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Review Article

**ALZHEIMER'S – CURRENT STRATEGIES FOR ITS
DIAGNOSIS AND TREATMENT****Jyotsana Bhatt* and Sayantan Mukhopadhyay¹**

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Abstract:

Alzheimer's disease is the most prevailing type of dementia worldwide with pathological hallmarks as neurofibrillary tangles and amyloid β plaque. A large number of research and studies are undergoing to determine the exact pathophysiology of the disease which may further lead to development of better treatment strategies. Based on the existing hypothesis a number of treatment and management therapies are utilised for prevention and control of disease. Conventional therapies based on AChE inhibitors (Donepezil, Rivastigmine and Galantamine) and NMDA receptor antagonist (Memantine) are most effective and frequently used but are only capable of controlling the disease progression and are not capable of treating the disease completely. New therapies include disease modifying therapies based on the concept of reducing the functioning of secretase enzymes which is primarily involved in conversion of APP into amyloid β plaque. Other promising therapies based on different hypothesis include the use of insulin, antioxidants, stem cell and also various herbal drugs which show remarkable decrease in progression of disease. This review also includes a number of compounds which are under different phases of investigation and clinical trials and may be used as an important tool for treatment of disease in near future.

Key words: Alzheimer's disease, APP, APoE-e4, Biomarkers, Secretase Inhibitors.

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1. INTRODUCTION:

Dementia refers to the acquired global impairment of intellect, memory and personality cognitive functions in the absence of gross clouding of consciousness or motor involvement. [1] There are several forms of dementia affecting a wide range of population worldwide. Among them, Alzheimer's disease accounts for more than 80% of the cases in elderly people. [2]

Alzheimer's disease (AD) was first discovered in 1906 by German physician Aloes Alzheimer and was named after him. It is a progressive neurodegenerative disorder that gradually affects the memory and progressively destroys the ability to learn, judge, communicate and carry out day to day activities. It is primarily known to effect elderly population over 65 years or more of age, which accounts for 50-60% of total dementia cases. According to the World Health Organisation, it has been observed that about 18 million people worldwide have been suffering from AD. It is estimated that this figure will reach to approximately 34 million by 2015. [3]

2. TYPES OF ALZHEIMER'S DISEASE –

There are two main types of AD – Early onset alzheimer's disease and late onset alzheimer's disease.

2.1 Early onset alzheimer's disease – This type of AD mainly occur to people who are younger than age

65, and are in their 40 or 50's when diagnosed with the disease. It is a rare type, up to 5% of all people with Alzheimer's have early onset AD. It also appears to be linked with a defect in a specific part of persons DNA – chromosome 14. People with Down syndrome have higher risk for it.

2.2 Late onset alzheimer's disease – Most common form of the disease, happens to people age 65 and older. Causes for this type of AD are still unknown. It may or may not run in families. [5]

3. STAGES OF ALZHEIMER DISEASE-

Alzheimer's disease advances at widely different rates, symptoms vary from person to person. People with Alzheimer's live an average of 8 yrs. after diagnosis, but may survive anywhere from 3 to 20 yrs.

Experts have documented a common pattern of symptoms progression that occurs in individuals with Alzheimer's disease. Based on these patterns, they developed several methods of "staging". It is important to note that all stages are artificial benchmarks in a continuous process that can vary greatly from person to person. [6,7]

The stages of Alzheimer's disease can be classified broadly according to the symptoms in each stage. Table 1 given below give a briefing about the various stages of Alzheimer's disease and their symptoms. [7,8]

Table 1: Various stages of Alzheimer's disease and their symptoms.

S.No.	Stages of Alzheimer's Disease	Symptoms
i.	Mild AD	Moderated learning capacity, postponed responses, begin talking more (more gradually than before), misguided thinking and settling on wrong choices, got to be discouraged and touchy or anxious, memory related problems, becoming withdrawn in socially and mentally challenging situations.
ii.	Moderate AD	Issues perceiving dear loved ones, turn out to be more eager (particularly in late evening and during the evening), forgetting home address and other basic things, require assistance in getting dressed or using toilet, major personality and behavioral changes (compulsive or repetitive behavior)
iii.	Severe or Serious AD	Require assistance in bathing, eating, no more know when to bite or swallow, issues with equalization and strolling, reflexes become abnormal and muscles become rigid, ability to respond to the environment is lost.

4. CAUSES OF ALZHEIMER DISEASE-

It is a known fact that Alzheimer's is caused by nerve cells death, but its actual causes and risk factors are still unknown to researchers. However, they have identified some risk factors that increase the probability of developing Alzheimer's.

4.1. Age – It is known as the greatest risk factor for the occurrence of Alzheimer's. Most individuals with the disease are 65 or older. About one-third of the people age 85 and older (32%) have AD. And of those with AD, the vast majority (82%) are age 75 or older.

4.2. Family history – Another risk factor include family history, research has shown that those who have a parent, brother or sister with AD are most likely to develop the disease.

4.3. Genetic factor – occurrence of AD basically depends upon two types of genes – risk genes and deterministic genes. While risk genes increase the likelihood of developing a disease but do not guarantee it, whereas deterministic genes directly cause a disease, guaranteeing that anyone who inherits will also develop it. A wide of range of genes are identified by researchers which increase the risk of AD, among them APOE –e4 is the first and strongest risk gene. Other common forms of APOE are – APOE-2, APOE-3. It is a known fact that everyone inherits a copy some form of APOE genes, those who inherit one copy of APOE-e4 are at greatest risk of developing AD. [9]

4.4. Brain vascular disease and high cholesterol- There is a strong link between cardiovascular disease and its risk factors with AD. [10] Dysfunctional blood vessels may impair nutrient delivery to neurons and decrease

the β -amyloid plaque clearance from the brain. [11] Also, vascular disease may accelerate amyloid deposition and increase amyloid toxicity to neurons. [12] Cardiovascular risk factors include hypertension, elevated low-density lipoprotein cholesterol, and particularly diabetes. [10]

4.5. Other risk factors include –

- There is a strong link between head injuries and future risk of AD.
- Many diseases can cause Alzheimer's such as patients suffering from depression have a high prevalence of AD.[9]

5. PATHOPHYSIOLOGY-

Pathology of Alzheimer's disease has been a topic of debate since 1907. Based on various causative factors, several hypotheses have been put forward which include – Amyloid hypothesis, tau hypothesis, cholinergic hypothesis, inflammation hypothesis. [2] Among which amyloid hypothesis is considered as the leading pathological model of Alzheimer's disease.

