Review Article

Health Economic Evaluations for Alzheimer’s Disease: Pathophysiology, Diagnosis and Pharmacological Approaches

ABSTRACT

Alzheimer's disease (AD) was first described by Alois Alzheimer in 1907 as a slowly progressing form of dementia that affects cognition, behavior, and functional status. It may be identified by the extracellular amyloid b (Ab) plaques as well as neurofibrillary tangle (NFT) deposits that are seen inside the neurons. Early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD) are the two main categories that form the base of AD presentation. EOAD is a condition that develops before the age of 65 and is linked to Mendelian inheritance, which results in a mutation in the genes APP, PSEN1, or PSEN2. So it is familial AD. While LOAD occur after age 65 years of age and, it is not related to a genetic cause. So it is sporadic AD. To assess and monitor the rate and pattern of cognitive loss, screening measures like the MMSE and the Montreal Cognitive Examination are utilized. Clinical biomarker testing is now available to assist physicians in determining the the presence and severity of AD pathologic alterations, as well as their lasting effects. Fibrillar (plaque) amyloid is detectable on PET. Despite the fact that AD is a public health issue, only two pharmaceutical classes—antagonists of N-methyl d-aspartate (NMDA) and inhibitors of the cholinesterase enzyme (naturally occurring, synthetic, and hybrid variants)—are allowed to be practiced to treat AD. AD is brought on by a decrease in the synthesis of acetylcholine (Ach) Increasing acetylcholine levels by decreasing acetylcholinesterase is one of the therapeutic interventions that enhances neuronal cells and cognitive function. Tacrine was the first cholinesterase inhibitor drug authorized by the FDA to be used for the treatment of AD.

KEYWORDS

Alzheimer’s disease, amyloid beta, PET, ICD-10, cholinesterase inhibitors, MMSE

1.INTRODUCTION

Alzheimer's disease (AD) was initially recognized by Alois Alzheimer in 1907 as a gradually worsening type of dementia that impairs cognition, behavior, and functional status. [1]. It may be identified by the extracellular amyloid b (Ab) plaques and neurofibrillary tangle (NFT) accumulation visible inside the neurons. When tau proteins are hyperphosphorylated, they form paired helical filaments (PHFs), whereas amyloid-B peptide aggregates form Ab. It is recognized that the hyperphosphorylated state facilitates tau aggregation in PHF, which causes microtubule instability, membrane deterioration, and neuronal injury. In AD, neurofibrillary tangles are found in the amygdale, hippocampal formation, parahippocampal gyrus, and temporal association cortex, whereas senile plaques are spread across the association neocortex and are seen in the striatum. The entorhinal cortex, amygdale, temporal association cortex (CA1), and subiculum of the hippocampus exhibit the most severe neurofibrillary degeneration. Microglial activation, in addition to amyloid plaques and NFTs, is important in neurodegeneration. Although the body's natural inflammatory response serves as a form of protection, an excessive inflammatory response can result in tissue damage and disease pathology. [2]. Research on naming, spontaneous speech, verbal fluency, naming to definition, vocabulary, knowledge of qualities, category knowledge, and conceptual priming reveals that AD patients perform noticeably worse than healthy older control participants. Two techniques to assess if conceptual information is lost or unavailable are (1) investigating the consistency of mistakes in numerous tasks that employ the same stimuli and (2) repeated administrations of the same task. Warrington (1975) demonstrated error consistency in three individuals with widespread brain lesions and atrophy (cause unknown in two, "arteriosclerosis" the cause in the third) using name and word-to-picture matching tasks with the same stimuli [3]. WHO declares AD a global public health priority because there is no enduring treatment available for it. Only the hypothesis about AD is known, with no knowledge of the actual etiology. It is found that females are more susceptible than males. And the persons having disease conditions like diabetes or hypertension have a higher risk of developing AD in the future [4]. AD, also called neurodegenerative deformation, is marked by intellectual disability, loss of physical and mental abilities, amnesia, etc. Almost 50 million individuals worldwide have dementia, and by 2050, 150 million instances are estimated. [5] According to the WHO, there are 50 million dementia sufferers worldwide, and 10 million new instances are discovered every year. Numerous prospective, long-term studies carried out in North America and Europe have contributed to a better understanding of the aetiopathogenesis of Alzheimer's disease; nevertheless, similar research in low- and middle-income countries (LMICs), such as South Asia (India, Pakistan, Afghanistan, Bangladesh, Nepal, Bhutan, Sri Lanka, and the Maldives), is failing. [6]. By 2020, it is anticipated that about 70% of the world's population will be over 60 and reside in developing nations, with 14.2% of that population being Indian [7]. In this article, we provide a broad brush overview of the current state of Alzheimer's disease, emphasizing recent advances and emphasizing the importance of thinking about Alzheimer's disease as a disease continuum that begins decades before the onset of memory loss. Thus, this review summarized the pathogenesis, diagnosis, and current emerging pharmacotherapies and alternative treatments utilized in clinical trials, outlining pertinent issues that might lead to a more accurate examination. We also demonstrate that certain cognitive tests, such as the MMSE and the ICD-10, have high predictive power for initial diagnosis.

2.PATHOGENESIS

There are two forms of AD based on how it manifests: early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD). EOAD develops before the age of 65 and is linked to Mendelian (often dominant) heredity, which results in mutations in the APP, PSEN1, or PSEN2. Hence, AD runs in families. LOAD doesn't have a hereditary basis, even if it develops just after age 65. AD is therefore sporadic [8]. The majority of studies concur that the classic pathological criteria for Alzheimer's disease, neuritic plaques and neurofibrillary tangles, can account for 40%–70% of the cognitive variability seen in older adults, with the remaining 40%–70% being accounted for by other pathologies like cerebrovascular disease and Lewy body pathology.

