Review Article

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

ABSTRACT

Alois Alzheimer first identified Alzheimer disease (AD) in 1907 as a slowly progressing form of dementia that affects cognition, behaviour, and functional status. It is distinguished by the intraneuronal deposits of neurofibrillary tangles(NFTs) and extracellular amyloid b (Ab) plaques. The basis of manifestation of AD is two type- Early-onset Alzheimer’s disease (EOAD), Late-onset Alzheimer’s disease (LOAD). EOAD occur before 65 years of age and is related Mendelian inheritance, which cause mutation in APP, PSEN1 or PSEN2. So it is familial AD. While LOAD occur after age 65 years of age and these is no related to genetic cause. So it is sporadic AD. Screening tests like the MMSE and the Montreal Cognitive Assessment are used to help with evaluation and tracking the rate and pattern of cognitive decline. Clinical biomarker testing is now available to assist physicians in determining the presence and extent of AD pathologic changes, as well as their downstream effects. Amyloid PET allows for the detection of fibrillar (plaque) amyloid. Although though AD is a public health concern, only two pharmacological classes are currently approved to treat AD: antagonists of N-methyl d-aspartate and inhibitors of the cholinesterase enzyme (naturally occurring, synthetic, and hybrid variants) (NMDA). Reduced acetylcholine (ACh) production is the cause of AD. One of the therapeutic approaches that improves cognitive and neural cell performance is increasing cholinergic levels by inhibiting acetylcholinesterase. The first cholinesterase inhibitor medicine for the treatment of AD that the FDA (Food and Drug Administration) approved was tacrine.

KEYWORDS

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

1.INTRODUCTION

Alois Alzheimer first identified Alzheimer disease (AD) in 1907 as a slowly progressing form of dementia that affects cognition, behaviour, and functional status[1].It is distinguished by the intraneuronal deposits of neurofibrillary tangles(NFTs) and extracellular amyloid b (Ab) plaques. When tau proteins are hyperphosphorylated, they form paired helical filaments (PHFs), whereas amyloid b peptide aggregates form Ab. It is recognised that the hyperphosphorylated state facilitates tau aggregation in PHF, which causes microtubule instability, membrane deterioration, and neuronal injury. The amygdale, hippocampal formation, parahippocampal gyrus, and temporal association cortex are the sites of neurofibrillary tangles in AD, whereas senile plaques are dispersed across the association neocortex and are located in the striatum. The most severe neurofibrillary degeneration is found in the entorhinal cortex, amygdale, temporal association cortex, and CA1 and subiculum of the hippocampus. 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]. Studies of naming, spontaneous speech, verbal fluency, naming to definition, vocabulary, knowledge of attributes, category knowledge, and conceptual priming show that AD subjects perform significantly worse than normal elderly control subjects. Two approaches to determining whether conceptual knowledge is lost or unavailable include (1) investigating the consistency of errors in multiple tasks that use the same stimuli and (2) repeated administrations of the same task. Warrington (1975) described error consistency in three patients with diffuse cerebral lesions and atrophy (cause unknown in two, "arteriosclerosis" the cause in the third) using naming and word-to-picture matching tasks with the same stimuli[3].WHO declares AD as a global public health priority because of not enduring treatment available for AD. Only the hypothesis known about AD, not knowing actual etiology. It is found that females are more susceptible then mans. And the persons having disease conditions like diabetes & hypertension has more risk chance to developed AD in future[4].AD also called neurodegenerative deformation, it is mark by intellectual disability, loss of physical & mental abilities, amnesia, etc. It is found that around 50 million people globally having dementia and it is awaited that by 2050, 150 million AD cases will reached[5]. The WHO estimates that 50 million individuals globally have dementia, with 10 million new cases being identified year. Deeper understanding of the aetiopathogenesis of dementia has been gained through a number of prospective, long-term studies conducted in North America and Europe; however, comparable studies in low- and middle-income countries (LMICs), such as South Asia (India, Pakistan, Afghanistan, Bangladesh, Nepal, Bhutan, Sri Lanka, and the Maldives), are lacking [6].It by 2020, it is expected that approximately 70% of the world's population will be over the age of 60 and above will live in developing countries, with India accounting for 14.2%[7].

2.PATHOGENESIS

On the basis of manifestation of AD is two type- Early-onset Alzheimer’s disease (EOAD), Late-onset Alzheimer’s disease (LOAD). EOAD occur before 65 year of age and is related Mendelian (usually dominant) inheritance, which cause mutation in APP, PSEN1 or PSEN2. So it is familial AD. While LOAD occur after age 65 year of age and these is no related to genetic cause. So it is sporadic AD[8]. Most studies agree that the classical pathological criteria for Alzheimer's disease, neuritic plaques and neurofibrillary tangles, can account for 40%-70% of the variance in cognition seen in elderly subjects, with additional pathologies such as cerebrovascular disease and Lewy body pathology accounting for the remaining 40%-70%.