5.1. Amyloid cascade hypothesis – Presence of neuritic plaque and neurofibrillary tangles in higher concentration in the cortical area and medial temporal lobe structure of the brain, give the confirmation of Alzheimer's disease. [12] Plaques from the Alzheimer's patient brain are the deposits of protein fragments called β -amyloid which builds up in the spaces between nerves cells obstructing the normal functioning of the region. β -amyloid is a short 4000 Da peptide which is proteolytic by-product of the transmembrane protein Amyloid precursor protein (APP). APP is an essential factor for growth, survival and post-injury repair of a neuron.[13]

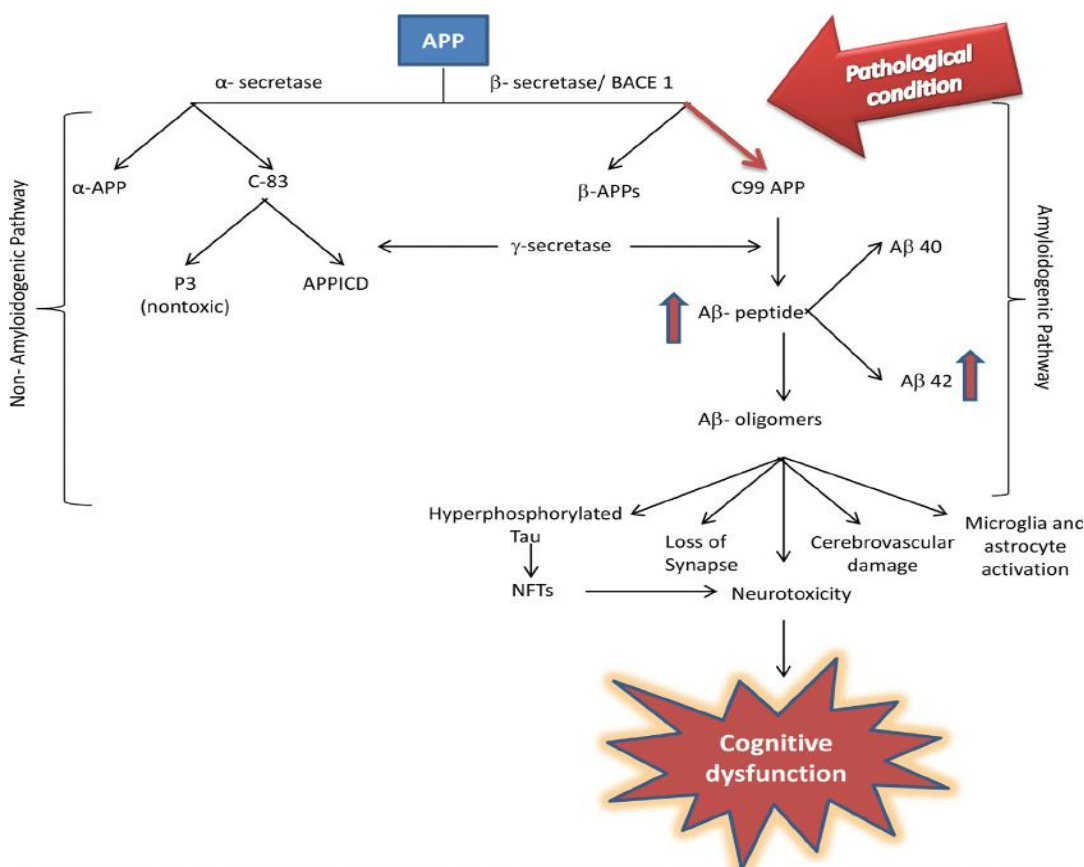


Fig.1. Amyloid precursor protein (APP) pathway process. [14]

According to the hypothesis, the process of production of β -amyloid by abnormal cleavage of amyloid precursor protein (APP) into smaller peptides ($A\beta_{1-40}$ and $A\beta_{1-42}$) is mainly dependent on the major APP cleaving enzymes (α -secretase and β and γ -secretase). Amyloid precursor protein is normally cleaved by the α -secretase from non-amyloidogenic pathway resulting in the smaller peptides which are non-toxic in nature, whereas cleavage through β - and γ -secretase by amyloidogenic pathway leads to abnormal processing of APP resulting in an imbalance between production and clearance of β -amyloid peptide. This is further responsible for spontaneous aggregation of β -amyloid protein into soluble oligomers which unite to form fibril insoluble β -sheet conformation and are eventually deposited in senile plaques.[2,14]

5.2. Tau hypothesis – Neurofibrillary tangles (NFT) which are considered as pathological hallmarks of the Alzheimer's disease basically constitute of twisted

fibers of another protein called Tau that builds up inside cells. After years of failed attempts to cure and constrain Alzheimer's disease by targeting β -amyloid, researchers have now moved on to targeting Tau for controlling it.