2.1 amyloid cascade hypothesis

The amyloid precursor protein (APP) is a member of the same family of proteins as the amyloid precursor-like proteins (APLP1 and APLP2) found in mammals. The soluble ectodomain generated by APP cleavage can perform the same tasks as APP in regulating cellular proliferation, motility, neurite growth, and cell survival. APP is created in enormous numbers in neurons and is quickly broken down. There are multiple different mechanisms for APP proteolysis, some of which yield the Aβ peptide and others do not. APP is supplied to the axon and moved to synaptic terminals by rapid axonal transport after being sorted in the endoplasmic reticulum and Golgi. On the surface of the cell, APP can be proteolyzed directly by α-secretase followed by γ-secretase, a procedure that does not lead to Aβ. Presenilin 1 (PS1) or PS2; nicastrin (Nct), a type I transmembrane glycoprotein; Aph-1 and Pen-2, two multipass membrane proteins; and nicastrin (Nct) make up the multiprotein complex known as beta-secretase. A considerable quantity of APP is

constantly metabolized to Aβ in the brain. Early in the onset of Alzheimer's disease, the level of Aβ42 in cerebrospinal fluid (CSF) starts to decline while it accumulates in the brain [9].

APP is broken down by secretase enzymes into different-sized alpha and beta amyloid oligomers. Beta amyloid oligomers with 40 or 42 amino acids make up amyloid plaques. These beta amyloid oligomers are neurotoxic in cell culture and are suspected to be implicated in tau protein hyperphosphorylation. According to the current theory, which is an adaptation of the original amyloid cascade hypothesis, beta amyloid oligomers rather than amyloid fibrils are to blame for the destruction that results in Alzheimer's disease. Moreover, by eliminating beta amyloid oligomers, amyloid plaques may decrease in destruction. The APP is created in the cell body, travels through the axon, and causes the development of an axonal bulb close to the tear. If neuronal injury results in neuronal death, the byproducts of APP are prone to misfold and induce amyloid deposition; in this situation, amyloid is a byproduct of neuronal death rather than its cause. The discovery that beta amyloid cleavage byproducts of APP are neurotoxic disregards the assumption that APP is protective [10]. A protein called fyn joins Aβ and tau. Recent research has revealed that tau, which directly binds FYN, targets this nonreceptor tyrosine kinase to postsynaptic locations in dendrites and favorably controls N-methyl-D-aspartate (NMDA) receptor activation. The fact that tau is ordinarily substantially concentrated in axons relative to dendrites but is significantly redistributed into the somatodendritic division in response to Aβ must be considered when interpreting the results of these trials. In AD dendrites, when excessive FYN coexists with excessive tau, it activates NMDA receptors, saturating the dendrites with potentially damaging calcium levels. Excitotoxicity brought on by calcium can harm postsynaptic locations and result in neuronal death. Decreased FYN dendritic concentration may therefore shield human neurons from the Aβ-induced, tau-dependent activation of NMDA receptors that takes place [11].

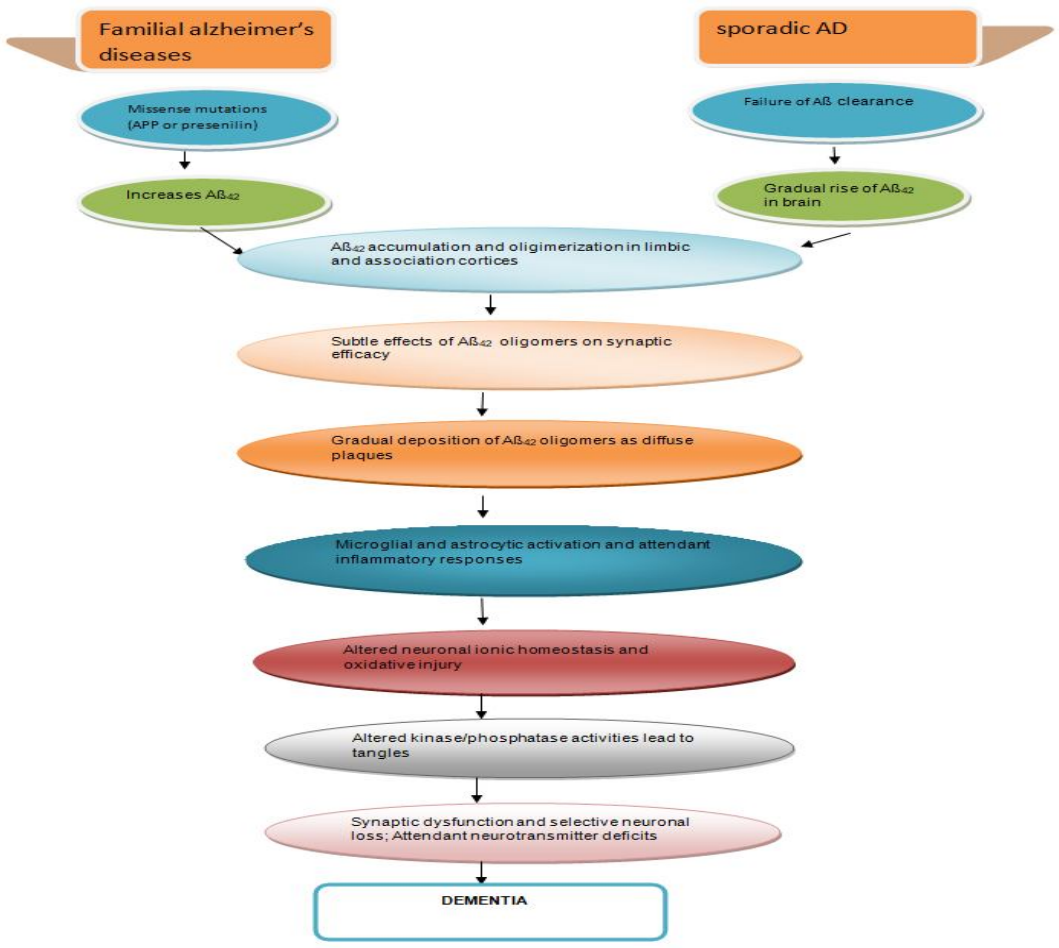

Figure 1**:** This hypothesis represents the conventional theory of AD's beginnings. Aß overproduction is a result of both familial and sporadic types of AD. [72]

