of amyloid plaques[20].These structural alterations eventually cause oxidative injury, neuronal injury, impaired neuronal ionic balance, progressive synapse loss, and gross brain atrophy. When Aβ is present in high concentrations, tau protein appears to oligomerize and become hyperphosphorylated, which results in widespread neuronal malfunction and cell death linked to neurotransmitter shortage [22]. Tau protein aggregation, the last stage in the aetiology of the disease, has also been linked to Aβ accumulation, according to research [23].

2. Tau hypothesis

The level of amyloid deposits did not correlate with the severity of cognitive impairment in AD, and sporadic cases of Alzheimer's disease were not properly described by the amyloid cascade hypothesis. This gave rise to the tau hypothesis, which contends that the development of neurofibrillary tangles and the deposition of tau protein constitute the fundamental pathophysiology of AD [6]. The crucial part of the pathogenesis of AD is played by tau protein. The microtubule-binding tau protein is the main focus of the tau hypothesis. The building and maintenance of the neuronal microtubule network, which is necessary for intracellular transport, is the principal function of tau proteins, which are mostly found in neurons [24].

In addition to extracellular beta amyloid aggregation, hyperphosphorylation of tau proteins results in pathogenic tau protein, which then assembles to form twisted paired helical filaments known as "neurofibrillary tangles" [23]. Before spreading to the entire cerebral cortex, they first appear in the hippocampus. NFTs decrease the quantity of tau that is available to bind microtubules and create a malfunction in the cytoskeleton's structural and regulatory functions, which in turn causes abnormalities in the morphology, axonal transport,

and synaptic functions of neurons, which ultimately result in neurodegeneration or cell death [25].

3. Mitochondrial cascade hypothesis

Swedlow and Khan were the first to put up the mitochondrial cascade theory in 2004, which proposed that mitochondrial failure was the main factor contributing to the deposition of Aβ, development of neurofibrillary tangles (NFT) and synaptic degeneration in AD [26]. The mitochondrial cascade hypothesis makes a number of conceptual leaps by assuming that the physiological mechanisms underlying Alzheimer's disease (AD) and brain ageing are identical, as this can't be the case given that AD mitochondrial dysfunction is systemic and cannot be a result of neurodegeneration. The implication of this concept was that amyloidosis, tau phosphorylation, and cell cycle re-entry may all be influenced by mitochondrial dysfunction in AD brains. Platelets, mitochondria, fibroblasts, and the brain are among the organs associated with AD that have been found to have mitochondrial dysfunction. The α-Ketoglutarate dehydrogenase complex, pyruvate dehydrogenase complex, and cytochrome oxidase are the three mitochondrial enzymes that are reported to be faulty with decreased activity. AD patient's brains have normal levels of cytochrome oxidase, but specialised testing reveals that the enzyme's structural makeup is different. It has also been proposed that elements like oxidative stress and protease malfunction make mitochondrial dysfunction more likely [27, 28].

4. Oxidative stress hypothesis

With its existence as both a cause and an effect of inflammatory processes generally acting as the features of neurodegenerative disorders, there is compelling evidence that oxidative stress caused by Amyloid beta (Aβ) is essential for the pathogenesis and progression of Alzheimer's disease (AD) [20]. The brain is an organ with high energy requirements, which are met by the mitochondrial oxidative phosphorylation process, which produces highly reactive oxygen species. Oxidative stress is caused by a surplus highly reactive oxygen species. As a result, the defence mechanisms are weakened, which leads to an accumulation of reactive oxygen species and makes neurons more vulnerable to excitotoxic injury. However, this mechanism is dependent on the Aβ fragments, whose accumulation encourages the decline of copper and iron levels in the brain. This is a crucial element in oxidative stress, which in these circumstances encourages DNA damage [29]. Aging and dementia result in an increase in the quantity of excitatory glutamate and aspartate neurotransmitters, which activate N-methyl-D-

aspartate (NMDA) receptors. A steady and hazardous rise in intraneural calcium is caused by a surge in glutamate in dementia, which causes excessive calcium channel opening. Additionally, it stimulates the activity of enzymes involved in metabolic processes such as lipid peroxidation and the production of free oxygen radicals [30].