2.1 amyloid cascade hypothesis

The amyloid precursor protein (APP) is a member of a protein family that includes the amyloid precursor-like proteins (APLP1 and APLP2) in mammals. APP regulates cell growth, motility, neurite outgrowth, and cell survival, functions that can be replicated by the soluble ectodomain released by APP cleavage.APP is produced in large quantities in neurons and is rapidly metabolised. There are several alternative pathways for APP proteolysis, some of which produce the Aβ peptide and others do not. After sorting in the endoplasmic reticulum and Golgi, APP is delivered to the axon and transported to synaptic terminals via fast axonal transport.On the cell surface, APP can be proteolyzed directly by α -secretase and then by γ -secretase, a process that does not produce Aβ. γ-secretase is a multiprotein complex composed of presenilin 1 (PS1) or PS2; nicastrin (Nct), a type I transmembrane glycoprotein; and Aph-1 and Pen-2, two multipass transmembrane proteins. In the brain, large amounts of APP are continuously metabolised to Aβ. The concentration of Aβ42 in cerebrospinal fluid (CSF) begins to fall early in the development of Alzheimer's disease, while the concentration of Aβ42 in the brain rises[9]. Secretase enzymes cleave APP into various sized alpha and beta amyloid oligomers. Amyloid plaques are made up of 40 or 42 amino acid of beta amyloid oligomers. In cell culture, these beta amyloid oligomers are neurotoxic and are thought to be involved in tau protein hyperphosphorylation. The current theory, a variation on the original amyloid cascade hypothesis, holds that beta amyloid oligomers cause the damage, rather than amyloid fibrils that leads to Alzheimer's disease. Indeed, amyloid plaques may reduce damage by absorbing beta amyloid oligomers. The APP is produced in the cell body, transported

along the axon, and results in the formation of a swelling (an axonal bulb) proximal to the tear.If neuronal death occurs as a result of neuronal damage, the breakdown products of APP are likely to misfold and lead to amyloid deposition; in this case, amyloid is a result of neuronal death rather than its cause. The observation is that beta amyloid cleavage products of APP are neurotoxic contradicts the idea that APP is protective[10]. Fyn is a protein that connects Aβ to tau. This nonreceptor tyrosine kinase that positively regulates N-methyl-Daspartate (NMDA) receptor activity has recently been shown to be targeted to postsynaptic sites in dendrites by tau, which binds fyn directly.The interpretation of these experiments must take into account that tau is normally highly enriched in axons relative to dendrites but is extensively redistributed into the somatodendritic compartment in response to Aβ. Excess fyn coexists with excess tau in AD dendrites, where it upregulates NMDA receptor activity, flooding the dendrites with potentially harmful calcium levels. Excitotoxicity caused by calcium can damage postsynaptic sites and cause neuron death. As a result, decreasing fyn dendritic content may protect human neurons from the Aβ-induced, tau-dependent hyperactivity of NMDA receptors that occurs[11].

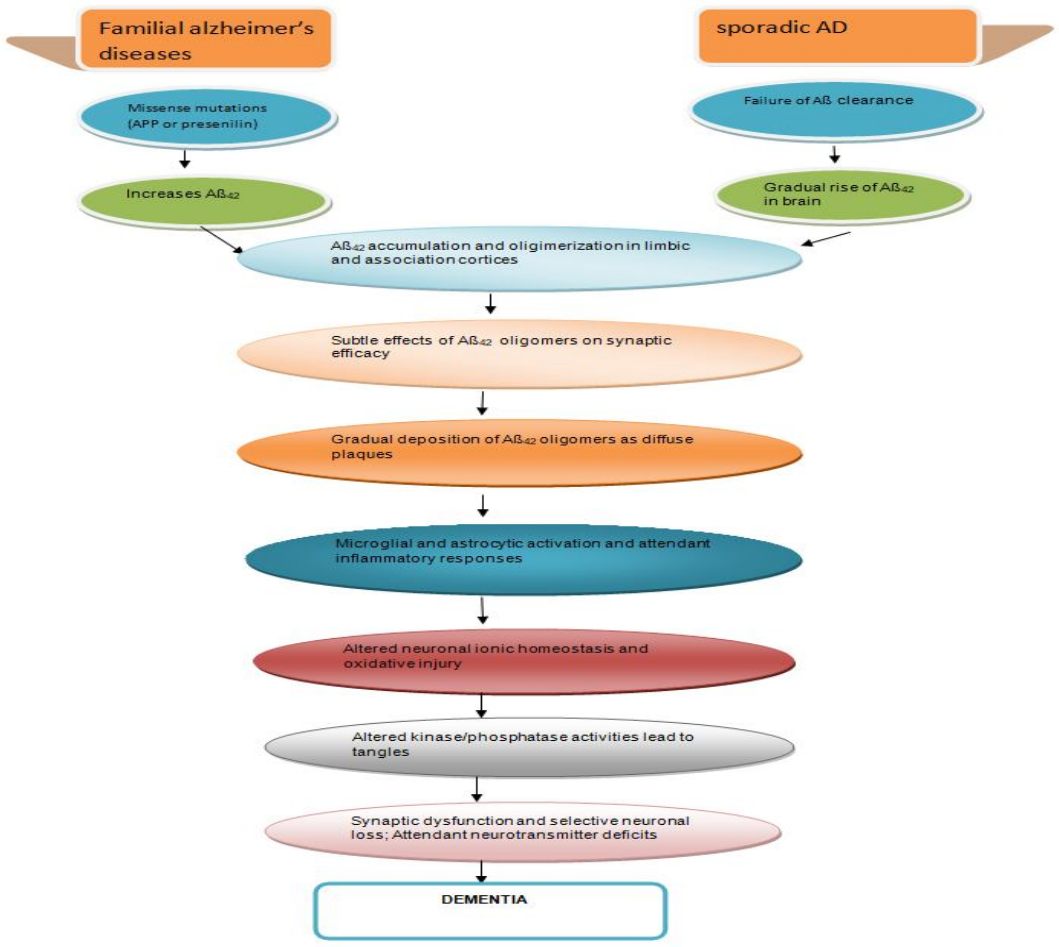

Figure 1: This hypothesis represents the classic theory of the origins of AD. Both familial forms of AD and sporadic AD leading to formation of excess Aß.