2.2 Neurofibrillary Tangles

NFT-containing neuronal perikarya, dendrites, and axons acquire aberrant filament bundles. These filaments are defined as two helicoidally twisted filaments that exhibit regular constrictions or seem straight. (Hence, "paired helical filaments," or PHF). There are different morphologically distinct kinds of NFT that are able to be differentiated, which most probably correspond to various evolutionary stages. The "Pretangle" stage is characterized by the buildup of phosphorylated tau in the somatodendritic compartment without PHF production. Early on, the soma and dendrites include a few tau-immunoreactive rods. Conventional NFTs are made up of bundles that are closely packed and occupy a section of the cell body before extending into dendrites. A significant desaggregation of NFT that occurs along with neuronal loss gives the tissue a looser look. Yet, NFT densities were shown to be more closely connected to the severity of dementia than senile plaques in numerous anatomo-clinical studies, showing that NFT production more directly corresponds with neuronal dysfunction. NFT are initially found in the transentorhinal cortex, a region that sits in between the entorhinal cortex and the temporal neocortex (stage I); NFT are next found in the layer pre-• of the entorhinal cortex (stage II); patients do not show any cognitive problems at these stages. The cerebellum, the spinal cord, and several primary motor and sensory

cortical sections of the brain remain mostly undamaged. Certain neuronal populations tend to be refractory to NFT production. Unlike Aß deposits, which can be plentiful in non-demented persons, numerous NFTs cannot be observed in people with normal cognitive function [12]. Tau, a microtubule-associated protein (MAPT), polymerizes tubulin into microtubules and contributes to the upkeep of the intricate microarchitecture of neuronal cells, particularly in the axon, by assisting in microtubule construction and stability. Tau is a phosphoprotein whose amount of phosphorylation regulates its biological function. Due to their high concentration of polar, glycine, and proline residues as well as their poor hydrophobic residue composition, tau variants are susceptible to disordering in the aqueous phase. They also have one or two cysteine residues that are easily oxidized and can produce adducts. Tau can harm the cell membranes and microtubules in neurons. Alteration in synaptic distribution and disturbance of synaptic protein interactions can affect neuronal function and potentially cause Alzheimer's disease [13].

2.3 The cholinergic hypothesis

Studies on humans have demonstrated that the basal and rostral forebrain cholinergic pathways, notably convergent projections to the thalamus, play critical roles in conscious awareness, attention, working memory, and a range of other mnemonic processes. For more than 20 years, researchers studying the brains of people with advanced age and Alzheimer's disease (AD) have consistently found abnormalities or destruction in these pathways, especially in basal forebrain projections, which have been shown to be closely correlated with the severity of cognitive decline. As a result, the "cholinergic hypothesis" was created, which essentially asserts that the decline in cholinergic activity in the central nervous system plays a significant role in the cognitive decline brought on by ageing and Alzheimer's disease. Moreover, cholinergic antagonists (more precisely, antimuscarinic medications) were shown to impair memory in rats more than 30 years ago, underscoring the importance of cholinergic activity in the brain to both memory and learning. Additionally, the same memory tasks that are hampered by cholinergic blockade are hampered by lesions in animals that interfere with cholinergic transmission from the basal forebrain to the neocortex or hippocampus (such as the nucleus basalis magnocellularis and the medial septum/diagonal band). Significant memory losses in people have also been linked to injury to comparable basal forebrain areas (as a result of arterial aneurysms or excision of an arterio-venous malformation) [14]. The most widely used pharmaceutical therapy for cognitive abnormalities in Alzheimer's disease today is cholinesterase inhibitors (ChEIs). Today, donepezil, rivastigmine, and galantamine are the three CHEIs that are most frequently used as recommended therapies for the pharmacological treatment of Alzheimer's disease patients who are in the clinically symptomatic stage. The above-mentioned body of knowledge indicating that age-related memory decline is influenced by a system thought to be crucial for memory mechanisms, together with evidence of degeneration of that system in Alzheimer's disease, has become the compressed "cholinergic hypothesis of Alzheimer's disease" and was believed to be the disease's cause [15]. In 1973, Shore identified the lipid-binding protein ApoE, which has a 34 kDa size, in extremely low-density lipoprotein. Chylomicron (CM), VLDL, and their metabolites are the main sources of it. Lipoprotein metabolism needs apoE. Together with the LDL receptor, it can also bind to certain HDL (ApoE) receptors, VLDL debris, and chylomicrons (CM) in the hepatic cell membrane. Triglycerides and cholesterol are transported by apoE in a variety of tissues. The apoE protein plays a crucial role in the metabolism of lipoproteins in both the brain and the periphery, and its expression regulation and types have a significant relationship to Alzheimer's disease (AD). The apoE gene has three isoforms: 2, 3, and 4. The apoE 3 allele is the most prevalent (77.9%), the 2 allele is the least prevalent (8.4%), and the 4 variant is in the middle (13.7%) [16]. We still don't know how the APOE genotype affects AD onset and progression. The extracellular protein apoE is mostly produced by astrocytes and overtaken by neurons in the brain, although it may also be produced by microglia and neurons under certain circumstances. Alzheimer's disease is three times more likely to strike those who have one copy of the APOE 4 gene, and it is ten times more likely to strike those who are homozygous for the gene. Moreover, the onset age is lower in the APOE 4 AD group. There is no known specific mechanism by which apoE affects AD. Two of the main characteristics of AD are the presence of extracellular A deposition, which results in the formation of amyloid plaques, and the development of neurofibrillary tangles (NFT), which are intracellular accumulations of tau protein that has been hyperphosphorylated. According to one hypothesis, the interaction between apoE and A peptides causes apoE and AD. Plaques from Alzheimer's disease have been found to contain apoE [17].