According to researcher's, Tau can be compared to rail road ties that stabilize a track which is used by brain cells to transport food, message and other vital cargo throughout neurons. In Alzheimer's structural and functional changes that occur in tau protein cause the track to become unstable in neurons of the hippocampus, the center of memory. Abnormal Tau builds up in neurons eventually leading to the death of these neurons. This abnormal tau then spreading from cell to cell affects brain's cortex, which is a principal region involved in the higher level of thinking, planning, behavior and attention. Thus, responsible for the behavioral changes in Alzheimer's. [13]

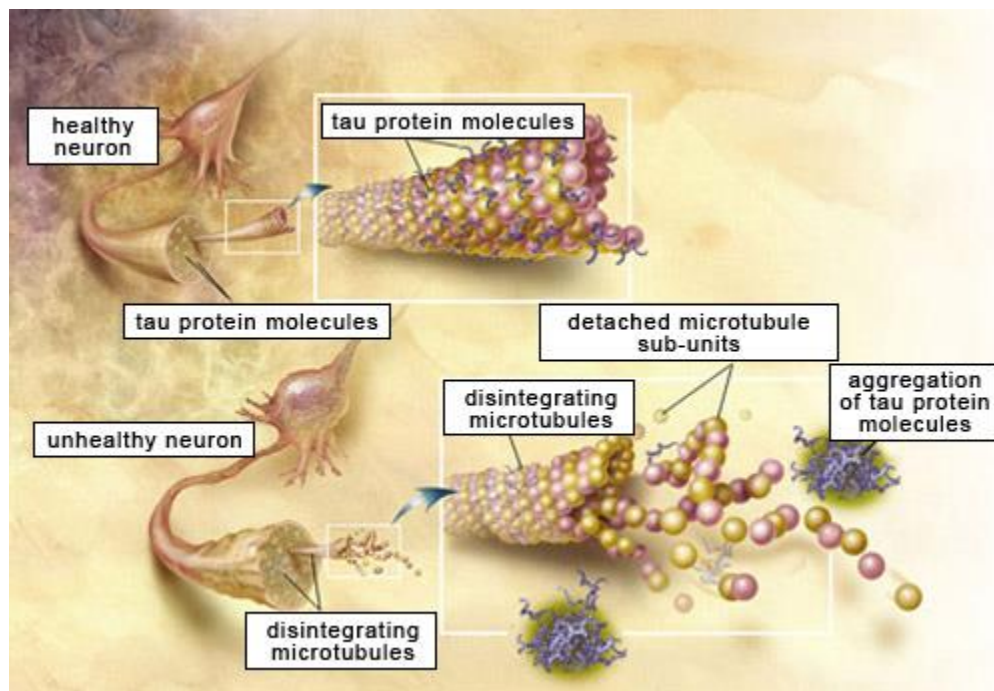


Fig. 2 Tau Phosphorylation. [13]

5.3. Cholinergic hypothesis – The cholinergic hypothesis targeted cholinergic cell loss as the source of memory and cognitive impairment in Alzheimer’s disease. A number of neuronal pathways are affected in Alzheimer’s disease, causing damage to the wide range of cells further leading to neurotransmitter deficit with cholinergic abnormalities being the prominent. [15] Cholinergic abnormalities supplements severity to the Alzheimer’s disease. In late AD, the no. cholinergic neurons are reduced, and there is a loss of nicotinic receptor in the hippocampus and the cortex. Presynaptic nicotinic receptors are known to controls the release of acetylcholine and other neurotransmitters which play a vital role in regulating the mood and memory. [16] The approach was vitiated because of two main reasons, firstly cholinergic cell loss is not considered as the primary pathological reason for Alzheimer’s disease and secondly, cholinergic neurons are not the only neuronal pathways destroyed. [17]

6. EPIDEMIOLOGY-

Alzheimer’s disease (AD) is the most common type of dementia. AD unassociated with any other pathology accounts for 50% to 60% of cases of late life cognitive dysfunction. The incidence increase to 30% if Alzheimer’s disease is in conjunction with other pathologic lesions is considered.[16]

It is a critical public health issue around the world with a significant health, social and financial burden on society. An estimated 5 million Americans have AD, with a new diagnosis made every 68 sec. In the United States, AD is the 5th leading cause of death among older adults. About \$200 billion are spent annually on direct care of individual living with dementia. Worldwide, it is estimated that 35 million people have AD or other type of dementia, and about 65 million people are expected to have dementia by 2030 (115 million by 2050).[18]

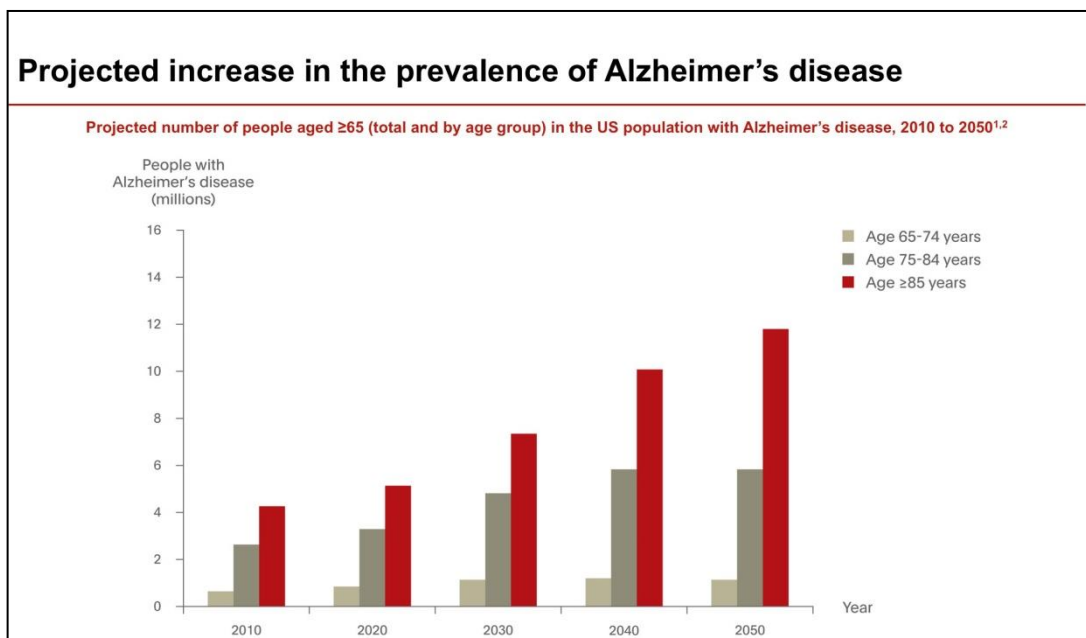


Fig. 3. Projected increase in the prevalence of Alzheimer's disease. [19]