2.2 Neurofibrillary Tangles

Bundles of abnormal filaments accumulating in neuronal perikarya, dendrites, and axons which is made up of NFT. These filaments are described as two helicoidally twisted filaments that show regular constrictions or appear straight. (hence their name 'paired helical filaments', PHF).There are several morphological types of NFT that can be distinguished, which most likely correspond to different evolutionary stages.The 'Pretangle' stage is distinguished by the accumulation of phosphorylated tau in the somatodendritic compartment in the absence of PHF formation. A few tau-immunoreactive rods appear in the soma and dendrites later on. Classical NFTs are composed of tightly packed bundles that fill a portion of the cell body and extend into dendrites. Neuronal death is accompanied by a partial desaggregation of NFT, resulting in a more loose appearance. However, in many anatomoclinical studies, NFT densities were found to be more closely linked to the degree of dementia than senile plaques, indicating that NFT formation more directly correlates with neuronal dysfunction.NFT are first discovered in the transentorhinal cortex, a transition area between the adjacent entorhinal cortex and the temporal neocortex (stage I); NFT are then discovered in the layer pre-• of the entorhinal cortex (stage II); patients do not exhibit any cognitive deficits at these stages.NFT become abundant in the entorhinal cortex and numerous in the hippocampus in the subsequent stages (III and IV), which correspond to clinically incipient Alzheimer's disease. NFT are abundant in neocortical association areas (where they are predominantly found in layers III and V) at the final stages (V and VI), and this stage corresponds to full-blown Alzheimer's disease. Several brain areas, including primary motor and sensory cortical areas, the cerebellum, and the spinal cord, are relatively unscathed. Some neuronal populations appear to be resistant to NFT formation. In contrast to Aß deposits, which can be abundant in nondemented people, abundant NFT are not seen in cognitively unimpaired individuals[12]. Tau, a microtubule-associated protein (MAPT), polymerizes tubulin into microtubules and helps to maintain the complex neuronal cell microarchitecture, such as microtubule assembly and stabilisation, especially in the axon.Tau is a phosphoprotein whose biological activity is controlled by the level of phosphorylation. Tau isoforms are prone to disordering in aqueous solution due to their abundance of polar, glycine, and proline residues, as well as their low hydrophobic residue content. Furthermore, they contain one or two cysteine residues that are prone to oxidation and adduct formation. Tau can damage the plasma

membrane and microtubules in neuronal cells. Changes in synaptic distribution and disruption of synaptic protein interactions can impair neuronal function and even lead to Alzheimer's disease[13].

2.3 The cholinergic hypothesis

A number of human studies have found that basal and rostral forebrain cholinergic pathways, including converging projections to the thalamus, play important functional roles in conscious awareness, attention, working memory, and a variety of other mnemonic processes. For more than two decades, studies of the brains of people with advanced age and Alzheimer's disease (AD) have consistently found damage or abnormalities in these pathways (particularly basal forebrain projections), which appeared to correlate well with the level of cognitive decline. The "cholinergic hypothesis" was created as a result, which basically asserts that a drop in cholinergic function in the central nervous system plays a substantial role in the cognitive decline brought on by advancing age and Alzheimer's disease. Indeed, the importance of cholinergic function in the brain to learning and memory was discovered more than 30 years ago, when cholinergic antagonists (specifically antimuscarinic agents) were discovered to impair memory in rats. Furthermore, lesions in animals that disrupt cholinergic input from the basal forebrain to the neocortex or hippocampus (e.g., nucleus basalis magnocellularis and medial septum/diagonal band) disrupt performance of the same memory tasks that are impaired by cholinergic blockade. It should be noted that damage to similar basal forebrain regions in humans (as a result of arterial aneurysms or resection of an arteriovenous malformation) has also been linked to severe memory deficits[14]. to this day, cholinesterase inhibitors (ChEIs) are the most commonly used pharmacological treatments for cognitive deficits in Alzheimer's disease. Currently, three ChEIs – donepezil, rivastigmine, and galantamine – are widely used as standard of care for the pharmacological treatment of clinically symptomatic stage Alzheimer's disease. The above body of ideas indicating that decline in a system regarded as fundamental for memory mechanisms contributes to age-associated memory losses, along with evidence of atrophy of that system in Alzheimer's disease, became the simplified "cholinergic hypothesis of Alzheimer's disease" , and was understood to be causative of the disease[15]. Shore discovered ApoE, a 34 kDa lipid-binding protein, in very low-density lipoprotein in 1973. It is primarily found in VLDL, chylomicron (CM), and their byproducts. ApoE is required for lipoprotein metabolism. It can bind to the hepatic cell membrane chylomicrons (CM), VLDL debris, and some HDL (ApoE) receptors in addition to the LDL receptor. ApoE transports triglycerides and cholesterol in various tissues. Based on ApoE protein's pivotal role in lipoprotein metabolism in the brain and the periphery, its expression regulation and expression types have an important connection with Alzheimer's disease (AD). There are three isoforms of the apoE gene: 2, 3, and 4, and the apoE 3 allele is the most common (77.9%), the 2 allele is the least common (8.4%), and the 4 allele is in the medium(13.7%)[16]. The mechanisms by which APOE genotype influences AD onset and progression remain unknown. apoE is an extracellular protein that is primarily expressed by astrocytes and taken up by neurons in the brain; however, under certain conditions, apoE can also be expressed by microglia and neurons. Carriers of one copy of the APOE 4 gene are three times more likely to develop Alzheimer's disease, and those who are homozygous for the APOE 4 gene are ten times more likely to develop the disease. Furthermore, the age of onset is younger in the APOE 4 AD population. The precise mechanism by which apoE influences AD is unknown. The presence of extracellular A deposition, forming amyloid plaques, and the intracellular presence of neurofibrillary tangles (NFT), composed of aggregations of hyperphosphorylated tau protein, are two of the major hallmarks of AD. One theory linking apoE and AD involves apoE and A peptides interacting directly. ApoE has been found in A plaques found in Alzheimer's disease brains[17].