2.4 Mitophagy associated with development of AD

In simple terms, mitophagy is the process of autophagy that rids the body of dead mitochondria. Mitophagy is started when an 'autophagosome,' a spherical structure with a cell membrane, develops. In order to keep cells healthy, mitophagy is a crucial activity. It boosts mitochondrial cycling and stops the buildup of defective mitochondria, which can cause cellular degeneration. Parkin and PINK1 are two proteins that control mitophagy. Autophagosomes are globular, double-layered, membrane-enclosed structures. It is an essential element in macroautophagy, a process that degrades cytoplasmic components inside cells. Lysosomes are formed by autophagosomes, after which they transfer cytoplasmic components to them. When the outer membranes of a lysosome and an

autophagosome come together, an autolysosome is produced. The lysosome's hydrolases break down both its inside and outside membranes. The emergence of autophagosomes is controlled by LC3 complexes and Atg genes. The conjugate of Atg12 and Atg5 also interacts with Atg16 to form larger complexes. The alteration of Atg5 by Atg12 is what causes the first membrane to elongate. The Atg12-Atg5:Atg16L1 complex separates from the autophagosome after taking on a spherical shape. ATG4 splits LC3 in two to produce LC3. LC3 cleavage is necessary for the ultimate fusion of an autophagosome with its target membrane. The outer membranes of an autophagosome and a lysosome come together to form an autolysosome. The lysosome's hydrolases break down both its inside and outside membranes. The emergence of autophagosomes is controlled by LC3 complexes and Atg genes. The conjugate of Atg12 and Atg5 also interacts with Atg16 to form larger complexes. The alteration of Atg5 by Atg12 is what causes the first membrane to lengthen. The Atg12-Atg5:Atg16L1 complex separates from the autophagosome after taking on a spherical shape. The protein LC3 is broken down by ATG4 to create LC3. LC3 cleavage is necessary for the ultimate fusion of an autophagosome with its target membrane [18]. The synthesis of phospholipids and myoglobin, calcium homeostasis, apoptosis activation, and the death of cells are only a few of the processes carried out by mitochondria in eukaryotes that provide energy [19]. There are four fundamental phases in mitophagy. (I) The beginning of the mitophagic processes (ii) The preparation of the mitophagy process for detection by the autophagic machinery (iii) The production of mitophagosomes and the engulfment of mitochondria. (iv) Degradation by lysosomes While under stress, ocular atrophy 1 (OPA1) initiates mitophagy, and mitofusins 1 and 2 (Mfn1 and 2) control the suppression of mitochondrial fusion. DRP1 is located in the endoplasmic reticulum membrane, which is connected to the mitochondria. PINK1 is stabilized on the outer mitochondrial membrane as a result of the suppression of matrix proteins, mitochondrial processed peptidase, and presenilin-associated rhomboid-like protease in damaged mitochondria. Simultaneously, parkin and ubiquitin are activated by PINK1, and they also instruct the autophagic apparatus to detect mitochondria by ubiquitinating a variety of OMM proteins and triggering the creation of mitophagosomes by interacting with microtubule-associated protein 1 light chain 3 (LC3). Afterwards, defective mitochondria are destroyed by the mitolysosome, which is created when the mitophagosome and lysosome combine to form the process. Ubiquitin-dependent and ubiquitin-independent mitophagy processes are the two main types[20].The ubiquitin-proteasome system (UPS) and autophagy are two significant cellular deterioration mechanisms in eukaryotes, both of which are crucial in trying to remove misfolded or unfolded proteins to maintain tissues and cells homeostasis, prevent aging-related changes, and prevent a variety of human diseases [21].

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3. DIAGNOSTIC STRATEGIES FOR AD

3.1 Clinical diagnosis and history of present illness

Alzheimer's disease is distinguished by a slow loss of cognitive ability as well as functional effects. Significant neuronal loss and gliosis in the CA-1 and subiculum of the hippocampus development are hallmarks of hippocampal sclerosis (HS). Patients constantly ask questions, repeat discussions, and struggle to recall specifics of recent or shared events as the disease gradually takes hold. Names of things and people are difficult to remember. Hippocampal sclerosis patients display a similar amnestic profile, although the progression of their cognitive abnormalities is slower than in AD. The results [22] show that patients with HS experience a slower decrease on the Mini-Mental State Examination (MMSE) than those with ADHS, which is now known to induce dementia in up to 25% of the "oldest old," despite being exclusively investigated in temporal lobe epilepsy [23].

3.2 Neurocognitive testing

Alzheimer's disease is characterized by decreased knowledge consolidation or storage, with registration and recall being comparatively unaffected [24]. To aid in diagnosis and monitor the rate and pattern of cognitive decline, screening exams like the MMSE and the Montréal Cognitive Assessments (MoCA) are used [25, 26]. The Mini-Cog, the Memory Impairment Screen, and the General Practitioner Assessment of Cognition (GPCOG) are additional screening exams advised by the Alzheimer's Association [27]. The MMSE should be used in some circumstances, especially during a first visit or when screening for clinical trials, because of its historical relevance and its broad usage by community practitioners. The MMSE's capacity to identify deterioration at examinations that are not more than three years apart has been questioned by some, despite its screening value [28]. The MoCA is divided into sections that roughly correspond to different cognitive domains. These sections include those on visual-spatial-executive, naming and language, memory (with sections on registration/immediate recall and both free and cued delayed recall—thought to be particularly sensitive to amnesia associated with Alzheimer's disease), attention, abstraction, and orientation). The "Memory Index Score," which is now part of Version 8, does track this important data and forecast the change from MCI to AD [29], even though the advantage of cued recall is not reflected in the overall score. Caregiver surveys like the Ascertain Dementia 8, the GPCOG informant interview

component, and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) Short Form may be helpful when the patient is hesitant or resistant to being screened [30].

3.3 Physical examination

The broad physical examination is often normal early in the illness process, but localized neurologic symptoms point to potential secondary or concomitant causes of cognitive loss. As the disease progresses, extrapyramidal symptoms may appear. These symptoms may be brought on by subcortical cerebrovascular disease or comorbid pathology such as dementia with Lewy bodies (DLB), cerebrovascular disease, progressive supranuclear palsy (PSP), corticobasal degeneration syndrome, normal pressure hydrocephalus, or other conditions. Examining the gait and referring the patient to physical therapy should be done in response to safety concerns. The first appointment should include a thorough physical and neurological assessment; following visits should focus more on specific areas. include vital indicators like weight and BMI, a pain evaluation, and other data (and follow them longitudinally). The following physical signs of end-organ failure should be kept an eye out for: jaundice, pedal edema, trophic vascular skin changes, other physical indicators of end-organ failure, delirium (asterixis or myoclonus, severe attentional impairments, a changeable level of awareness), abuse, neglect, or falls (ecchymosis, burns, and other symptoms) [31].