7. DIAGNOSIS-

Alzheimer's disease is considered as a most prevalent type of dementia worldwide. Data collected from current studies state that in every 33 seconds a new case of Alzheimer's disease is noted, leading to million cases every year. Earlier the preliminary diagnosis of Alzheimer's was carried out using a combination of clinical studies including mental status test, neurological examination, and brain imaging. But these studies were inefficient when it comes to detection of early stages of Alzheimer's disease. Hence, there was considered a need of biomarkers for detection and conclusive diagnosis of early stage or mild Alzheimer's. [20,21]

Biomarkers or biological markers can simply be defined as detectors or indicators of normal biological process, which can measure any change in/outside of the body and also indicate the pharmacological response to a therapeutic intervention. According to the National Institute of Health Biomarkers Definition Working Group in 1998 "Biomarkers are evidence of any biological, pathogenic or pharmacogenomics response when administered to any therapeutic range". [20, 21]

Presently, diagnosis of Alzheimer's is done using cerebrospinal fluid (CSF) with established biomarkers as amyloid β protein, tau protein, and phosphor tau. CSF is used as a source of biomarkers because of its presence and direct contact in the brain and spinal cord and also it gives a complete description of various bio-chemical and metabolic

profile of brain. However, the procedure for drawing CSF is both invasive and painful, which give this method a disadvantage. New methods and analyzing procedure are constantly being developed to make the diagnosis more efficient.

Various criteria for establishing a good biomarker for diagnosis of dementia are –

- Reflect aging process.
- Describe basic pathophysiological processes of the brain.
- Response upon pharmacological intervention.
- Highly sensitive.
- High specificity for differentiation of different disease.
- Allow reproducibility.
- Should be non-invasive.
- Should be safe and easy to perform.
- Should be inexpensive and rapid. [21]

7.1. CSF biomarkers –

7.1.1. $A\beta$ (1-42) – AD is commonly depicted as extracellular deposition of amyloid β plaque. Amyloid β is mainly formed by cleavage of Amyloid precursor protein (APP) by secretase leading to the production 42 amino acid peptides ($A\beta$ 1-42) which aggregate in the brain under certain conditions. [20] $A\beta$ 42 is primarily used as a biomarker for detection of Alzheimer's disease. Studies suggest that on analysis of CSF, a significant reduction in $A\beta$ 42 concentration is noted in Alzheimer's patients ($<500\text{pg/ml}$) as compared to control group ($<794\pm 20$)

pg/ml) which indicates reduced clearance of A β from the brain to blood/CSF. Hence, resulting in the deposition of plaque in the brain. [12]

7.1.2. Total tau – The second potent biomarker for the detection of Alzheimer's disease are intraneuronal inclusions of the microtubules associated protein tau. [20] In contrast with amyloid β protein, its concentration in Alzheimer's patients is elevated as compared to the nondemented elderly subjects. This factor is utilized as an indicator of disease. According to various studies conducted, level of tau protein in CSF increase with age in the following manner <300 pg/ml (21-50 yrs), <450 pg/ml (51-70 yrs) and <500 pg/ml (>70 yrs.) whereas tau protein concentration exceed more than >600 pg/ml in Alzheimer's disease. However, elevated tau concentration is used as a potent marker for differentiation of Alzheimer's disease patients from normal individuals, but is a relatively inefficient indicator for differentiation of Alzheimer's disease from other neurodegenerative disorders, thus limiting the utility of tau protein. [20]

7.1.3. P-tau – Tau being the primary component of intraneuronal neurofibrillary tangles is known to be elevated in the CSF of the Alzheimer's patients. The abnormal tau phosphorylation is probed as an efficient marker of AD pathology. It is stated that nearly 30 phosphorylation sites of P-tau have been identified and assay techniques have been developed for them. P-tau has been utilized as an efficient marker in the early diagnosis of disease. Data collected from various studies suggest that different forms of P-tau are used to differentiate symptoms of different neurodegenerative disorders from Alzheimer's. Like P-tau 231 is used to differentiate AD from frontotemporal dementia while P-tau 181 may provide better diagnostic specificity for AD and may improve differentiation between AD and dementia with Lewy bodies (DLB). P-tau 396-404 and the ratio of P-tau 396-404, have been utilized to the differentiation between AD and vascular dementia. [22]

7.2. Plasma biomarkers –

As discussed earlier, that diagnosis of Alzheimer's and different types of dementia from Cerebrospinal fluid (CSF) have several limitations. Thus, there was a need to identify a new biomarker in other body fluid like serum, saliva, urine etc. which are easily accessible, less invasive and cheaper. However, saliva and urine can be easily accessible, but blood analysis is a primary choice as it can be more specifically related to Alzheimer's disease.

7.2.1. miRNA – miRNA or microRNAs, a subset of non-coding RNAs, are ~22-nt long endogenously-initiated short RNA molecules that are considered to post transcriptionally regulate cleavage of target

mRNA or just repress their translation. The changes in the miRNA expression in peripheral blood can serve as a potent biomarker for the diagnosis of Alzheimer's disease. According to studies conducted by Schipper (2001), a remarkable no. of down regulated miRNA was identified when compared to 16 sporadic AD patients with 16 controls using a microarray chip. Another research carried by Geekiyanage and Chan in 2012 showed a reduced level of miR-137, miR-181c, miR-9, and miR-29a/b in neurological regions of AD patients. Various researches allude the contribution of miRNA in cellular function such as redox defense and DNA repair thus establishing the importance of miRNA as a potential therapeutic biomarker in near future. [20]

7.2.2. Plasma Amyloid β – Although the utility of Amyloid β as CSF biomarkers in the diagnosis of AD is well established several other researches are being followed to evaluate Amyloid β in plasma as a potent biomarker. Studies have shown that plasma A β (1-42), A β (1-40) levels can be elevated, reduced and even unchanged in AD as compared to the control patients. It is reported that the instability in plasma level of A β may be due to the following reasons:-

- Influence of medication to Amyloid β .
- Binding property of Amyloid β protein to other protein.
- Fluctuation in the concentration of Amyloid β during various stages of Alzheimer's.
- Blood platelets contain a high amount of Amyloid β protein thus affecting plasma level of it.