5. Cholinergic hypothesis

The cholinergic hypothesis is one of the AD-related pathways that have received extensive research. It was listed as the original pathophysiology theory for AD [20]. According to the cholinergic theory, acetylcholine neurotransmitter production in neurons is diminished in AD, which leads to the disease. The cholinergic theory, developed more than 30 years ago, postulates that the malfunctioning of acetylcholine-containing neurons in the basal forebrain significantly contributes to the cognitive deterioration in AD patients. In the early stages of the illness, cholinergic neurons in the entorhinal cortex and basal nucleus are both destroyed, but in the final stages of AD, more than 90% of the cholinergic neurons in the basal nucleus are gone [31]. This theory states that cholinergic neuron degeneration in the basal forebrain area and the loss of central cholinergic transmission cause the onset of cognitive and non-cognitive symptoms in AD patients. The acetyl transferase concentration, which is essential for the production of acetylcholine transmitters in the cortex and hippocampus regions, has significantly decreased and the meynert basal nucleus has lost cholinergic neurons. These two factors are also features of the cholinergic hypothesis. A lack of Ach, nor-adrenaline, and serotonin is caused by the neurons malfunction and cell death in certain transmission network, which is supported by the cholinergic hypothesis. Despite the fact that 4 of the 5 approved pharmaceuticals work on this mechanism, the cholinergic hypothesis has not received widespread support because treatments for acetylcholine deficit have not been highly successful [32].

Genetic mechanisms involved in AD

Over the years, genetic variables have been identified as having a significant impact on AD development [33]. 70% of instances of AD have genetic causes; the majority of EOAD cases are inherited in an autosomal dominant manner, and mutations in the dominant genes Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), Presenilin-2 (PSEN-2), and Apolipoprotein E (ApoE) are linked to AD[34].

1. Amyloid precursor protein (APP)

The transmembrane protein of type-I APP is encoded on chromosome 21, which is cleaved by α, β and γ-secretase to liberate Aβ and other proteins. Thirty mutations in the APP gene have been identified, of which 25 are linked to AD and result in the accumulation of Aβin high concentrations. On the other hand, A673T works as a preventive mechanism against AD by reducing the secretion of Aβ, Aβ-40, and Aβ-42 [35].

2. Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2)

PSEN-1 and PSEN-2 genes are also the autosomal dominant form of EOAD located on chromosomes 14 and 1. PSEN-1 and PSEN-2 are homologous, sharing 67% of their similarities, with the N-terminus and the hydrophilic region being different. PSEN-1 has more than 200 mutations, but PSEN-2 has less than 40[36]. A crucial role in the synthesis of Aβ from APP is played by PSEN-1, a key protein that activates the γ-secretase complex. PSEN-1 gene mutations lower the levels of Aβ40 while increasing the ratio of Aβ40/Aβ42. On the other hand, PSEN-2 mutations are uncommon and have a little impact on the synthesis of Aβ [37].

3. Apolipoprotein E (ApoE)

The synthesis of myelin and optimal brain function depend on the apolipoprotein (apoE), a glycoprotein that is extensively expressed in the liver, brain astrocytes, and certain microglia. It functions as a receptor-mediated endocytosis ligand for cholesterol-containing lipoprotein particles[38]. The ApoE gene, which has the three isoforms ApoE2, ApoE3, and ApoE4, is found on chromosome 19. In contrast to ApoE2 and ApoE3 alleles, which are linked to a lower risk and protective impact, ApoE4 alleles represent a significant risk factor for both EOAD and LOAD. The cerebral amyloid angiopathy (CAA), which serves as a diagnostic for AD[39], is caused by ApoE4 and plays a significant role in the deposition of Aβ as senile plaques. Although the existence of just one ApoE4 allele does not always result in Alzheimer's disease (AD), people who have two alleles are 90% more likely to get the disease[40].