3.4 Biomarkers of AD

Physicians may now use diagnostic biomarker testing to help them identify the presence and severity of AD pathologic changes as well as those changes' subsequent repercussions. (1) The AD pathology continuum is unique for the presence of low Ab42 levels in CSF or a positive amyloid PET scan. In this new biologic definition of Alzheimer's disease, Ab42 defines at least the existence of an underlying Alzheimer's pathologic alteration. (2) Thereafter, the existence of underlying AD requires the detection of increased phosphorylated tau in CSF or positive tau PET (not yet clinically accessible). AD is physiologically identified by the presence of the biomarkers phosphorylated tau and Ab42. (3) Lastly, the underlying "Alzheimer's continuum" cannot be determined by neuronal damage indicators such as higher CSF total tau, atrophy on an MRI of the brain, or temporo-parietal hypometabolism on an FDG PET scan. Elevated CSF total tau, shrinkage on MRI, and hypometabolism on FDG PET are indicators of neuronal damage, however, and they might be helpful in assessing the severity of the underlying illness and concomitant pathologic change. These indicators open the way for a more "biologically" oriented (as opposed to signs and symptoms-focused) research approach, even if their broad usage in ordinary clinical practice would be prohibitively expensive. The presence or absence of amyloid, tau, and/or neurodegeneration characterizes this "ATN" staging [32]. When there are atypical manifestations (behavioral, verbal, or visual variations; young age) or when the diagnostic criteria for alternative etiologies (especially fronto-temporal dementia) are satisfied, it is practically important to gather biomarker data to support a clinical diagnosis of AD. With the exception of hippocampal shrinkage, conventional biomarkers for Alzheimer's disease are not anticipated to be evident in limbic-predominant age-related TDP-43 encephalopathy [33]. Beginning with MRI and FDG-PET, which can demonstrate a specific pattern of hippocampal and parietal atrophy (on MRI) and lateral and mesial temporoparietal hypometabolism, which is characteristic of AD and decreases the likelihood of alternative etiologies, is a common phase in the process. CSF examination or amyloid PET can be employed, depending on resources, to conclusively determine the presence of AD pathology [34, 35].

3.5 Magnetic resonance imaging (MRI)

It is generally known that brain atrophy, which can be accurately diagnosed via quantitative MR image analysis, is linked to Alzheimer's disease (AD) and other neurodegenerative illnesses. Medial temporal lobe structures can exhibit considerable atrophy, which is consistent with histologic results when structural MR images are quantified. Such tissue loss is typically accompanied by increases in ventricular volume, notably in the inferior region of the lateral ventricle. Quantitative MR imaging may also help in the early identification of neuropathologic conditions associated with AD. Mild cognitive impairment is commonly assigned to patients who do somewhat poorly on one or more standardized cognitive function tests (MCI). If one of the impacted cognitive areas is memory, people are more likely to acquire AD. It has been discovered that medial temporal atrophy can indicate whether a patient with MCI will experience a quick deterioration or remain stable. Several studies have shown that patterns of progressive brain atrophy that may be recognized by quantitative MR image analysis are consistently linked to neurodegenerative illnesses. So, by giving objective, quantifiable proof of a disease process, volumetric study of regional brain regions may help characterize a patient's state. These metrics may also be prognostic, aiding in the identification of individuals most at risk for fast clinical decline. Nevertheless, the approaches that are now available to extract quantitative volumetric data from MR images are only suitable for small-scale research projects [36, 37].

3.6 Amyloid PET

Amyloid fibrillar (plaque) amyloid can be found with amyloid PET. The FDA presently allows Amyvid (18F-Florbetapir), Neuraceq (18F-Florbetaben), and Vizamyl (18F-Flutemetamol), despite the fact that there are several experimental tracers available [38]. The purpose of this test, according to the FDA, is to "measure Ab neuritic plaque density in adult patients with cognitive impairment being examined for AD and other causes of cognitive decline." A negative scan disqualifies Alzheimer's in favor of other forms of dementia, even though a positive scan does not provide an absolute diagnosis of the condition. The threshold for amyloid positivity is expected to be influenced by factors such as age, genetic risk factors, and cognitive status [39]. Clinical care of patients with MCI and AD dementia has changed as a result of the adoption of amyloid PET, according to research [40]. Only research objectives may use additional tau and synapse PET scans [41]. For now, atrophy, hypometabolism, and cognitive impairment are the conditions that tau PET imaging best corresponds with. To assess fluid quantities of Ab or phosphorylated tau, CSF analysis is occasionally achieved [42].

3.7 Fluorodeoxyglucose positron emission tomography (FDG-PET)

FDG-PET imaging is the marker for neurodegeneration. When a patient has dementia, the brain's metabolic activity decreases. FDG-PET scales the decreased brain glucose consumption, which is slightly associated with astrocyte activity. So the FDA-PET is used for evaluation and diagnosis of the range of metabolic activity and also shows neuronal abnormalities. FDG-PET imaging testing is very useful in the diagnosis and early detection of AD. It detects earlier neurodegeneration in patients with impaired cognition who will develop dementia prior to MRI scanning. The test is also helpful for identifying the stage of disease. Since the models of brain hypometabolism are nearly linked with the type and intensity of cognitive problems. When we talk about the five-phase strategic plan defined to stimulate and advance clinical validation or objective evidence, the FDG-PET is the PET biomarker, which shows the excellent and more modern phase of validation [43]. In Alzheimer's disease, there is a decrease in cerebral metabolism. These same changes are seen in the cognitively normal person at high risk for AD because of the manifestation of the APOE4 allele [44]. FDG-PET is also used to differentiate AD from other dementias, and it will estimate or track the decline from general cognition to AD, so it will identify the patient as being at risk for AD before the onset of cognitive symptoms. In the last 30 years of the FDG-PET study, it has been found that, first of all, AD is marked by specific regional models and patterns of CMRglc reductions. In the AD patients, they regularly show CMRglc deficiency in the parieto-temporal area, the posterior cingulate cortex, and at MTL. At later stages of the disease, progressive frontal associations cortexes are also involved, and other areas like the striatum, primary visual cortex, cerebellum, basal ganglia, and sensorimotor cortexes stay preserved. Without a decrease in the CMRglc, the clinical presentations are not shown in AD. And CMR-GLC is extremely well matched with clinical incapacity dysfunction. The standard disease-exclusive PET models are classified as 92% DLB, 94% FTD, 94% NF, and 95% AD [45]. Reduction FDG-PET magnificence reflects abnormality, and tau proteins arbitrate neuronal injury. There were comparative studies done for AD, and it was found that FDG gave good results compared to MRI scanning [46]. FDG-PET has value as a neurodegenerative disease prognostic marker, and it will shorten clinical outcomes while also determining the staging and progression of AD[47].