2.4 Mitophagy associated with development of AD

Mitophagy is simply the removal of dead mitochondria through autophagy. The formation of a spherical structure double membrane 'autophagosome' initiates mitophagy. Mitophagy is an important process in maintaining cell health. It increases mitochondrial turnover and prevents the accumulation of dysfunctional mitochondria, which can lead to cellular degeneration. Mitophagy is regulated by PINK1 and Parkin proteins. A double-layered membrane-enclosed, spherical structure is an autophagosome. It is a crucial component of macroautophagy, which breaks down cytoplasmic materials inside cells. Autophagosomes transfer cytoplasmic components to lysosomes after they have formed. An autolysosome is created when the outside membranes of an autophagosome and a lysosome combine. The contents and inner membrane of the lysosome are degraded by its hydrolases. Atg genes and LC3 complexes control the development of autophagosomes. Additionally, the Atg12-Atg5 conjugate interacts with Atg16 to create bigger complexes. The elongation of the first membrane depends on Atg12's modification of Atg5. After the spherical shape is formed, the Atg12-Atg5:Atg16L1 complex separates from the autophagosome. LC3 is cleaved by ATG4 to generate LC3. The final fusion of an autophagosome with its target membrane requires LC3 cleavage An autolysosome is created when the outside membranes of an autophagosome and a lysosome combine. The contents and inner membrane of the lysosome are degraded by its hydrolases. Atg genes and LC3 complexes control the development of autophagosomes. Additionally, the Atg12-Atg5 conjugate interacts with Atg16 to

create bigger complexes. The elongation of the first membrane depends on Atg12's modification of Atg5. After the spherical shape is formed, the Atg12-Atg5:Atg16L1 complex separates from the autophagosome. ATG4 breaks down proteins LC3 to produce LC3.The final fusion of an autophagosome with its target membrane requires LC3 cleavage[18]. The production of energy in eukaryotes, including the synthesis of phospholipids and heme, calcium homeostasis, apoptosis activation, and cell death, is carried out by mitochondria, which are essential to appropriate cellular function[19]**.** Mitophagy is comprised of four basic steps. I Initiation of mitophagic process. (ii) Mitophagy process preparation for identification by autophagic machinery. (iii) Mitochondrial engulfment and mitophagosome formation. (iv) Lysosomal degradation. When under stress, mitofusin 1 and 2 (Mfn1 & 2) govern the inhibition of mitochondrial fusion, and optic atrophy 1 (OPA1) starts mitophagy. DRP1 becomes localised at the mitochondrial associated endoplasmic reticulum membrane. In injured mitochondria, matrix protein mitochondrial processing peptidase and presenilin-associated rhomboid-like protease are suppressed, which stabilises PINK1 on the outer mitochondrial membrane (OMM). Parkin and ubiquitin are both phosphorylated by PINK1, and they also signal the autophagic machinery to recognise mitochondria by ubiquitinating a number of OMM proteins and starting the production of mitophagosomes by binding to microtubule associated protein 1 light chain 3 (LC3). Following that, the fusion of mitophagosome and lysosome produces mitolysosome, which leads to the elimination of faulty mitochondria. In general, there are two types of mitophagy mechanisms: ubiquitin-dependent and ubiquitin-independent[20]**.** Two important cellular degradation mechanisms in eukaryotes are the ubiquitin-proteasome system (UPS) and autophagy, both of which are essential in removing misfolded/unfolded proteins to preserve cell and tissue homeostasis, prevent aging-related alterations, and a variety of human diseases[21]**.**

3. DIAGNOSTIC STRATEGIES FOR AD

3.1 Clinical diagnosis and history of present illness

Alzheimer's disease is characterised by a gradual decline in cognitive function, as well as functional consequences. Hippocampal sclerosis (HS) is characterised by severe neuronal loss and gliosis in the hippocampal formation's CA-1 and subiculum. The onset is gradual, with patients asking questions repeatedly, repeating conversations, and having difficulty remembering details of shared or current events. Names of objects and people are difficult to recall. Patients with hippocampal sclerosis exhibit a similar amnestic profile, but their cognitive deficits progress more slowly than in AD. Results show that patients with HS have a slower decline on the Mini-Mental State Examination (MMSE) than those with AD[22]. Despite being studied primarily in temporal lobe epilepsy, HS is increasingly being recognised as the cause of dementia in up to 25% of the "oldest old "[23]**.**