A no. of analytical techniques is equipped to overcome the instability problem and supplement the accountability of plasma amyloid β as a biomarker for diagnosis of AD in near future. [21]

7.2.3. Inflammatory Markers – Neuroinflammatory processes like microglia activation and astrocytes recruitment are commonly seen in the brain of AD patients. The accumulation of such component leads to increased cognitive decline and neuronal cell death in some cases. According to the recent studies, the combination of 18 selected biomarkers (chemokine's, cytokines, growing factors and binding protein) in blood allowed the diagnosis of AD and MCI (mild cognitive impairment) with nearly 90% accuracy. In spite of the accuracy, this method still needs proper validation before being used as an efficient diagnostic tool for Alzheimer's disease. [21]

8. TREATMENT-

The major goal of the treatment therapies of AD is to increase the cholinergic functioning of the brain, and slow the progression of the disease. Early approaches include the use of precursors of acetylcholine such as choline chloride and phosphatidylcholine, but these supplements failed to induce significant effects. A

more successful approach has been used lately, which include the use of acetylcholinesterase (AChE) inhibitors. Four acetylcholinesterase (AChE) inhibitors which are approved by USFDA include – Tacrine (1,2,3,4-tetrahydro-9-aminoacridine; Cognex), Donepezil (Aricept), Rivastigmine (Exelon) and Galantamine (Razadyne). Other ongoing strategies include the use of N-methyl-D-aspartate receptor antagonist, NSAIDS, secretase inhibitors, insulin etc. This class has a single drug Memantine. Non-pharmacological approaches include treatment with Natural product and referral to social service agencies or support organizations. [21]

8.1. Cholinesterase Inhibitors –

Cholinesterase inhibitors are the main class of drugs, available for the symptomatic treatment of AD. They inhibit the activity of cholinesterase and increase the cholinergic synaptic transmission. AChE inhibitors are the first group of substance for which an indisputable and relevant efficacy in treatment of the cognitive disturbance in AD.

Following are the various cholinesterase inhibitors used in the treatment of Alzheimer's disease. [4, 23-27]

Table 2: List of Cholinesterase Inhibitors.

Drug	Type of inhibition	Duration of action	Main side effects	Dose	Note
Tacrine	Short acting, reversibly effects both AChE and BuChE.	~ 6 hrs.	Cholinergic side effects include nausea and abdominal cramps.	10 mg orally Four times a day for 6 weeks.	First acetylcholinesterase effective for AD, monitoring for hepatotoxicity required.
Donepezil	Short acting, reversible AChE inhibitor.	~24 hrs.	Slight cholinergic side effects.	Dose initiated at 5 mg once a day. (Maximum recommended dose is 10 mg once a day).	Most efficient for treatment of mild to severe Alzheimer's.
Rivastigmine	Reversible non selective AChE inhibitors (effects both AChE and BuChE)	~8 hrs.	Cholinergic side effects that tend to reduce with continuing treatment.	Dose initiated at 1.5 mg twice a day. (maximum recommended dose is 6 mg twice a day)	Gradual dose escalation to minimize side effects.
Galantamine	Reversible non selective. Also enhance nicotinic acetylcholine receptor activation by allosteric mechanism.	~8 hrs.	Nausea, vomiting, headache, blurred vision.	4 mg twice a day. (Maximum recommended dose is 16 to 24 mg/day).	Dual mechanism of action postulated.

8.2. NMDA receptor antagonist-

Overstimulation of NMDA receptor by glutamate causes neuronal damage and affects the memory. Memantine block the voltage dependent, uncompetitive NMDA receptors, thereby diminishing the entry of calcium (Ca⁺⁺), leading to the decreased glutamate release and inhibiting the process. Memantine is a new drug approved by FDA for the treatment of moderate to severe stages of AD. It has low to moderate affinity and is well tolerated with common side effects as dizziness. The daily dose of memantine is 10 mg twice daily, achieved by a 3-

week, three-step, and titration schedule starting with 5 mg daily. A 20mg once daily preparation has recently been introduced. [28, 29]

8.3. NSAIDS –

Various inflammatory mediators along with activated microglia are commonly seen in case of AD. This enhances the importance of NSAIDS in treatment of AD. A study conducted in Rochester, Minnesota, between 1980-89 reported protective effects of NSAIDS in AD. [21] Another study states that if a person regularly takes NSAIDS for 2 years or more it will reduce the risk of getting Alzheimer's by 60% as

these drugs are known to reduce cell death due to inflammation. Research conducted on animal model shows that oxidative stress was remarkably reduced by anti-inflammatory cyclooxygenase-2 (COX-2) inhibitors (rofecoxib) but non-specific COX inhibitors (flurbiprofen and ibuprofen) do not show any specific effects. Studies have reported that both naproxen and COX-2 inhibitors each restore memory. However, a recently published review by Wang et.al highlights the limitation of evidence for the use of NSAIDS in the treatment of AD, as no randomized clinical trial support the use of NSAIDS in AD. [21, 30]

8.4. Secretase inhibitors –

Secretase are the enzymes involved in breakdown of Amyloid precursor protein (APP) into Amyloid β by

amyloidogenic and anti amyloidogenic pathways. β secretase enzyme complex participates in the initial stage of the amyloidogenic APP processing pathway whereas γ secretase complex is responsible for the final stage of amyloidogenesis leading to the generation of $A\beta$ (1-40) and $A\beta$ (1-42). Secretase inhibition was initially considered as a strategy for development of therapeutic treatment modifying the course of disease. However, multiple failure of drug candidates in clinical trial have led researcher to question the feasibility of this strategy.

Following are the principal targets and clinical trials of the compound aimed at reducing Amyloid β formation and plaque. [31]

Table 3: Principal Compounds for reducing Amyloid β formation.

