International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1185-1192 www.ijprajournal.com ISSN: 2249-7781

Alzheimer's Disease: A Potential Threat in Future

Ojasvita Anil Khole*, Ms.Rutuja Vijay Pagare
PRES College of Pharmacy (for women) Chincholi, Sinnar 422102 Maharashtra, India

Submitted: 12-01-2023 Accepted: 25-01-2023

ABSTRACT
Alzheimer's Disease (AD) is a neurological condition that worsens over time. The primary use of dementia is a condition that results in deterioration of brain cells. The World Health Organization (WHO) reports that 5% of men and over 60 years old are afflicted with dementia of the Alzheimer's type globally. The mainstay of treatments for these conditions currently include acetylcholinesterase inhibitors (Rivastigmine, galantamine, donepezil) and N-methyl-D-aspartate receptor antagonists (Memantine) Alzheimer's condition. In order to create effective treatments that can slow or alter the progression of AD, research is currently concentrating on understanding the pathology of AD by focusing on several mechanisms, including abnormal tau protein metabolism, beta-amyloid, inflammatory response, and cholinergic and free radical damage. The key to putting this notion to the test in clinical trails is the development of earlier positron emission tomography neuroimaging techniques. This review examines the currently available medications as well as potential treatments for AD, including chaperones, and disease-modifying therapies like aducanumab, gantenerumab, lithium, masitinib, posiphen etc and also vacuolar sorting protein 35 (VPS35). Additionally, it contains molecules that block or modulate the secretases, which target amyloid plaques, as well as compounds that speed up the destruction of amyloid plaques.

Keywords: neurodegenerative disorder, beta-amyloid, tau protein, anticholinesterases, diagnosis

I. INTRODUCTION

The most frequent form of dementia, Alzheimer's disease (AD), named after the German psychiatrist Alois Alzheimer, is defined clinically by a progression from episodic memory issues to a gradual decline in cognitive function[1]. As a result of the accumulation of amyloid-beta peptide (Aβ) in the brain's most affected region, the medial temporal lobe and neocortical structures, it can also be described as a slowly progressing neurodegenerative disease that is marked by neuritic plaques and neurofibrillary tangles[2].When Alois Alzheimer examined the brain of his first patient, who experienced memory loss and a change in personality before passing away, he found the existence of amyloid plaques and a tremendous loss of neurons. He defined the illness as a terrible disease of the cerebral cortex[3]. There are currently about 50 million AD sufferers globally, and it is predicted that this s number will double every five years to reach 152 million by 2050.

The pathology of AD is characterised by a complex interplay of several biochemical changes, such as modifications in the metabolism of amyloid precursor proteins, oxidative stress, diminished energetics, mitochondrial dysfunction, inflammation, membrane lipid dysregulation, and disruption of neurotransmitter pathways[4]. The majority of these clinical characteristics are directly related to metabolic abnormalities, and it is now understood that metabolic dysfunction plays a significant role in AD[5]. For instance, decreased cerebral glucose absorption, an unchanging aspect of AD, develops decades before the start of cognitive loss[6]. Alzheimer's disease can be brought on by a number of reasons, including substance abuse, infections, abnormalities of the pulmonary and circulatory systems that reduce the amount of oxygen delivered to the brain, dietary deficiencies, vitamin B12 deficiencies, tumors, and others[7,8].

The five drugs (N-methyl-D-aspartate and four cholinesterase inhibitors) often prescribed, and their usage has been recommended by numerous reputable organisations. There are no known alternatives to these drugs as of this writing. These medications do not seem to change the course of the disease; rather, they are supportive or palliative, as opposed to curative or disease modifying therapy[9].

Dementia can be affect a person in different ways, and progression of the disease depends upon the impact of the disease itself and the person's personality and state of health.
Dementia can be divided in three stages:

- Early stage – first year or two .