4. ATP binding cassette transporter A_1 ($ABCA_1$)

The vast ABC transporter family, which includes apolipoproteins-AI (APOAI) and apolipoprotein E (APOE), and ATP-binding cassette transporter A1 (ABCA1), is crucial in

controlling cholesterol efflux into the bloodstream and the brain. Additionally, ABCA1 acts as a mediator for the production of high density lipoprotein (HDL) and preserves the stability of ApoE limitation. Humans with Tangier disease is caused by mutations in ABCA1 have low plasma levels of high-density lipoprotein (HDL) and APOAI, an accumulation of cholesterol in tissues and the development of AD [41].

5. Cluster in gene (CLU) and Bridging Integrator 1(BIN1)

The unique risk factors for LOAD were found to be the cluster in gene (CLU) and Bridging Integrator 1 (BIN 1) genes. CLU is a prospective biomarker of AD because it was found on chromosome 8 and is elevated in the cortex, hippocampus, cerebrospinal fluid (CSF) and plasma in AD patients. Through interactions with Aβ, CLU either performs a neurotoxic role by inhibiting Aβ clearance or a protective role by encouraging Aβ clearance[42]. The Bin-Amphiphysin-Rvs (BAR) adaptor protein BIN1 is primarily involved in the generation of membrane curvature and other cellular processes related to endocytosis. BIN1 was identified as the second most significant risk factor for LOAD after ApoE, which is a key player in the generation of Aβ as well as a modulator of tau and NFT pathology[43].

Diagnosis

The first clinical diagnostic criteria were established in 1984, and subsequent methods were created by the Diagnostic and Statistical Manual of Mental Disorders (DSM IV), the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), and the Alzheimer Disease and Related Disorders Association (ADRDA) in collaboration [44]. For the purpose of analysing cognitive function, memory evaluation, and language impairment, neuropsychological and psychometric tests are used in the initial diagnosis stage. The various tests performed are listed below.

Cognitive assessment	• Mini-Mental State Examination (MMSE) • Information Memory Concentration Test (IMC)
Memory assessment	• Delayed Recall Test • Rey Auditory Verbal Learning Test (RAVLT) • Memory Logic of Wechsler Memory Scale (WMS)
Language assessment	• Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) test • Boston Naming Test (BNT) • Neuropsychological Battery Test (NEUROPSI) • Cambridge Assessment Test
Attention Assessment	• Random Letter Test • Digit Extension Test (Direct and Reverse) • Trail Making Test
Constructive Skills	• Clock Drawing Test (CDT) • Geometric designs of Consortium to Establish a Registry for Alzheimer Disease (CERAD) neurocognitive battery test
Speech Skills	• Voice analysis using Artificial intelligence [45]

Typically, the diagnosis is made after a thorough physical, neurological, and cognitive assessment of the patient. However, pathological illness diagnosis achieves an accuracy of 70–90%. The most accurate way to diagnose AD is to look for amyloid plaques and neurofibrillary tangles (NFT) in the brain during an autopsy [20]. Neurodegeneration and amyloidosis of the brain are both detected by the laboratory blood test. The blood test includes a complete blood count (CBC), the level of serum urea, creatinine, thyroxine (T4), albumin, liver enzymes (SGOT, SGPT, gamma GT), vitamin B12, calcium, a serological test for syphilis, and a comprehensive HIV serology test is required in patients under the age of 60 [46]. The following neuroimaging studies are performed to integrate a stage of Alzheimer disease.

Imaging Techniques	Assessment
Computed Tomography (CT) Single Photon Emission Computed Tomography (SPECT)	Subdural hematoma, cerebrovascular lesions, tumour or normal pressure hydrocephalus Differentiate Alzheimer and Dementia through lewy bodies
Magnetic Resonance Imaging (MRI) Hippocampal Functional MRI	Gross cerebral cortical Atrophy Measures excitability of neurons and shows topographic pattern
Positron Emission Tomography (PET) Fluorodeoxyglucose (FDG) PET	β-amyloid plaque markers in cerebral neuronal tissue Measures Cerebral Metabolic rate of glucose and distinct phenotype of dementia
Magnetic Resonance Spectroscopy (MRS)	Identify changes in MicroRNA (MiRNA) due to deregulation of genes APP, $BACE_1$, MAPT
Electroencephalography (EEG) Quantitative EEG (qEEG)	Estimate brain hyper excitability during sleep Early detection of neuronal dysfunction and correlate molecular and imaging biomarkers
Magnetoencephalography (MEG)	Measures disruption of neuronal rhythm and predicts conversion from MCI to AD [47]