3.2 Neurocognitive testing

The hallmark of Alzheimer's disease is impaired information consolidation or storage, with relatively spared registration and recall[24]**.** Screening tests like the MMSE and the Montreal Cognitive Assessment (MoCA) are used to help with evaluation and tracking the rate and pattern of cognitive decline[25,26]**.** Additional Alzheimer's Association-recommended screening tests include the General Practitioner Assessment of Cognition (GPCOG), the Mini-Cog, and the Memory Impairment Screen[27]. The MMSE's historical significance and continued widespread use by community clinicians justify its inclusion in some settings, particularly during an initial visit or in screening for clinical trials. Despite its screening value, some have questioned the MMSE's ability to detect decline at assessments less than three years apart[28]. The MoCA is divided into sections that loosely correspond to specific cognitive domains, such as 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. Although the benefit of cued recall is not reflected in the total score, the "Memory Index Score," which is now included in version 8, does track this valuable information and predicts the transition from MCI to AD[29]**.** When the patient is unwilling or uncooperative to be screened, caregiver questionnaires such as the Ascertain Dementia 8, the GPCOG informant interview component, and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) Short Form can be useful[30].

3.3 Physical examination

Early in the disease process, the general physical examination is usually normal; focal neurologic signs raise the possibility of alternative or comorbid reasons for cognitive decline. Extrapyramidal symptoms, which could be caused by subcortical cerebrovascular disease or comorbid pathology like dementia with Lewy bodies (DLB), cerebrovascular disease, progressive supranuclear palsy (PSP), corticobasal degeneration syndrome, normal pressure hydrocephalus, or other conditions, could develop as the disease worsens. Gait should be examined, and concerns about safety should prompt a referral to physical therapy. Comprehensive physical and neurologic examinations should be performed during the initial visit, with more focused examinations performed on subsequent visits. Include vital signs, such as weight/BMI and a pain assessment (and followed longitudinally). Jaundice, pedal edoema, trophic vascular skin changes, and other physical indicators of end-organ failure, delirium (asterixis or myoclonus, severe

attentional impairments, changeable degree of awareness), and abuse, neglect, or falls (ecchymosis, burns, and other symptoms) should all be observed[31].

3.4 Biomarkers of AD

Clinical biomarker testing is now available to assist physicians in determining the presence and extent of AD pathologic changes, as well as their downstream effects. (1) The presence of low Ab42 levels in CSF or a positive amyloid PET scan is specific for the AD pathology continuum. Ab42 defines at least the presence of underlying Alzheimer's pathologic change in this new biologic definition of Alzheimer's disease. (2) The presence of elevated phosphorylated tau in CSF or positive tau PET (not currently clinically available) is then required for the presence of underlying AD. The presence of Ab42 and phosphorylated tau biomarkers biologically defines AD. (3) Finally, neuronal injury markers such as elevated CSF total tau, atrophy on MRI brain, or temporo-parietal hypometabolism on fluorodeoxyglucose (FDG) PET scan are neither necessary nor sufficient to define the underlying "Alzheimer's continuum." However, elevated CSF total tau, atrophy on MRI, and hypometabolism on FDG PET are biomarkers of neuronal injury that can be useful in staging the severity of the underlying disease and comorbid pathologic change. While their widespread use in routine clinical practise would be prohibitively expensive, these biomarkers pave the way for a more "biologically" based (rather than signs and symptoms-based) research framework. This "ATN" staging is defined by the presence or absence of amyloid, tau, and/or neurodegeneration[32]. The practical importance of obtaining biomarker evidence to support a clinical diagnosis of AD arises in the context of atypical presentations (behavioural, language, or visual variants; young age) or when diagnostic criteria for other etiologies (particularly frontotemporal dementia) are met. Although there is limited data, typical biomarkers for Alzheimer's disease (with the exception of hippocampal atrophy) are not expected to be present in limbic-predominant age-related TDP-43 encephalopathy late[33]. A stepwise approach is frequently used, beginning with MRI and FDG-PET, which can show a distinct pattern of hippocampal/parietal atrophy (on MRI) and lateral and mesial temporoparietal hypometabolism, which is typical of AD and makes alternative etiologies less likely. Depending on available resources, CSF evaluation or amyloid PET can be used to definitively establish the presence of AD pathology[34,35].

3.5 Magnetic resonance imaging (MRI)

It is well established that Alzheimer's disease (AD) and related neurodegenerative disorders are associated with brain atrophy, which can be reliably detected using quantitative MR image analysis. Quantification of structural MR images can reveal significant atrophy in medial temporal lobe structures, which is consistent with histologic findings. Increases in ventricular volume, particularly in the inferior portion of the lateral ventricle, are usually associated with such tissue loss. Quantitative MR imaging may also aid in the early detection of AD-related neuropathologic disorders. Patients who perform moderately poorly on one or more standardised cognitive function tests are frequently classified as having mild cognitive impairment (MCI). Individuals are more likely to develop AD if memory is one of the cognitive domains involved. Medial temporal atrophy has been found to predict whether a patient with MCI will decline rapidly or remain stable. Several studies have demonstrated that neurodegenerative disorders are consistently associated with patterns of progressive neural atrophy that can be identified using quantitative MR image analysis.Volumetric analysis of regional brain structures may thus aid in the characterization of a patient's condition by providing objective quantitative evidence of a disease process. Such measures may also have prognostic value, assisting in identifying patients who are most at risk of rapid clinical deterioration. Existing methods for obtaining quantitative volumetric information from MR images, however, have been limited to small-scale research studies[36,37].