3.8 Mini mental state examination(MMSE)

The mini-mental state examination (MMSE) is one of the most plausible scales for the verification of neurocognitive disorders. The 30 MMSE were first used to identify the difference between psychiatric and neurological patients. During the use of MMSE, it is seen that MMSE shows both good test-retest credibility (0.80-0.95) as well as admissible susceptibility (0.86) and specialty or predominance (0.92), through which the mental disorders are defined. It is mainly used to find out the therapeutic agent’s effect on patients and also for follow-up [48]. In the MMSE test, there is a set of 30 questions evaluating perceptional functions that estimate consideration and orientation, language, remembrance, count, registration, memory, and the caliber to exert a complex polygon. However, it has been discovered that the MMSE is ineffective at detecting dementia at an early stage or predicting dementia stages, the development of chronic or long-term dementia, or different types of dementia. But the advantage of MMSE is the higher rate of acceptance by health professionals and testers, or clinicians, for diagnostic instruments in multiple languages and fast administration. The result is based on the total score [49]. The MMSE is one of the most commonly applied, concise neurocognitive examinations for assessing and monitoring the advance of dementia in old age [50]. Rapid cognitive loss is explained by the MMSE when the loss occurs at 4 or more points and is greater than 4 points on the MMSE in 6 months. The expected average reduction in MMSE score in an AD patient varies between 2 and 4 points per year. So a loss of four or more points denotes a rate of reduction that is at least twice as fast as is commonly required [51].

3.9 The ICD-10 criteria for vascular dementia

"To establish and amend as necessary international nomenclatures of diseases and causes of death," is one of the World Health Organization's constitutional obligations. The tenth revision of the "International Statistical Classification of Diseases and Related Health Problems" (ICD), which was the most recent, was released in 1992 [52**].** Vascular dementia is a term that has not yet been well defined, despite the fact that vascular diseases are the second most common cause of dementia. Frequently, such as in the widely used DSM-III-R, the term "mucosal infarct dementia" is used to describe all types of VAD. Differentiation of VAD subtypes is permitted by the new ICD-10 criteria.

3.10 Introduction of the new ICD-10

The World Health Organization (WHO) introduces ICD-10. The ICD-10's Chapter V, which is titled "Mental and behavior disorders, including disorders of psychological development," adheres to the ICD-10's basic principles and organizational framework and is largely used to store statistics on morbidity and mortality. The first character in the new coding scheme is both a letter and a number, F in chapter V. There are 100 major three-character categories in every chapter. While VAD has the code F01, organic mental diseases have F0. Additionally, a description and explanation of the disorders are provided in Chapter V. The ICD-10's Chapter V is available in three different versions. The term "clinical descriptions and diagnostic guidelines" (cDDG) refers to a version intended for general clinical use. It includes a thorough explanation of the disorder's fundamental clinical idea as well as operationalized diagnostic recommendations, some points on differential diagnosis, and other information. The ICD-10 research criteria for VAD are compiled in Table 2. The ICD permits a differentiation of VAD, in contrast to the DSM-III-R. Table 3 lists the features of the various VAD subtypes [53**].**

"Table 1. ICD-10 research criteria for dementia ." [53]

G1.1.	A loss in memory, which is most noticeable when acquiring new material; in more extreme situations, the ability to recall information previously learned may also be impaired. The disability is present in both verbal and nonverbal language.
G1.2.	A reduction in other cognitive functions characterised by a decline in judgement and thinking, such as planning and organising, as well as information processing in general. It is necessary to establish performance degradation from a prior higher level.
G2.	preservation of environmental awareness (i.e., lack of clouding of consciousness, as described by ICD-10 F05) for a long enough period of time to allow the unmistakable evidence of Gl. The diagnosis of dementia should be postponed when delirium episodes are present as well.
G3.	A loss of emotional control or motivation, as well as a shift in social behaviour. At least one of the following symptoms may be present: emotional lability, irritability. Apathy, as well as a coarsening of social behaviour.
G4.	If the time since the manifest onset is less than six months, the criteria GI should have been obviously present for at least that long in order to make a solid clinical diagnosis. The prognosis is only tentative.

"Table 2. ICD-10 research criteria for VAD." [53]

G1.	Evidence of dementia that satisfies a certain level of severity as outlined by the general dementia criteria
G2.	Lack of equality in the distribution of higher cognitive function impairment. Others largely unaffected while some are harmed. Thus, memory may suffer quite a bit whereas thinking, reasoning, and information processing may only suffer slightly.
G3.	Evidence of localized brain damage includes at least one of the following symptoms: unilateral extensor planter response, unilaterally enhanced tendon reflexes, unilateral spastic weakening of the limbs, and pseudobulbar palsy
G4.	There is evidence of substantial cerebrovascular illness from the past, present, or results of tests, which could be interpreted as having an etiological relationship to dementia (history of stroke, evidence of cerebral infarction).

"Table 3: Characteristics of the VAD subtypes in the ICD-10." [53]

VAD subtypes		
Acute onset	F01.0	After a series of strokes or (rarely) after a single massive infarction, dementia sets in quickly (often within a month but no later than three months). After several small ischemia episodes, dementia begins to develop more gradually (i.e., within 3-6 months). Comments: It is assumed that the brain parenchyma has an

Multi-infarct	FOl.1	accumulation of infarcts. There may be times of true clinical improvement in between the ischemic episodes. (a) A history of hypertension.
Subcortical	F01.2	(b) Evidence of vascular discase in the deep white matter of the cerebral hemispheres, with preservation of the cerebral cortex, based on clinical examination and special investigations.
Mixed cortical and subcorticol	F01.3	Clinical characteristics may lead one to believe that the VAD has mixed cortical and subcortical components, inquiry findings, or both.
Other Unspecified	FO1.8 F01.9	In the ICD-10 research criteria no specific diagnostic guidelines for these VAD subtypes are given.