Further the diagnosis accuracy is increased with specialised PET scan using PET ligands such as Florbetapir, Florbetaben and Flutemetamol. It is not widely used as it is expensive. Fluorescent probes such as Thioflavin T (Th T) and 1-anilino-8-naphthalene sulphonate (ANS) are used in Near-Infrared (NIR) for detection and imaging of amyloidβ (Aβ) in brain. Amyloid imaging agent is [^{11}C]-Pittsburgh compound B (PiB) binds to Aβ aggregates that differentiate between AD and healthy individuals [48].

Biomarkers

A biomarker is a measure of a biological molecule found in blood and other body tissues that shows a healthy or abnormally diseased condition [49]. Biomarkers act as diagnostic tools that indicate changes in biological or biochemical processes. The peripheral markers of AD in blood and cerebrospinal fluid (CSF) include plasma A42/40 protein, plasma-p-tau-181, plasma-p-tau-217, plasma neurofilament light (NfL), neurogranin, monocyte chemoattractant

protein (MCP), and amyloid tau. Neurofibrillary tangle (A/T/N) framework elements are detected accurately by using a fully automated immunoassay [50].

Bio-markers	Significance
Elevated T-tau (Total tau)	Reflects intensity of neuronal degeneration
Elevated P-tau (Phosphorylated tau)	Reflects formation of Neurofibrillary tangles (NFT)
Elevated Neurogranin (Ng) synaptic protein	Reflects synaptic dysfunction and degeneration
Declined $A\beta_{42}$	Indicates aggregation and deposition of Aβ plaques[51].

Recent meta-analysis and cross-sectional and longitudinal data analysis of the dominantly inherited Alzheimer Network (DIAN) cohort found significant elevated neurofilament light (NfL) levels in both CSF and plasma, which showed high diagnostic sensitivity for AD. Other approaches to distinct AD biomarkers are genomics, transcriptomics, metabolomics, lipidomics, and proteomics [52]. The potential plasma biomarkers are altered microRNAs, decreased platelet levels of disintegrin and metalloproteinase (ADAM), gamma secretase, -secretase, and presenilin[53].

Treatment

FDA approved medicines

There is no medication to treat AD, thus drug therapy are the main options for symptom alleviation. Drugs that have been approved by the FDA specifically target glutamatergic and cholinergic neurotransmissions. Acetylcholinesterase inhibitors (AChEIs), such as donepezil and galantamine, act by inhibiting this enzyme. These inhibitors improve mental function by increasing acetylcholine levels in the brain. As a result, it is used to treat mild to moderate AD [54]. Memantine, a drug from a different family, controls the excitement or hyperactivity of the NMDA glutamate receptor to prevent the entry of intracellular calcium and excitotoxicity [55]. Combination therapy with the drugs memantine and donepezil (28 mg and 10 mg/OD) improves linguistic challenges, behavioural problems, and cognitive judgement. Therefore, mild to severe AD is treated with it [56].

Targeting therapies of AD

The Alzheimer drug development pipeline presently undergoing clinical trials divide into 4 groups viz.

- Disease modifying biologics
- Disease modifying small molecules
- Treatment against neuropsychiatric symptoms
- Cognitive enhancers [57].

Aβ targeted therapy

Reduced Aβ plaque development, distribution, and deposition in the brain is the goal of Aβ focused therapy. There is currently no comprehensive animal model to evaluate the efficacy of the amyloid hypothesis. Active immunisation, passive immunisation and secretase inhibitors are Aβ's main targets in clinical trials. According to the study report, five drugs that target the generation, aggregation and clearance of A are now being tested in phase III clinical trials [58].

Active immunization

Administration of an exogenous chemical that stimulates the immune system to develop antibodies or an immunological response is known as active immunisation. Short-term delivery of active immunisation leads to long-term development of antibodies. Human Aβ-42 peptide full length was used in the first effective active immunotherapy for PDAPP mice, and this treatment significantly reduced amyloid plaques. As a result, the human Aβ immunotherapy trial of AN-1792, which consisted of a synthetic human Aβ42 peptide with QS-21 adjuvant, was developed. But it was a failure because 6% of patients developed aseptic meningoencephalitis as a result. This is caused by the full-length Aβ-42 peptide being administered, which causes a pro-inflammatory response from T cells that are specific for the A-protein[59].