3.6 Amyloid PET

Amyloid PET allows for the detection of fibrillar (plaque) amyloid. Although there are several experimental tracers available, the FDA currently approves Amyvid (18F-Florbetapir), Neuraceq (18F-Florbetaben), and Vizamyl (18F-Flutemetamol)[38]. The FDA approved this test to "estimate Ab neuritic plaque density in adult patients with cognitive impairment being evaluated for AD and other causes of cognitive decline." Although a positive scan is not conclusively diagnostic of Alzheimer's disease, a negative scan rules out Alzheimer's in favour of other types of dementia. Cognitive status, age, and genetic risk factors are all likely to influence the threshold for amyloid positivity[39]. The use of amyloid PET has been linked to changes in the clinical management of patients with MCI and AD dementia[40]. Additional tau and synapse PET scans are available only for research purposes[41]. At this time, tau PET imaging correlates best with atrophy, hypometabolism, and cognitive decline. CSF analysis is obtained on occasion to determine fluid concentrations of Ab, total and phosphorylated tau[42].

3.7 Fluorodeoxyglucose positron emission tomography (FDG-PET)

FDG-PET imaging is the marker for neurodegeneration. When the patient having dementia the brain of patient having a decreased rate of metabolic activity. FDG-PET scales the decreased brain glucose consumption is slightly associated to astrocyte activity. So the FDA-PET is used for evaluation & diagnosis of the range of metabolic activity & also shows neuronal abnormality. FDG-PET imaging testing is very useful in the diagnosis the early detection of AD. Its finds earlier neurodegeneration prior then MRI scanning in the patient with impaired cognition which will go to develop dementia. The test is also helpful for the identify staging of disease. Since the models of brain hypometabolism nearly linked with the type and intensity of cognitive problem. When we talk about five phase strategic plan defined to stimulate & advance clinical validation or objective evidence the FDG-PET is the PET biomarker which shows the excellent & more modern phase of validations[43]. Decreased in the cerebral metabolism is seen in AD. These same changes are seen in the cognitively normal person at are high risk for AD because of the manifestation of APOE4allele[44]. FDG-PET is also used to differentiate AD from other dementia and it will estimate or track downfall from general cognition to AD, so it will identify the patient is at risk for AD before to onset of cognitive symptoms. By the last 30 years of FDG-PET studying it is found that first of all AD is mark by specific regional models & patterns of CMRglc reductions. In the AD patients they regularly shows CMRglc deficiency in the parieto temporal area, at posterior cingulate cortex and at MTL. At later disease is progressive frontal associations cortices is also involved and other areas like striatum, primary visual, cerebellum, basal ganglia and sensorimotor cortices where stay preserved. Without decreased in the CMRglc the clinical presentation are not shown in AD. And CMRglc is extremally match up with clinical incapacity dysfunction. The standard disease exclusive PET models are classified 92% DLB, 94% FTD, 94% NF & 95% AD[45]. Reduction FDG-PET magnificence reflects abnormality and tau arbitrate neuronal injury. There were comparative studies were done for AD & it is found that FDG were given good result compare to MRI scanning[46]. FDG-PET is create value for characteristic prognostic of neurodegenerative disease and it will vaticinate of shortend clinical outcomes and also finding the staging ang progression of AD[47].

3.8 Mini mental state examination(MMSE)

The mini mental state examination (MMSE) is one of the most plausible scale for the verification of the neurocognitive disorders. The 30 MMSE were firstly used to identify the difference between the psychiatric patient and neurological patients. During the use of MMSE it is see that MMSE shows both good test- retest credibility (0.80-0.95) and admissible susceptibility (0.86) and specialty or predominance (0.92) through which defines the mental disorders. It is mainly used to find out the therapeutic agent effect on patient and also for follow up[48]. In the MMSE test there is a set sat of 30 questions evaluations of perceptional function that estimate consideration and orientation, language, remembrance, count, registration, memorize and the caliber to exert a complex polygon. But it is found the MMSE is not useful to identify the dementia at early stage and also not identify to predict stages of dementia, development of chronic or long term dementia & not able to differ different types of dementia. But the advantage of MMSE is including the higher rate of acceptance by health professionals & tester or clinicians for diagnostic instrument in multiple languages, fast administration. The result is founded through total score[49]. MMSE is one of the most applied concise neurocognitive examination for trial and monitoring the advance of dementia in old age[50]. Rapid cognitive loss is explained by MMSE, when the loss occurred 4 points and greater then 4 points on the MMSE in the 6 months. The expected average reduction on MMSE score in an AD patient differ between 2 and 4 points per year. So the loss of 4 or more then 4 points describes a rate of reduction at least two times that commonly required[51].

3.9 The ICD-10 criteria for vascular dementia

"To establish and amend as necessary international nomenclatures of diseases, of 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 “mum i-infarct dementia” is used to describe all types of VAD. Differentiation of VAD subtypes is permitted by the new ICD-10 criteria.

3.10Introduction of the new ICD-10

The world health organization (WHO) introduces the 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 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 DSM-III-R. Table 3 lists the features of the various VAD subtypes[53].

"Table 1. ICD-10 research criteria for dementia ."

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."

G1.	Evidence of dementia meeting a specific level of severity as defined 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."