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1185-1192 www.ijprajournal.com ISSN: 2249-7781

- Middle stage – second to fourth or fifth years .
- Late stage – fifth year and after

Early Stage	Middle Stage	Late Stage
Relatives and friends (and sometimes professionals as well) see it as "old age", just a normal part of aging process. Because the onset of the disease is gradual, it is difficult to be sure exactly when it begins	As the disease progresses, limitations become clearer	The last stage is one of nearly total dependence and inactivity. Memory disturbances are very serious and the physical side of the disease becomes more obvious
Become forgetful, especially regarding things that just happened	Become very forgetful, especially of recent events and people's names	Usually unaware of time and place
May have difficulty with communication, such as difficulty in finding words	Have difficulty comprehending time, date, place and events; may become lost at home as well as in the community	Have difficulty understanding what is happening around Them
Become lost in familiar places	Have increasing difficulty with communication (speech and comprehension)	Unable to recognize relatives, friends and familiar objects
Lose track of the time, including time of day, month, year, season	Need help with personal care (i.e. toileting, washing, dressing)	Unable to eat without assistance, may have difficulty in swallowing
Mood and behaviour; may become less active and motivated and lose interest in activities and hobbies may show mood changes	Unable to live alone safely without considerable support	May have bladder and bowel incontinence
Have difficulty making decisions and handling personal finances	Unable to successfully prepare food, cook, clean or shop	Increasing need for assisted self-care (bathing and toileting
	Behaviour changes may include wandering, repeated questioning, calling out, clinging, disturbed sleeping, hallucinations (seeing or hearing things which are not there)	Change in mobility, may be unable to walk or be confined to a wheelchair or bed

Source: World Alzheimer's Report 2009[10].

Pathology

A lot of study is being done to clarify the fundamental pathological process since the primary pathological aetiology of Alzheimer's disease is not entirely understood. Numerous theories regarding the pathophysiology of AD have been proposed in light of current knowledge. The most commonlyacknowledged of these are the following:

- Amyloid Cascade Hypothesis

The most frequently held theory is this one. The primary disease is thought to be Aβ42-amyloid plaque deposition in the brain. By the sequential action of α-secretase and β-secretase, Aβ42 is produced from Amyloid Precursor Protein (APP). Insoluble Aβ42 aggregates to form plaques, which inflict oxidative harm and start inflammatory processes that eventually result in neuronal death. Following amyloid deposition, tau proteins are hyperphosphorylated and deposit as neurofibrillary

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Volume 8, Issue 1 Jan-Feb 2023, pp: 1185-1192 www.ijprajournal.com ISSN: 2249-7781

tangles. There are two types of Alzheimer's disease: familial and sporadic versions.

- Tau Hypothesis

The level of amyloid deposits does not correspond with the severity of cognitive impairment, and the amyloid cascade hypothesis is unable to adequately explain sporadic cases of Alzheimer's disease. This gave rise to the tau hypothesis, which contends that the primary disease is the deposition of tau and the development of neurofibrillary tangles, with the deposition of amyloid occurring secondarily. The protein tau, which is associated with microtubules, attaches to and stabilises the microtubules used for intracellular transport. Tau's ability to bind to microtubules is decreased by hyperphosphorylation, and tau's availability to do so is decreased by sequestration of hyperphosphorylated tau in neurofibrillary tangles (NFTs). As a result, the microtubules break down, which reduces axonal transport and causes cell death.

- Mitochondrial Cascade Hypothesis

Alzheimer's disease is thought to start with impaired mitochondrial function to manage free radicals[11].

Phases of Alzheimer's Disease

According to personality, each person with Alzheimer's disease will present differently. Although there will be variations in emotional, behavioural, and cognitive changes, doctors and researchers generally accept the stage model, which outlines general characteristics[12].