Additional new peptide vaccines of the second generation were created to specifically target Aβ T-cell activation without causing inflammation. Novartis' CAD106 (Amilomotide), an active vaccine in a phase III clinical study, is made up of the peptides Aβ1-6 joined to a virus-like particle Qβ. Clinical investigations have shown that it reduces the amount of

amyloid that accumulates in humans. Another vaccine in phase II clinical trials is ABVac40, which combines the carrier protein KHL (Keyhole Limpet Cyanine) or liposome adjuvant with additional B cell epitopes (A-1-12, A-33-40, and A-1-15).The second strategy involves combining the T-cell memory-stimulating B call epitope (A-1-12) with T-cell epitopes generated from Tetanus Toxoid. LuAF20513 is one such active vaccination. DNA-based vaccinations are an alternative approach that has not yet been successful in clinical trials. DNA is translated into a peptide that prompts an immune response and the production of an A-specific antibody[60].

Passive immunotherapy

Exogenous monoclonal antibodies (mAbs) were directly delivered during passive immunotherapy to elicit an immune response. The drawback of prolonged therapy is its high price. It results in an overactive innate and adaptive immune system, which can have catastrophic consequences including cerebral vasculitis. The best antibody dosage is necessary for passive immunotherapy to pass through the blood-brain barrier (BBB) and reach the target region of neurons. Another challenge is the necessity to prevent neuro-inflammation caused by excessive microglia activity[61].

Mostly, the anti-Aβ mAbs prevent the aggregation of Aβ fibrils. Some of the mAbs failed at various stages of clinical trials as they did not show improvement in cognition or functional ability. They are listed below.

Monoclonal antibodies	Source
Bapinezumab	Humanised version of mouse 3D6 antibody
Solanezumab	Human murine mAb m266 composed of $A\beta_{13\text{-}28}$
Crenezumab	Human IgG_4 mAb targets both Aβ oligomers and fibrils
Gantenerumab	Human IgG_1mAb composed of both N-terminal and central Amino acid of Aβ
Donanemab	Human IgG_1mAb that target pyroglutamate form of Aβ

These monoclonal antibodies are failed at various stages of clinical trials as they have not shown improvement in cognition and functional ability[62].

FDA accelerated approval pathway

A procedure designed to speed up the approval of medicines for the treatment of serious illnesses if there is a gap in available medical care. An intermediary or substitute clinical endpoint serves as the foundation for approval. "Accelerated approval pathway" is the name given to this process. The mAbs listed below have FDA approval.

Aducanumab

Since 2003, Aduhelm (aducanumab) was the first new medicine to get FDA approval through the accelerated approval pathway. It is a human IgG1mAb with the amino acids $A\beta_{3-7}$ at its N-terminus, and it lowers amyloid beta plaques in the brain. Thus, it aids in the disease's defence. Aduhelm comes with a list of precautions that includes the possibility of hypersensitivity reactions such angioedema and urticaria as well as amyloid-related imaging abnormalities (ARIA). Biogen of Cambridge, Massachusetts manufactures Aduhelm [63].

Lecanemab

The USFDA has granted Leqembi (lecanemab) approval under the accelerated approval process. In a phase III randomised, controlled clinical trial, this medication supported the clinical benefit, such as the reduction of amyloid plaques. A humanised variant of murine mAb 158, Leqembi previously known as BAN2401 selectively binds to soluble Aβ protofibrils. In a dose- and time-dependent manner, it moderately slows mild cognitive impairment and lowers the level of Aβ plaques. Lecanemab recommended dosage is 10 mg/kg every two weeks.The symptoms of Leqembi include flu-like symptoms, changes in blood pressure, and Amyloid-related Imaging Abnormalities (ARIA), which are transient swellings in parts of the brain that cause headache, nausea, dizziness, vision changes, confusion, and seizures. Eisai R&D Management Co., Ltd. was given permission [64].