Activity	Principal compound	Clinical trial
Inhibitors of β -secretase	i. E2609 ii. MK-8931 iii. LY2886721	i. NCT01600859 ii. NCT01739348 iii. NCT01807026 and NCT01561430
Inhibitors and modulators of γ -secretase	i. Semagacestat (LY450139) ii. Avagacestat	i. NCT00762411, NCT01035138, NCT00762411 ii. NCT00810147, NCT00890890, NCT00810147, NCT01079819
Selective γ -secretase modulators	i. Ibuprofen, sulindac, indomethacin, and R-flurbiprofen (Tarenflurbil) ii. NICS-15	i. NCT00322036 ii. NCT00105547

8.5. Insulin –

According to recent studies, Alzheimer's disease is identified as a brain specific form of diabetes. Rotterdam study identified the connection between diabetes and dementia; it states that diabetes increases the risk of AD. However, brain was once considered as insulin resistance organ but recent research has established insulin as an important factor for neuronal survival and brain functioning. It is also considered important factor in maintaining synaptic plasticity, learning, and memory. Thus, any defects in insulin signaling lead to neuronal dysfunctioning and decline cognitive function, which are the characteristics of AD.

It is also an established fact that brain insulin signaling decline with age, which is also a major risk factor for AD thus, rejuvenating insulin signaling may reduce cognitive impairment. According to various studies, intranasal administration of insulin is preferred route, which is known to enhance verbal memory and reduce side effects. Several alternative

approaches are developed to enhance insulin signaling, among them glucagon-like peptide 1 receptor (GLP-1R) agonists are the leading option, and they work by activating pathways common to insulin signaling and enhance hippocampal synaptic plasticity. [32]

8.6. Immunization -

Immunization therapy has been utilized lately in contending histopathological changes in AD. Within this field, research is being carried on monoclonal antibody therapy, cytokines, β -amyloid phagocytosis through microglia, immunomodulatory drugs etc. [33]

Two types of immunotherapies are being developed to target AD- Active and Passive. The neurotoxic species like mature $A\beta$ fibril are responsible for development of antibody that identify "aggregation epitope" thus, helps in inhibition of protein aggregation further reducing risk of AD. Some of the major antibodies are discussed below. [4]

Table 4: List of Antibodies and their functions.

Compound	Type	Current Phase	Function
Bapinezumab	Humanized monoclonal antibody	Phase III (ongoing)	Decrease plaque formation and encourage clearance of A β being specific to N-Terminus of the A β protein.
Aducanumab (BIIB037)	Humanized monoclonal antibody	Phase III (ongoing)	Target A β soluble oligomers along with insoluble fibrils.
Solanezumab	Clinical antibody	Phase III (ongoing)	Capture A β and form A β -anti-A β complex crystal structure.
BAN2401	Humanized monoclonal antibody	Phase II (ongoing)	Selectively bind , neutralise and eliminate protofibrils.
Gantenerumab	Anti-amyloid beta monoclonal antibody	Phase II and III	Targets the N-Terminus and central portion of A β .

8.7. Stem cell therapy –

Stem cells are characterized by their unique property of self-renewal and their ability to differentiate into different lineage can be utilized in the treatment of AD. Stem cells in the body are broadly classified into Embryonic and somatic (adult) stem cells. Among which embryonic stem cell is further classified into neural stem cell (NSC) and mesenchymal stem cell (MSCs). NCS resides within brain, and found in subgranular zone (SGZ) a part of brain which is important in learning and memory formation. Therefore, NCSs are the obvious choice for replacement of damaged neurons. Qu et al. (2001) were one of the earliest groups to prove this by implanting human NSCs into the brains of aged and mature rats. [34] Recent research and practice have helped in transformation of neural cells into different types of neurons and glial cells. Several studies are being carried to establish the utility of stem cell therapy. However, it will take a long time to evaluate the therapeutic potential of such therapies. [21]

8.8. Antioxidant –

Alzheimer's disease is a highly disabling disorder and among the major types of dementia. The disease is characterized by progressive neurodegeneration alteration leading to reduced cognition. Several therapies are developed and used for the treatment of AD. Among them, a leading class of treatment involves use of antioxidant. According to the free radical and oxidative stress theory of aging, oxidative damage is a major player in neuronal degeneration thus leading to AD.

Antioxidants, on the other hand, are a group of endogenous or exogenous molecule that even in low concentration delay or inhibit the oxidation of the substrate. These help in removing scavenging reactive oxygen species, ROS (Reactive oxygen species) precursors and other free radicals. Based on data obtained from various studies a number of compounds with antioxidant activity are proposed including vitamin E, Flavonoids, Resveratrol, Pramipexole, ubiquinone, lipoic acid, idebenone, N-acetyl cysteine. [35]

Table 5: The Summary of Clinical trials with Antioxidants in MCI and AD.

Compound	No. of subjects and disease	Intervention	Primary endpoint	Main result
Vitamin E[36]	341 patients with AD	Daily vitamin E 2000 IU, selegiline 10 mg, vitamin E and selegiline or placebo for 2 years.	Time to the occurrence of the death, institutionalization loss of ability to perform activities of daily living, or severe dementia.	Delays in the time to institutionalization in patients treated with selegiline, vitamin E, or both.
Vitamin E (<i>Clinicaltrials.gov</i> v <i>NCT00040378</i>)	840 patients with AD	Vitamin E 2000 IU+memantine 20 mg or vitamin E 2000 IU or memantine 20 mg or placebo for 3 years	ADCS-ADL	Ongoing.
Epigallocatechin gallate (EGCG) (<i>Clinicaltrials.gov</i> v <i>NCT00235716</i>)	50 patients with AD	EGCG (increasing dose from 200 to 800 mg) daily or placebo add on to donepezil for 18 months	ADAS-cog score	Ongoing
Resveratrol (<i>Clinicaltrials.gov</i> v <i>NCT00678431</i>)	60 patients with AD	Resveratrol with glucose and malate supplementation or placebo for 1 year	ADAS-cog score	Ongoing
Pramipexole (<i>Clinicaltrials.gov</i> v <i>NCT01388478</i>)	20 patients with AD	Increasing dose (from 100 to 300 mg daily) pramipexole for 24 weeks	Safety issues and effects on cognitive performance	Ongoing
Latrepirdine (<i>Clinicaltrials.gov</i> v <i>NCT00829374</i>)	1050 patients with AD	Latrepirdine or placebo add on to donepezil for 1 year	ADAS-cog and ADCS-ADL scores	Ongoing
Lipoic acid (<i>Clinicaltrials.gov</i> v <i>NCT01058941</i>)	100 patients with AD	Lipoic acid 600 mg+fish oil 3 g for 18 months	ADAS-cog and ADL	Ongoing
Idebenone [37]	300 patients with AD	Idebenone 30 mg, 90 mg or placebo t.i.d. for 6 months	ADAS-total score	Improvement of ADAS-tot scores after 6 months at the highest dosage
Neutraceutical containing N-acetyl cysteine (<i>Clinicaltrials.gov</i> v <i>NCT01370954</i>)	800 subjects with early memory loss	N-acetyl cysteine 600 mg+methylcobalamin 2 mg+L-methylfolate calcium 6 mg for 12 weeks	Quality of life assessed by Quality of Life Alzheimer's disease scale	Ongoing.