4. THERAPEUTIC APPROACHES IN THE TREATMENT OF AD

4.1 Pharmacological approaches in the treatment of AD

Currently, only two types of drugs—N-methyl-d-aspartate antagonists (NMDA) and cholinesterase enzyme inhibitors—have been licensed to treat AD (naturally occurring, synthetic, and hybrid versions). Acetylcholinesterase inhibitors (AChEIs), which may be classified as reversible, irreversible, or pseudo-reversible, work by preventing the cholinesterase enzymes (AChE and BChE) from degrading ACh, which raises the concentration of ACh in the synaptic cleft [54]. On the other hand, excessive NMDAR activation causes elevated amounts of influxed Ca2+, which encourages synaptic malfunction and induces apoptosis. NMDAR antagonists stop NMDAR glutamate receptor overactivation, which leads to Ca2+ influx, and return it to its normal activity. Although these two classes have a therapeutic effect, they only work to treat AD symptoms; they have no curative or preventive effects [55]. Studies have demonstrated that activating the brain's vascularization, plasticity, and neurogenesis, as well as lowering inflammation by cutting back on A production, all improve cognitive function in older adults. Additionally, it has been demonstrated that exercise improves brain health and lowers the risk of AD. Additionally, the Mediterranean diet (MD), intellectual pursuits, and higher education may all help to improve intellectual capabilities and slow the progression of AD and memory loss. A multi-domain strategy that addresses lifestyle factors (diet, exercise, and cognitive training), the management of AD symptoms, and the reduction of cardiovascular risk factors, according to a variety of studies, can improve or maintain cognitive function and lower the risk of developing AD in older people. [56]. The medications that are currently available and the theories that underpin the development of novel AD therapies are summarized below. There have been reports of the negative pharmacological effects of anticholinergic drugs on human memory and learning at least since the 1970s [57]. Increased anticholinergic drug use was linked to decreased cognitive function. [58]. In addition, a recent meta-analysis showed that taking anticholinergic medications increased the risk of cognitive impairment in older adults with cardiovascular disease [59].

4.1.1 Cholinesterase Inhibitors

According to the cholinergic hypothesis, acetylcholine (ACh) synthesis is reduced in AD. Increasing cholinergic levels by blocking acetylcholinesterase is one treatment strategy that enhances neuronal cell and cognitive function (AChE). AChEIs are used to stop synapses from reducing acetylcholine, which causes persistent ACh accumulation and activation of cholinergic receptors. Tacrine (tetrahydroaminoacridine), which raises ACh in muscarinic neurons, was the first cholinesterase inhibitor medicine to earn FDA (Food and Drug Administration) clearance for the treatment of AD. Due to frequent side effects like hepatotoxicity and a lack of benefits that were observed in numerous trials, tacrine was quickly taken off the market. Eventually, a number of AChEIs were developed, including donepezil, rivastigmine, and galantamine, and these are now used to treat the symptoms of AD[60,61]. The synthesis of acetylcholine at the presynaptic terminals rises as choline reuptake increases, which may help cure AD. The choline transporter (CHT1), which provides choline for the manufacture of ACh, can be targeted to do this. Future AD treatments may involve creating medications that can raise CHT1 at the plasma membrane[62].

4.1.1.1 Donepezil

In the early 1980s, a central cholinergic deficiency was postulated to be related to Alzheimer's disease (AD), leading to the development of cholinesterase inhibitors (AChEIs) (such as donepezil, rivastigmine, and galantamine) for treating AD. Efficacy,

safety, and at least some pharmacoeconomic advantage are crucial factors in determining if a medicine will be successful. While 79% of the recovered dosage was found in the urine and the remaining 21% in the feces, renal excretion is the predominant mechanism for the clearance of both the parent drug and its metabolites in healthy volunteers. Also, the parent molecule is the main urine elimination product.

4.1.1.2 Rivastigmine

Rivastigmine is a butyrylcholinesterase (BuChE) and AChE pseudo-irreversible inhibitor. It works by attaching to the two active sites of AChE (anionic and estearic sites), which stops ACh metabolism. In the healthy brain, BuChE is mostly located in glial cells, with only 10% of AChE activity. In the AD brain, however, BuChE activity is elevated to 40–90%, and since ACh activity is concurrently lowered, this may indicate mild to severe dementia. Since it dissociates more slowly than AChE and is degraded at synapses by both AChE and BuChE, rivastigmine is referred to as a "pseudo-irreversible" medication. Medication is used in mild to moderate AD situations. It enhances everyday activity and cognitive processes. Negative side effects from the drug's oral administration include nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss. [64,65]

4.1.1.3 Galantamine

For mild to severe instances of AD, galantamine is recognized as a traditional first-line therapy. The selective tertiary isoquinoline alkaloid GAL can bind allosterically to the nicotinic acetylcholine receptor's -subunit and activate them in addition to competitively inhibiting AChE. Similar to other AChE inhibitors, GAL has high effectiveness and tolerability and can improve behavioral symptoms, daily activities, and cognitive performance [66].

4.1.2 N-methyl D-aspartate (NMDA) Antagonists

NMDAR is believed to have a prominent role in the pathogenesis of AD. Ca2+ influx induced by NMDAR activation enhances signal transduction and, as a result, causes the transcription of important genes for the establishment of long-term potentiation (LTP), which is essential for synaptic neurotransmission, plasticity, and memory formation. By overactivating NMDARs, glutamate, the main excitatory amino acid in the brain, is overstimulated, which causes excitotoxicity, synaptic dysfunction, neuronal cell death, and a decline in cognitive performance. [67,68].