Secretase inhibitors

The Aβ level of production can be reduced by inhibition of β and gamma secretase. β-secretase is known as the beta-site amyloid precursor protein cleaving enzyme (BACE1). BACE is a transmembrane glycoprotein composed of an extracellular aspartic acid protease domain that initiates the production of Aβ. Gamma secretase is a complex protein composed of presenilin, nicastrin, anterior pharynx defective-1 (APH-1) and presenilin enhancer-2 (PEN-2). It cleaves amyloid precursor protein (APP) and generates the Aβ peptide[65].

BACE-1 inhibition limits only plaque formation and does not interfere with established plaques. The studies suggest that BACE-1 inhibitors can be used alone to prevent the development of pathology. It can also be combined with Aβ-directed monoclonal antibody to provide synergistic action such as clearance of Aβ deposition and prevent formation of Aβ. The following table shows the list of BACE-1 and gamma secretase inhibitors that ever reach clinical trials[66].

Name	**Company**	**Phase of Study**	**Outcome**
BACE-1 inhibitors			
LY2811376	Eli Lilly	Phase I	Decline Aβ level in plasma and CSF but Withdrawn due to toxicity-eye damage
LY2886721	Eli Lilly	Phase II	Reduce multiple Aβ isoforms but withdrawn due to abnormal elevation of liver enzymes.
RG7129 (RO5508887)	Roche	Phase I	Terminated due to liver toxicity
BI 1181181	Vitae pharmaceuticals	Phase I	Single dose tolerated with reduction of Aβ but withdrawn due to skin allergies with multiple doses
JNJ-54861911 (Atabecestat)	Janssen	Phase II/III	Well tolerated and reduce Aβ level but terminated due to liver toxicity
LY3314814 (AZD 3293, Lanabecestat)	AstraZeneca and Eli Lilly	Phase III	Inhibits BACE-1 and BACE-2 but discontinued as it worsens cognition and reduce brain volume
MK-8931 (Verubecestat)	Merck	Phase III	Discontinued due to worsen of cognitive function
E2609 (Elenbecestat)	Biogen and Eisai Co Ltd.	Phase III	Terminated due to no potential efficacy with worsen in adverse

			effect
CNP-520 (Umibecestat)	Novartis and Amgen	Phase II/III	Discontinued due to decline in cognition and brain atrophy
LY 3202626	Eli Lilly	Phase II	Discontinued due to no significant effect
PF-06751979	Pfizer	Phase I	Reduce Aβ in CSF and plasma but they ended their development
CTS21166	Co Mentis with Astellas pharma	Phase I	Reports were not published and further not conducted human studies
HPP854	High point pharmaceuticals	Phase I	Reports were not published and further not conducted human studies
Gamma Secretase inhibitors[67]			
Semagacestat	Eli Lilly	Phase III	Failed due to interfere with notch signaling proteins results in severe side effects
Avagacestat (Aryl Sulfonamide)	Bristol Myers Squibb	Phase III	Failed due to worsening of daily function and also cause skin cancer
Tarenflurbil	Myriad Genetics	Phase III	Failed due to low brain penetration and no efficacy
NIC5-15 (Pinitol – a natural cyclic sugar alcohol)	Humanetics pharmaceuticals	Phase II	Improve cognition function and available as food supplement

The studies revealed that inhibition of gamma secretase results in severe side effects. The development of drug that binds to Amyloid Precursor Protein (APP) cleavage site, prevents the activity of gamma secretase. This may overcome the drawback of gamma secretase inhibitors[62].

Tau targeting therapy

The strategies involved in tau targeting therapy are:

- Post-translational modification of Tau
- Inhibition of Tau aggregation
- Stabilization of microtubules
- Tau clearance by immunotherapy

Post Translational Modifications (PTMs)

Post translational modifications (PTMs) accelerate tau pathology that leads to formation of neurofibrillary tangles (NFT) and progress AD. Not all the PTMs results in progression of AD, it is based on the location, type and quantity of modifications occurred. The following table shows modification and its outcome [68].