ADAS - Alzheimer Disease Assessment Scale (Cog: cognitive score)

ADAS-ADL - Alzheimer disease cooperative study- activity of daily living.[35]

8.9. Influence of Estrogens on AD –

Estrogen or estrogen is a female sex hormone and is known to have neuroprotective activity, therefore considered as essential part of treatment therapy for AD. [38] According to the data from Framingham study, women's 65 years old or more without dementia had a 20% chance of developing dementia compared to men with 17% .[9] Women who experience early menopause are at a greater risk of

dementia. It is a proved fact that longer the women's exposed to estrogen, the better they are protected from estrogen. Fox et.al reported that with every extra month of estrogen exposure there is 0.5% reduction. Estrogen has both direct and indirect neuro protective actions which are as follows:-

- It also acts as antioxidant.

- It is known to stimulate choline acetyltransferase, which produces acetylcholine.
- It stimulates the degradation of amyloid β , thus decreasing formation of amyloid β .
- It also reduces hyper phosphorylation of tau further decreasing in formation of neurofibrillary tangles.
- It is known to enhance synaptic plasticity by stimulating an increase of dendritic spines and synapses in hippocampal CA1 pyramidal cells.

Hence, we can conclude that estrogen has direct neuroprotective action which can help in reducing the progression of Alzheimer's disease. [38]

8.10. Melatonin –

Melatonin (N-acetyl-5-methoxy tryptamine) which is also called as hormone of darkness, help human body adapt to diurnal variation which influence the human physiology and behaviour. Melatonin is reported to regulate energy metabolism, free radical scavenging, inflammation growth and development and aging, which are characteristic risk factor of AD. It is also reported as principal factor for inhibiting A β fibril formation. Melatonin level has been reported to reduce nearly half in elderly patients with AD as compared to young control subjects. Thus reduction in melatonin level leads to the symptoms of AD in elderly subjects. According to a study involving the analysis of isolated brain mitochondria from mice indicate reduction in mitochondrial A β by 2 to 4 folds in different regions of brain. However, after treatment with melatonin a nearly complete restoration of Mitochondrial respiratory rate and ATP level was recorded. [39]

8.11. Combination therapies for AD –

The symptoms of AD become increasingly severe over a period of years, thus decreasing the efficiency of monotherapy with the progression of disease. Cholinesterase inhibitors like Donepezil, Rivastigmine and Galantamine and NMDA receptor antagonist who include Memantine are essentially effective in the treatment of mild to moderate stage of AD, but these therapies lack in treatment of severe stage of AD. Hence, there was a need of combination therapy. Combination therapy with both treatment types has been used to treat patient in the moderate to severe stages of AD.

According to a study conducted in 404 patients for 6 months using a combination of NMDA receptor antagonist and AChE inhibitors (Donepezil), remarkable therapeutics effects were observed when compared with Donepezil treatment alone. [23]

8.12. Herbal therapy –

8.12.1. Curcumin longa Linn (Zingiberaceae)

Curcuma longa linn or Turmeric is an herbal medicinal plant used in India primarily for its anti-inflammatory and antioxidant properties. The chief constituents derived from turmeric is curcuminoids (~6%), of which curcumin constitute (50-60%). [40] It is a yellow coloring principle which has reported to shown remarkable effect in treatment of AD. According to a report, curcumin when fed to aged mice with advanced plaque deposition similar to those of AD; it reduced the amount of plaque deposited. It is also known to reduce oxidative damage and reversed the amyloid pathology in an AD transgenic mouse. Direct injection of curcumin into the brain of mice with AD not only hindered plaque development but also reduce plaque level. [9] The crude drug is used in the dose of 3-9g daily. The dose can be reduced by making it colon targeted. [40]

8.12.2. Huperzia serrate (Lycopodiaceae)

It is a Chinese folk medicine containing a larger group of alkaloids called "lycopodium alkaloids". Huperzine A is the chief constituent of the medicinal plant used to enhance memory and learning. According to various studies, it is found to preserve Ach longer than Tacrine, Donepezil, and Galantamine. Normally acetylcholinesterase is found in different molecular forms in human brain G1, G2, G3, and G4. In which G4 is in large amount as compared to all other. Huperzine A primarily known to inhibits G4. It is mainly used in treatment of AD because it decreases β amyloid induction in hippocampus and cortex part of brain. It protects neurons from cytokines induced by amyloid β and free radicals. [41, 42]

8.12.3. Bacopa Monnieri linn (Scrophulariaceae)

Bacopa Monnieri or Nira Brahmi is a traditional medicine mainly used as a brain tonic to enhance memory development, learning and concentration. Chief constituents derived from a plant which is responsible for cognitive effects are Bacosides A and B. The triterpenoid saponins and their bacosides are responsible for bacosides ability to enhance nerve impulse transmission. It helps in repairing damaged neurons by enhancing kinase activity, neuronal synthesis, and restoration of synaptic activity ultimately nerve impulse transmission. According to a clinical study, it has been used to treat neuritis. The dosage of the powdered drug is 5-10g and infusion of 8-16 ml is used in case of Alzheimer's disease. [40,44]