The First Phase, sometimes known as the "forgetfulness phase," is characterised by difficulties remembering recent events and a propensity to misplace objects[13]. Prior familiar names of people and locations may be difficult to remember, and a general disorientation and poor short-term memory persist.The "confusional phase" is the Second Recognized Phase. Memory loss is accompanied by a declining attention span and a drop in general intellectual function. Disorientation in the environment, difficulty finding words, and other speech modifications may be seen[14].Complex jobs are generally performed awkwardly or inaccurately, and frequently the skills that were taught most recently will be the first to be forgotten. It doesn't take long for a person to lose interest in the news and surroundings, which can be very upsetting to family andfriends[15]. Third Phase, sometimes known as the "dementia phase," is characterised by the person acting randomly and occasionally bizarrely without any apparent reason. People in this stage experience additional declines in memory, calculating ability (dyscalculia), and portions of language are badly impaired and eventually lost. Remaining intellectual and selfcare abilities require regular supervision. For self-care activities including clothing, grooming, using the restroom, and feeding, constant support is needed. Additionally, a physical wasting that will require assistance walking can be noted. Sometimes a period of one to two years in a nearly vegetative condition occurs until the end. In those who are susceptible, environmental variables may play a part in precipitating Alzheimer's disease. For many years, a link between aluminium and Alzheimer's disea.se has been proposed[16].

Therapies

1. Disease Modifying Therapy

DMTs, or disease-modifying therapies, slow the course of AD by addressing a number of pathophysiological pathways. This contrasts with symptomatic therapy, which focuses on enhancing cognitive abilities and reducing signs of illness like depression or delusions without altering or affecting the condition. Orally administered DMTs, such as immunotherapies or small compounds, are being developed to halt the progression of AD or prevent it altogether. A number of DMTs have been created and are currently undergoing clinical trials, including AN-1792, a synthetic Aβ peptide (human $A\beta_{1-42}$ peptide of 42 amino acids with the immune adjuvant QS-21), and the first active immunotherapy for AD, which entered phase II clinical trials but was abandoned due to side effects that caused meningoencephalitis in 6% of the patients. Other medications, such as anti-Aβ antibodies (solanezumab and bapineuzumab), γ-Secretase inhibitors, and β-Secretase inhibitors, were also created but failed in clinical trials (BACE). Failures of DMTs can be attributed to a number of things, including improper drug dosages, starting therapy too late, treating the wrong primary target, and not understanding the pathophysiology of AD. Numerous immunotherapies listed in Table 3 have been developed over the years, including: CAD106, an active Aβ immunotherapy that induces Aβ antibodies in animal models and consists of multiple copies of the Aβ 1-6 peptide coupled to the Qβ coat protein,which resembles a virus; this immunotherapy is still in clinical trials;

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1185-1192 www.ijprajournal.com ISSN: 2249-7781

and CNP520, a small molecule that inhibits beta-scretase-1 (BACE-1) and, CNP520, which is still undergoing clinical trials, has been shown to decrease Aβ plaque deposition and Aβ levels in the brain and CSF in rats, dogs, and healthy individuals older than 60. Additionally, the human Aβ monoclonal antibodies aducanumab, gantenerumab, and crenezumab are still being investigated in the clinical stages in combination with other DMTs. They all bind to aggregated Aβ with a high affinity. [Table.2][17, 18-23]

Table 2. Disease modifying agents for treatment of AD in clinical trials.

Disease Modifying Agents	Mechanism of Action
	Phase 3 Clinical Trials
Aducanumab	Monoclonal antibody—targets βamyloid and removes it.
Gantenerumab	Monoclonal antibody—binds and removes βamyloid.
	Phase 2 Clinical Trials
Lithium	Neurotransmitter receptors ion channel modulator—improves neuropsychiatric symptoms
Posiphen	Selective inhibitor of APP—reduces amyloid, tau, and α-synuclein production
	Phase 1 Clinical Trials
anle138b	Aggregation inhibitor—reduces tau aggregation
Lu AF7908	Monoclonal antibody—removes tau