Post-translational modification	**Outcome**
Hyper-phosphorylation of tau	Reduce binding ability and stability of microtubules. Self-aggregation of tau forms oligomer, NFTs and inhibit ubiquitin-proteasome activity which leads to neurodegeneration
Acetylation	Inhibits degradation of tau protein and promotes aggregation
N-glycosylation	Stimulates tau polymerization which is affected by the enzyme O-GlcNAcase
Nitration of tau Tyr-29	Affects tau polymerization and promotes tau aggregation
Caspase cleaved tau (delta-tau)	Accelerates the formation of tangles, also cause mitochondrial and synaptic damage
Lysine methylation	Protects against tau aggregation
Dityrosine (DiY) crosslinks of tau	Enhance the stability and insolubility of aggregates cause degradation resistance. Crosslinks occurs due to oxidative stress [69]

Tau Phosphorylation inhibitors

The inhibition of tau phosphorylation is important to maintain normal neuronal function. The level of tau phosphorylation can be determined by the balance of certain kinases and

phosphatases. The hyper-activation of protein kinases are GSK3β and Cyclin Dependent Kinase [CDK-5], whereas inhibition is protein phosphatase-2A (PP_2A). Thus, the strategy in tau therapy is inhibition of protein kinase and enhancing phosphatase.

1. GSK-3β inhibitors:

The glycogen synthase kinase (GSK-3) is a protein kinase that phosphorylates either serine/threonine. It controls various activities such as glycogen metabolism, cell signalling, cellular transport, cell cycle, gene expression and others. The two isoforms of GSK-3 in brain are GSK-3alpha and GSK-3beta, encoded with separate genes. It mediates hyper-phosphorylation of tau which results in formation of Paired Helical Filament (PHF) tau. PHF tau is a component of NFT which cause disruption of neuronal function like impairment in learning and memory. It also cause microglial mediated inflammation[70]. The drugs that reach clinical trials are described below.

A) Tideglusib (NP031112, Zentylor™) is an irreversible GSK-3β inhibitor. It prevents inflammation and edema formation in hippocampal rat. It is withdrawn from the clinical trial due to no efficacy in cognition.

B) Lithium is in phase 4 clinical trial. The studies reported that lithium decreases the progression of cognitive decline and reduce phosphorylated tau in CSF. It also prevents Aβ induced neurotoxicity.

C) AR-A014418 is a thiazole compound developed by AstraZeneca selective GSK-3 inhibitors.

D) AZD-1080 oxindole derivative and AZD-2858 Pyrazine derivative, both are orally active and showed dose dependent inhibition of tau phosphorylation. They are withdrawn in phase II clinical trial due to toxic histopathological changes.

E) SB-216763 improves spatial learning, memory and reduced tau phosphorylation in preclinical study. It is failed as it did not show any selective function towards structurally similar kinase.

F) SAR 502250 developed by Sanofi. The drug discontinued in preclinical studies due to safety issues and it is failed to modify the anxiety behaviours.

G) PF-04802367 developed by Pfizer. It is a highly selective GSK-3 inhibitor and reduces tau phosphorylation. It also acts as a radiotracer in PET imaging techniques due to its potential penetrating ability in brain.

The other derivatives like Isonicotinamide, triazolopyridinone are orally effective and acts as specific GSK-3 inhibitor. Further studies revealed that inhibition of AChE and GSK-3 provides synergistic effect by enhancing ACh level[71].

2. CDK_5 inhibitors:

Cyclin-Dependent Kinase-5 is a proline directed serine/threonine protein kinase. It plays an important role in function of neurons, astrocytes, endothelium, cell adhesion signalling, ion transmission and cytoskeletal remodelling. CDK_5 is activated either by P_{35} and P_{39} or cleavage products P_{25} and P_{29}. The accumulation of P_{25} and P_{29} causes hyper-activation of CDK_5 which results in hyper-phosphorylation of substrates. The studies revealed that silencing of CDK-5 results in neuroprotective effect. The use of endogenous microRNA (miRNA-30) composed of exogenous CDK_5 ShRNA using adeno-associated viral vector (AAV 2.5) and small molecules like Roscovitine were studied but its reports not yet published. Till now, no small molecules were successfully reported to inhibit CDK_5 kinase selectively[72].