4.1.2.1 Memantine

Memantine, a low-affinity, non-competitive antagonist of the glutamate receptor subtype NMDAR, prevents AD sufferers from having an overactive glutaminergic pathway that results in neurotoxicity. Memantine is used to treat mild to severe AD, either alone or in combination with AChEI. Memantine inhibits the excitatory receptor without interfering with typical synaptic transmission because of its low affinity, which is easily displaced from NMDAR by high glutamate concentrations. This makes the medicine safe and well-tolerated. This avoids a recurring obstruction. The latter has been associated with severe negative consequences, including those that impair memory and learning[69].

4.2 Promising Future Therapies

4.2.1 Disease-Modifying Therapeutics (DMT)

By addressing a number of pathophysiological pathways, disease-modifying therapy (DMT) slows the course of AD. This contrasts with symptomatic therapy, which focuses on enhancing cognitive abilities and reducing signs of the disease—such as sadness or delusions—while leaving the condition unaffected or unaltered. DMTs, which can be either small compounds or immunotherapies, are taken orally and are being developed to stop or slow AD's progression. There have been several DMT developments and clinical studies. [70,71]

Clinical studies of disease-modifying drugs for the treatment of Alzheimer's disease

Phase 3 Clinical Trials	
Disease Modifying Agents	**Mechanism of Action**
Aducanumab	Monoclonal antibody—targets β-amyloid and eliminates it.
Gantenerumab	Monoclonal antibody—binds and eliminates β-amyloid.

CAD106b	Amyloid vaccine— encourages the production of anti-amyloid antibodies.
BAN2401	Monoclonal antibody—supress protofibrillar β-amyloid.
TRx0237 (LMTX)	Inhibitor of tau protein aggregation.
AGB101	Low-dose levetiracetam— enhances synaptic function while decreasing amyloid-induced neuronal hyperactivity
ALZT-OP1 (cromolyn + **ibuprofen)**	RAGE (Receptor for Advanced Glycation End-products) antagonist—decreases inflammation and amyloid transport into the brain
BHV4157 (troriluzole)	Glutamate modulator— lowers glutamate levels in synapses and enhances synaptic function
Masitinib	Tyrosine kinase inhibitor— modifies inflammatory mast cells and decreases phosphorylation of amyloid protein and tau

"Table 4: Disease modifying agents in Phase 3 clinical trials"[73]

Phase 2 Clinical Trials	
Disease Modifying Agents	**Mechanism of Action**
Crenezumab	Monoclonal antibody— focuses on soluble oligomers and removes β-amyloid
ABBV-8E12	Monoclonal antibody— stops the spread of tau
ABvac40	Active immunotherapy— β-amyloid is targeted and removed
BAN2401	Monoclonal antibody— lowers amyloid plaques and eliminates amyloid protofibrils
BIIB092	Monoclonal antibody— tau is removed and tau propagation is reduced
LY3002813 (donanemab)	Monoclonal antibody— recognises the aggregated pyroglutamate form of Aβ and eliminates it
LY3303560 (zagotenemab)	Monoclonal antibody— eliminates soluble tau aggregates
Semorinemab (RO7105705)	Monoclonal antibody— eliminates extracellular tau
APH-1105	Alpha-secretase modulator— decreases amyloid
Daratumumab	Monoclonal antibody— CD38-targeting immunomodulator that modulates microglial activity
Dasatinib + **Quercetin**	Tyrosine kinase inhibitor (dasatinib) + flavonoid (quercetin)—decreasess senescent cells and tau aggregation
IONIS MAPTRx (BIIB080)	Epigenetic, Tau Antisense oligonucleotide—decreases production of tau
Lithium	Neurotransmitter receptors ion channel modulator—enhance neuropsychiatric symptoms
Nilotinib	Tyrosine kinase inhibitor— encourages the removal of amyloid and tau proteins
Posiphen	Selective inhibitor of APP— inhibits the development of amyloid, tau, and α -synuclein

PTI-125	Filamin A protein inhibitor— decreases tau hyperphosphorylation, synaptic dysfunction, and the interaction of the α7 nicotinic cholinergic receptor.
PQ912	Glutaminyl cyclase (QC) enzyme inhibitor—decreases amyloid plaques and pyroglutamates Aβ production
Riluzole	Glutamate receptor antagonist— supress glutamate-mediated excitotoxicity
Thiethylperazine (TEP)	Activates ABCC1 (ATP binding cassette subfamily C member 1 transport protein)—eliminatess amyloid

"Table 5: Disease modifying agents in Phase 2 clinical trials" [73]

Phase 1 Clinical Trials	
Disease Modifying Agents	Mechanism of Action
BIIB076	Monoclonal antibody— eliminates tau and reduces tau propagation
Lu AF87908	Monoclonal antibody— eliminates tau
anle138b	Aggregation inhibitor— supress tau aggregation
RO7126209	Monoclonal antibody— eliminate amyloid
TPI-287	Stabilizes tubulin-binding and microtubules while reducing cellular damage caused by tau.

"Table 6: Disease modifying agents in Phase 1 clinical trials" [73]

CONCLUSION

The prevalence of AD is rising globally, making it one of the most prevalent causes of dementia. Disease pathology starts years before symptoms show up. A precise diagnosis can be made using spinal fluid, imaging, and neuropsychological testing. Although there is no cure for dementia or Alzheimer's disease, managing cognitive and behavioral symptoms can significantly improve the quality of life for both patients and caregivers. Phospho-tau neurofibrillary tangles and amyloid plaques make up the pathogenesis of Alzheimer's disease. AD pathology can affect asymptomatic, slightly affected (MCI), or demented individuals. We give a general summary of the present state of AD in this article, focusing on recent developments and emphasizing the significance of a paradigm shift to consider AD as a continuum of disease that begins decades before the beginning of memory loss.

ABBREVIATIONS:

AD: Alzheimer disease

NFTs :neurofibrillary tangles

EOAD: Early-onset Alzheimer's disease

LOAD : Late-onset Alzheimer's disease

Ach: Acetylcholine

MMSE: mini mental state examination

PET: Positron emission tomography

ICD: International classification of diseases

APP :The amyloid precursor protein

MRI : Magnetic resonance imaging

Availability of data and materials: Not applicable.

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