2. Chaperones:

Hazardous protein aggregations originate from toxic protein misfolding brought on by mutations or environmental factors, and their buildup leads to neurodegenerative diseases like AD. Cells naturally create protein quality control (PQC) systems that prevent protein misfolding before it has a chance to cause harm. This equilibrium changes as we age, and the misfolded shapes overwhelm the PQC system. This, in turn, activates the unfolded protein response (UPR), which inhibits protein synthesis and boosts the production of chaperones. Human cells typically contain proteins that enable other proteins to function and reach their intended locations within the cell. Chaperones are the name given to these proteins. Protein folding and increasing the effectiveness of the PQC system are both aided by chaperones. As a result, it is viewed as a prospective candidate for the treatment of neurodegenerative illnesses. It can be divided into three categories: Heat shock proteins (Hsps), which are overexpressed and act as neuroprotective agents, are examples of molecular chaperones. Pharmacological chaperones are low molecular weight substances (enzymes, receptorligands, or selective binding molecules) that cause proteins to refold, stabilise their structure, and regain their function. Chemical chaperones are also low molecular weight substances that induce protein refolding. Both of these groups' members lack a distinct mechanism of action and require high doses to have a therapeutic effect[24].

3. Vacuolar Sorting Protein 35 (VPS35):

Cellular protein homeostasis is disturbed by protein build up in neurons and glial cells. Proteins are transported by the endosomal-lysosomal pathway for recycling and breakdown. Numerous disorders, including Alzheimer's disease, can develop as a result of any systemic problem. Sorting nexin (SNX1, 2, 5, 6) and vacuolar sorting proteins (VPS26, 29, 35) make up the complex of regulator proteins known as retromer, which is in charge of moving cargo molecules from the endosome to the trans-Golgi network. Downregulation of VPS35 due to retromer malfunction can result in cognitive deficits, synaptic dysfunction, and an increase in beta production, all of which have been linked to AD patients[25,26]. A study was done on the 3xTg mouse brains to see how VPS35 overexpression affected memory performance. The research demonstrated that overexpression of VPS35 was related with a significant decrease in Aβ peptide and tau neuropathology (soluble, insoluble, and phosphorylated tau), as well as a decrease in neuroinflammation and improvement of synaptic dysfunction[27].VPS35 is a crucial and prospective therapeutic target for the treatment of AD as a result. A promising therapeutic molecule for neurodegenerative diseases is a small pharmacological chaperon molecules called

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1185-1192 www.ijprajournal.com ISSN: 2249-7781

R55(thiophene-2,5-diylbis(methylene) dicarbamimidothioatedihydrochloride), which is a thiophenethiourea derivative. R55 can increase retromer proteins, shift AOO from the endosome, and reduce pathogenic processing of APP to improve retromer stability and function[28].

4. Anti-amyloid therapy

Up until recently, a number of high-profile clinical studies of pharmaceuticals intended to alter this amyloid cascade were conducted, with mainly unsatisfactory outcomes. The gamma or beta-secretase enzymes involved in APP cleavage, as well as directly targeting Aβ, were the three main target sites for these drugs[40].

- Beta-secretase enzyme: When compared to controls, small molecule beta-secretase inhibitors showed decreased levels of CSF beta-amyloid. Two agents, AZD3293 and MK-8931, are undergoing phase II/III clinical trials that should be finished in 2019[41].
- Gamma-secretase enzyme: Semagacestat, a small molecule gamma-secretase inhibitor[42], is undergoing phase III clinical studies. were stopped in 2010 due to no improvement in cognition in the trial group and poorer cognition at higher doses compared to controls[43]. This included more than 3,000 patients. In the study group, skin cancer incidence was similarly greater. Tarenflurbil, a drug linked to the NSAID flurbiprofen, has been proven to lower levels of A via altering the gammasecretase enzyme, however phase III trials involving nearly 1,700 patients found no benefit in cognition or function when compared to placebo[44].