3. Phosphatase activator:

The activation of Phosphoprotein Phosphatase 2A (PP2A) leads to reduction of tau hyperphosphorylation. PP2A regulates cellular phosphorylation networks. The structural features which can activate PP2A are Sphingoids, Phenolics, Cations, anions and other small molecules such as palmitic acid, melatonin, troglitazone, progesterone, dithiolethione, 1,8-naphthyridine and ebelactone. The anionic compound sodium selenate activates PP2A which showed selective reduction in phosphorylated tau with no adverse effects[73].

Targeting tau glycosylation

In the nucleus and cytoplasm, O-glycosidic bonds are formed by linking N-acetyl glucosamine (GlcNAc) and the hydroxyl group of serine or threonine in proteins. O-GlcNAcylation is one of the post-translational modification forms that have a significant role in signal transduction, gene expression, the cell cycle, and proteosomal degradation. It also reduces tau aggregation and NFT formation by inhibiting GSK-3. The enzyme O-GlcNAcase (OGA) catalyses O-GlcNAc. Thus, OGA inhibitors are developed to enhance O-GlcNAc

modifications. The drug undergone in the Phase II clinical trial is LY3372689, expected to be completed in 2024. The phase I study revealed that it is safe and well tolerated without any adverse events [74, 75].

Targeting tau acetylation

Tau acetylation leads to axonal damage and pathological tau mislocalization. Salsalate is an NSAID that inhibits the acetylation of tau. Preclinical studies reported that salsalate can prevent hippocampal atrophy, reduce tau pathology, and restore spatial memory. But in the phase I trial, it did not show efficacy in preventing disease progression [76].

Tau Truncation

The enzymes, such as Calpain and caspase-mediated fragmentation of tau at the N and C terminals, are one of the factors that cause AD. This truncation is an irreversible process; once fragmented by protease, tau fragments promote aggregation, propagation between neurons through synapses, and further cause cytotoxicity. Thus, the current therapeutic strategy for tau truncation is focused on small molecules that can inhibit caspase-2 function and prevent tau cleavage at the Asp314 site [77, 78].

Metal Chelators

The elevation of metal ions (such as copper, iron, and zinc) leads to interactions with A at His 13, His 14 residues, and sometimes His 6 residues, which induce A1–40 aggregation and result in metal-mediated A toxicity. The levels of Cu (0.4±0.1 mg/g of the wet weight of the plaque) and Zn (1.2±0.2 mg/g) are found to be high in senile plaques of the AD brain [13]. In chelation therapy, chelators are used to prevent metal-mediated neurotoxicity of A by chelating the excess metal ions in the brain. Cu-Zn chelators like Clioquinol are used to inhibit Aβ accumulation.

The coordination of metal ions and Aβ on the chemical reduction of metals generates hydrogen peroxide (H_2O_2) as a reactive oxygen species. In the absence of detoxifying enzymes such as catalase and glutathione peroxidase, it produces toxic hydroxyl radicals, which results in Aβ toxicity. The cellular toxicity can be prevented by the addition of catalase and chelation therapy. Thus, metal chelators act as neuroprotective agents [79].

CONCLUSION

Today, Alzheimer's disease is viewed as a global health threat. Understanding the natural history of Alzheimer's disease is improving gradually but steadily. At this time, growing experimental evidence is in favour of amyloid beta's harmful involvement in the pathophysiology of AD. For a more precise diagnosis of AD, a number of criteria have been put forth, including clinical biomarkers, body fluids, and imaging tests. In spite of this, AD treatment is still asymptomatic. Drugs like NMDA antagonists like memantine and cholinesterase inhibitors like galantamine, donepezil, and rivastigmine only work as cognitive enhancers and do not stop the progression of disease. The development of a completely successful medicine for AD therapy is hampered by the multifaceted character of the disease's pathogenic process. In conclusion, early detection, proper therapy involving lifestyle changes, and patient monitoring for disease progression utilising biomarker analysis are all essential for the effectiveness of AD treatment. Additionally, treatments that target the tau pathology and combination therapy may be able to halt the development of AD pathology. Therefore, the development of a potent, highly selective, and effective medicine is urgently required to treat AD sufferers as well as those who are at risk of developing the illness.

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