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).
Multi-infarct	FOl.1	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 accumulation of infarcts. There may be times of true clinical improvement in between the ischemic episodes.
Subcortical	F01.2	(a) A history of hypertension. (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

There are currently just two kinds of medications that have been approved to treat AD, which are N-methyl-d-aspartate antagonists (NMDA) and cholinesterase inhibitors (naturally occurring, synthetic, and hybrid versions). Acetylcholinesterase inhibitors (AChEIs) which are classified as reversible, irreversible, and pseudo-reversible, act by blocking cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, which results in increasing ACh levels in the synaptic cleft[54]. On the other hand, overactivation of NMDAR leads to increasing levels of influxed Ca2+, which promotes cell death and synaptic dysfunction. NMDAR antagonist prevents overactivation of NMDAR glutamate receptor and hence, Ca2+ influx, and restores its normal activity. Despite the therapeutic effect of these two classes, they are effective only in treating the symptoms of AD, but do not cure or prevent the disease[55]. Activating the brain's vascularization, plasticity, and neurogenesis, as well as reducing inflammation by reducing Aβ production, have all been shown in studies to improve cognitive function in older adults. Physical activity also has been shown to reduce the risk of AD and increase brain health. In addition, the Mediterranean diet (MD), intellectual pursuits, and higher education may all slow the deterioration of AD and memory loss as well as improve cognitive abilities. According to a number of studies, a multi-domain approach that addresses lifestyle factors (diet, exercise, and cognitive training), the management of AD symptoms, and the reduction of cardiovascular risk factors can improve or maintain cognitive function and reduce the risk of developing AD in older people. [56]. Below, we provide a summary of the medications currently on the market as well as the ideas supporting the discovery of novel AD therapies. Since at least the 1970s, there have been reports of the harmful pharmacological effects of anticholinergic medications on human memory and learning[57]. Reduced cognitive performance was associated with increasing anticholinergic drug use. [58]. Furthermore, a recent meta-analysis demonstrated that the exposure of older adults with cardiovascular disease to anticholinergic drugs was associated with an increased risk of cognitive impairment[59].

4.1.1 Cholinesterase Inhibitors

The cholinergic theory holds that AD results from a decrease in acetylcholine (ACh) production. One of the therapeutic approaches that improves cognitive and neural cell performance is increasing cholinergic levels by inhibiting acetylcholinesterase (AChE). AChEIs are used to prevent the synapses from degrading acetylcholine, which leads to continual ACh buildup and activation of cholinergic receptors. The first cholinesterase inhibitor drug for the treatment of AD to receive FDA (Food and Drug Administration) approval was tacrine (tetrahydroaminoacridine), which increases ACh in muscarinic neurons. Tacrine was quickly taken off the market due to a high incidence of side effects like hepatotoxicity and a lack of benefits, which were seen in several trials.Later on, several AChEIs were introduced, such as donepezil , rivastigmine , and galantamine , and are currently in use for the symptomatic treatment of AD[60,61]. Increased choline reuptake leads to an increase in acetylcholine production at the presynaptic terminals, which may aid in the treatment of AD.This can be achieved by targeting choline transporter (CHT1) which is responsible for supplying choline for the synthesis of ACh. Developing drugs that are capable of increasing CHT1 at the plasma membrane may become the future therapy of AD[62].

4.1.1.1 Donepezil

inhibitors (AChEIs) (ie, donepezil, rivastigmine, galantamine) developed for the treatment of Alzheimer’s disease (AD) after the postulation in the early 1980s that AD was associated with a central cholinergic deficit[63] . Major issues for a drug to be successful include efficacy, safety, and at least some pharmacoeconomic benefit. Donepezil is hepatically metabolised in healthy volunteers, and renal excretion is the primary pathway for the clearance of both the parent drug and its metabolites, as 79% of the recovered dose was discovered in the urine and the remaining 21% in faeces. Moreover, the primary urine elimination product is the parent molecule.

4.1.1.2 Rivastigmine

Rivastigmine is a pseudo irreversible inhibitor of AChE and butyrylcholinesterase (BuChE) that acts by binding to the two active sites of AChE (anionic and estearic sites), which results in preventing ACh metabolism. BuChE is found mostly in glial cells with only 10% of AChE activity in the normal brain, whereas in the AD brain, its activity is increased to 40–90%, while BuChE action may point to a moderate to severe dementia since ACh activity is decreased concurrently. Rivastigmine is known as a pseudo-irreversible because it dissociates more slowly than AChE and is metabolised at the synapses by both AChE and BuChE. In cases of mild to moderate AD, the medication is used. It improves cognitive functions and daily life activities. Oral administration of the drug is associated with adverse effects such as nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss. [64,65]

4.1.1.3 Galantamine

For mild to severe cases of AD, galantamine is regarded as a conventional first-line treatment. AChE is competitively inhibited by the selective tertiary isoquinoline alkaloid GAL, which also has the ability to bind allosterically to the α-subunit of nicotinic acetylcholine

receptors and activate them. Similar to other AChE inhibitors, GAL can enhance behavioural symptoms, everyday activities, and cognitive performance with good efficacy and tolerability[66].

4.1.2 N-methyl d-aspartate (NMDA) Antagonists

In the pathophysiology of AD, NMDAR is thought to play a starring role. Ca2+ influx brought on by NMDAR stimulation increases signal transduction and, as a result, triggers the transcription of key genes for the development of a long-term potentiation (LTP), which is crucial for synaptic neurotransmission, plasticity, and memory formation. The principal excitatory amino acid in the Brain, glutamate, is overstimulated by excessive NMDAR activation, which results in excitotoxicity, synaptic malfunction, neuronal cell death, and a loss in cognitive abilities. [67,68].