5. Tau Target Therapy

Agents to stop hyperphosphorylation as well as those that target microtubule stability and aggregation are examples of tau-targeted therapies that are now undergoing clinical studies[29]. Valproic acid and lithium may both work to prevent tau phosphorylation[30], however randomised controlled trials of these drugs were unsuccessful[31]. More recently, a phase II clinical trial of the tau aggregation inhibitor methylthioninium showed modest cognitive advantages in patients with mild and moderate AD after 50 weeks of treatment, and phase III trials are now being planned[32].

Future Trends For Diagnosis Of AD

- Neuroimaging

In the past, structural neuroimaging in AD was employed to rule out alternate diagnoses, such as brain tumours, when symptoms were unusual. However, by monitoring cerebral metabolic rates of glucose metabolism (CMRglc), a proximate marker for neuronal activity, functional imaging modalities like 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) are now able to detect loss of neuronal function in asymptomatic individuals[33]. Reduced CMRglc is seen in the parietotemporal, frontal, and posterior cingulate cortices of patients with early AD[33]. Additionally, it has been demonstrated that patients with MCI and people who are genetically predisposed to AD experience these alterations prior to the development of symptoms[34,35]. The hypometabolic areas linked to AD and other dementia subtypes do have certain similarities, though, and the additional use of amyloid PET, which can calculate the surface area of amyloid plaques, boosts diagnostic precision[36]

- Cerebrospinal Fluid Biomarkers

The amyloid and tau CSF indicators reflect the underlying neuropathology of AD and are accurate diagnostic techniques for identifying dementia. Patients with AD have lower CSF Aβ42 levels, which may be related to the peptide being deposited in plaques[37]. A lower Aβ42/Aβ40 ratio, rather than just Aβ42, seems to be a more accurate indicator. Raised total tau is a very sensitive indicator of AD, although it is also present in frontotemporal dementia and other forms of dementia. In contrast, elevated phosphorylated tau, the main constituent of NFTs, is more specific than total tau. Combinations of these CSF markers have been utilised to strengthen diagnostic potential in the early stages of AD, for instance, it was discovered that MCI patients who also had low Aβ42 and high tau levels had a significantly higher risk of developing AD[38]. Despite this, CSF biomarkers' discriminatory ability in the differential diagnosis as a standalone diagnostic test[39] is still somewhat suboptimal, and current presymptomatic screening methodologies combine the results with neuroimaging findings.

II. CONCLUSION:

As Alzheimer's disease is increasingly seen as a global health concern, the National Institute on Aging- Alzheimer's Association reclassified and modified by the 1984 NINCDSADRDA criteria for greater specificity, sensitivity, and early detection of people at risk of

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1185-1192 www.ijprajournal.com ISSN: 2249-7781

developing AD. For a more precise AD diagnosis, a number of factors have been put forth, including clinical physiological fluids, imaging tests, and biomarkers. Memory and alertness are enhanced by cholinesterase enzyme inhibitors like galantamine, donepezil, and rivastigmine and NMDA antagonist like memantine, but progression is unaffected. Recently, research has shifted its attention to pathogenic aspects of AD like Aβ and p-tau proteins. Other DMTS, including those that target the Aβ-and tau pathologies and include aducanmub, gantenerumab, creezumab, tideglusib, lithium, and others are still being studied. Other potential chemicals are known as Chaperones, such as heat shock proteins and vacuolar sorting protein 35, let other proteins operate normally and safely reach their destinations in the cell, and can thus be employed to treat neurodegenerative illness. Furthermore, while the emphasis on the discovery of novel medicines is highly welcome, we must keep in mind that dementia is a diverse, complex disease that necessitates a multidisciplinary approach to care. Our focus in managing dementia patients must remain broad and comprehensive, focusing not just on pharmacological therapy but also on complicated biopsychosocial aspects of caring for this group of patients. It is hoped that this will also enlighten service providers in terms of increasing people's access to services with both learning impairments and dementia.

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