4.1.2.1 Memantine

Memantine is a low-affinity, non-competitive antagonist of the NMDAR, a subtype of glutamate receptor, which stops the glutaminergic system from becoming overactive and causing neurotoxicity in AD cases. When combined with AChEI or administered alone, memantine is used to treat moderate to severe AD. Due to memantine's low affinity, which is displaced quickly from NMDAR by high glutamate concentrations, the medication blocks the excitatory receptor without interfering with normal synaptic transmission, making it safe and well-tolerated. This prevents a chronic blockage. The latter is linked to serious adverse effects, particularly those that affect memory and learning[69].

4.2 Promising Future Therapies

4.2.1 Disease-Modifying Therapeutics (DMT)

Disease-modifying treatment or therapy (DMT) alter the progression of AD by working on several pathophysiological mechanisms. This is in contrast to symptomatic therapy which works on improving the cognitive functions and decreasing symptoms such as depression or delusions without affecting or modifying the disease. DMTs, either immunotherapies or small molecules, are administrated orally and are being developed to prevent AD or decrease its progression. Several DMTs have been developed and entered the clinical trials[70,71]

Disease modifying agents for the treatment of Alzheimer’s disease in clinical trials

Phase 3 Clinical Trials	
Disease Modifying Agents	**Mechanism of Action**
Aducanumab	Monoclonal antibody—targets β-amyloid and removes it.
Gantenerumab	Monoclonal antibody—binds and removes β-amyloid.
CAD106b	Amyloid vaccine—stimulates production of antibodies against β-amyloid.
BAN2401	Monoclonal antibody—reduces protofibrillar β-amyloid.
TRx0237 (LMTX)	Tau protein aggregation inhibitor.
AGB101	Low-dose levetiracetam—improves synaptic function and reduces amyloid-induced neuronal hyperactivity
ALZT-OP1 (cromolyn + ibuprofen)	RAGE (Receptor for Advanced Glycation End-products) antagonist—reduces inflammation and amyloid transport into the brain
BHV4157 (troriluzole)	Glutamate modulator—reduces synaptic levels of glutamate and improves synaptic functioning
Masitinib	Tyrosine kinase inhibitor—modulates inflammatory mast cell and reduces amyloid protein and tau phosphorylation

“Table 4: Disease modifying agents in Phase 3 clinical trials”

Phase 2 Clinical Trials	
Disease Modifying Agents	**Mechanism of Action**
Crenezumab	Monoclonal antibody—targets soluble oligomers and Removes β-amyloid
ABBV-8E12	Monoclonal antibody—prevents tau propagation
ABvac40	Active immunotherapy—targets β-amyloid and removes it
BAN2401	Monoclonal antibody—removes amyloid protofibrils and reduces amyloid plaques
BIIB092	Monoclonal antibody—removes tau and reduces tau propagation
LY3002813 (donanemab)	Monoclonal antibody—removes amyloid by recognizing aggregated pyroglutamate form of Aβ
LY3303560 (zagotenemab)	Monoclonal antibody—neutralizes soluble tau aggregates
Semorinemab (RO7105705)	Monoclonal antibody—removes extracellular tau
APH-1105	Alpha-secretase modulator—reduces amyloid
Daratumumab	Monoclonal antibody—immunomodulatory that targets CD38 and regulates microglial activity
Dasatinib + Quercetin	Tyrosine kinase inhibitor (dasatinib) + flavonoid (quercetin)—reduces senescent cells and tau aggregation
IONIS MAPTRx (BIIB080)	Epigenetic, Tau Antisense oligonucleotide—reduces tau production
Lithium	Neurotransmitter receptors ion channel modulator—improves neuropsychiatric symptoms
Nilotinib	Tyrosine kinase inhibitor—promotes clearance of amyloid and tau proteins
Posiphen	Selective inhibitor of APP—reduces amyloid, tau, and α-synuclein production
PTI-125	Filamin A protein inhibitor—reduces tau hyperphosphorylation, synaptic dysfunction, and stabilizes soluble amyloid and the α7 nicotinic acetylcholine receptor interaction
PQ912	Glutaminyl cyclase (QC) enzyme inhibitor—reduces amyloid plaques and pyroglutamates Aβ production
Riluzole	Glutamate receptor antagonist—reduces glutamate-mediated excitotoxicity
Thiethylperazine (TEP)	Activates ABCC1 (ATP binding cassette subfamily C member 1 transport protein)—removes amyloid

"Table 5: Disease modifying agents in Phase 3 clinical trials"

Phase 1 Clinical Trials	
Disease Modifying Agents	Mechanism of Action
BIIB076	Monoclonal antibody—removes tau and reduces tau propagation

Lu AF87908	Monoclonal antibody—removes tau
anle138b	Aggregation inhibitor—reduces tau aggregation
RO7126209	Monoclonal antibody—removes amyloid
TPI-287	Stabilizes tubulin-binding, microtubule, and reduces cellular damage mediated by tau

"Table 6: Disease modifying agents in Phase 3 clinical trials"[70,71]

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. Neuropsychological, imaging, and spinal fluid tests can all be used to make a precise diagnosis. Although there are no treatments available to slow the disease process, managing the cognitive and behavioural symptoms of Alzheimer's disease dementia can significantly improve the lives of patients and carers. The pathology of Alzheimer's disease consists of -amyloid plaques and phospho-tau neurofibrillary tangles. Asymptomatic, mildly affected (MCI), or demented people can all have AD pathology. We give a general summary of the present state of AD in this article, focusing on recent developments and emphasising 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

Ethical approval :Not applicable.

Consent to participate: Not applicable

Consent to publication :Not applicable.

Availability of data and materials: Not applicable.

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