8.12.4. Ginkgo Biloba (Ginkgoaceae)

It is an herbal medicine mainly used in traditional Chinese medicine system for thousands of years. It is used to treat memory loss and enhance brain activity. It acts by improving blood flow to the brain and other body tissues and it is also known to enhance cellular metabolism. According to the studies conducted by

Medical Research Council of New Castle General Hospital, the ginkgolides present in ginkgo biloba act as antioxidant, neuroprotective. It enhances the protection against amyloid β protein-induced oxidative damage by trapping reactive oxygen species. The dosage of powdered drug is 120-240mg. [40, 46]

8.12.6. *Convolvulus pluricaulis* –

Convolvulus pluricaulis or Shankpushpi possesses a beneficial memory enhancing, antioxidant property. The chief constituents of Shankpushpi include triterpenoid, flavonol glycosides, anthocyanins, and steroids which are responsible for its nootropics and memory enhancing properties. According to the recent studies, ethanolic extract of CP (*Convolvulus Pluricaulis*) and its ethyl acetate significantly improve learning and memory in rats. Similarly, administration of CP extract for 7 days enhanced memory in aged mice. [9]

8.12.7. Other medicinal herbs –

Several other medicinal herbs are used in treatment and prevention of AD. Herbs with antioxidant and anti-inflammatory properties are widely used to reduce inflammation of brain tissues and improve cognition. Some examples of these types of medicinal herbs include:- *Centella Asiatica* (Brahmi), *Salvia officinalis* (Sage), *Rosmarinus officinalis* (Santapatrika), *Melissa officinalis* (Lemon Balm), *Glycyrrhiza glabra* (Licorice Root), *Galanthus Nivalis* (snowdrop), *Huperzia Serrata* (firmosses), *Commiphora Wighitti* (Guggul), *Tinospora Cordifolia* (Guduchi), *Withania Somnifera* (Ashwagandha), *Catharanthus roseus* (Alkaloid-Vinpocetine), *Crocus Sativus* (Saffron), *Eclipta alba* (Bhringaraj) etc.[40] Given below are some examples of crude/ semi-purified plant extracts with Anti-Alzheimer's activity.[42]

Table 6: Crude/ Semi-purified plant extract with Anti-Alzheimer's activity.

Source plant (parts/ crude or semi-purified extracts)	Family	In-vitro/in-vivo models/Human trial	Mode of action
<i>Allium sativum</i> L., aged garlic extract (AGE) [43].	Amaryllidaceae	Transgenic Swedish double mutant mouse AD model Tg2576. A β (25-35) induced PC12 cells	Increased Anti-amyloidogenic, increased anti-inflammatory, increased anti-tangle
<i>Angelica Gigas</i> , ethanolic extract. [44]	Apiaceae	A β (1-42)-induced mice	Decreased memory impairment
<i>Bacopa Monnier</i> (L.) Wettst., alcoholic extract [45].	Plantaginaceae	Male Wistar rats AD model induced by ethylcholine aziridinium ion (AF64A)	Increased cognitive function, increased cholinergic neuron
<i>Crocus sativus</i> L. (saffron) [46].	Iridaceae	Patients with mild-to-moderate AD	Increase efficacious in mild and moderate AD.
<i>Salvia officinalis</i> L., alcohol extract [47]	Lamiaceae	Patients with mild to moderate AD	Increased efficacious against AD, Decreased agitation
<i>Ginkgo biloba</i> L., special extract EGb 761 and donepezil [48].	Ginkgoaceae	AD patients with mild to moderate dementia	Increased efficacious against dementia
<i>Magnolia officinalis</i> Rehder & E.H.Wilson, 4-O-methyl honokiol (4-O-MH) (an extract) [49]	Magnoliaceae	A β (1-42)-induced mice	Increased memory, increased antioxidation, increased glutathione, decreased p38 MAPK
<i>Panax ginseng</i> C.A. Mey., [Korean red ginseng (KRG)], total powder capsule from roots [50].	Araliaceae	AD patient	Increased efficacy against dementia
<i>Valeriana amurensis</i> P. Smirn. ex Kom., AD-effective fraction [51].	Caprifoliaceae	A β (1-42) induced mice	Increased cerebral cholinergic function, decreased apoptosis
<i>Vitis amurensis</i> Rupr., methanol extract from the leaf and stem [52]	Vitaceae	A β (25-35)-induced rat cortical neurons, mice	Decreased A β -induced neurotoxicity, decreased dementia
<i>Zataria multiflora</i> Boiss., essential oil [53].	Lamiaceae	A β (25-35)-induced rat hippocampus	Increased AChE inhibitory activity, increased antioxidant act.

8.13 Stimulatory Therapies –

The stimulatory therapies include physical exercise, cognitive training, music, socialization, etc. These are

generally thought to facilitate cognitive function. According to various studies these therapies with their different mechanisms reduce the progression of

AD. The advantage and disadvantage of stimulatory therapies are summarised below:-

Table 7: Stimulatory therapies for AD. [54]

Activity	Advantage	Disadvantage
Physical exercise	Increase blood to brain, improves vascular function, aids sleep, reduce inflammation, elevate mood, increase synaptic plasticity, aids neurogenesis	Little research specifically on AD patients.
Cognitive training	Improve many cognitive functions	More research indicated
Socialization	Preserve cognitive functioning, may improve mood.	Little research
Music	Reduce stress and depression, improves cognition by aiding the destruction of dysfunctional cells, increase melatonin levels, facilitating neurogenesis and plasticity.	Little research
Psychological factors	A positive attitude may stimulate patients to exercise and engage in activities that are beneficial.	No research specific to AD.

9. CONCLUSION:-

Alzheimer's disease is an increasingly common condition with increased incidence rate in the population. To date, treatment of disease is mainly dependent on cholinesterase inhibitors and NMDA receptor antagonist but these therapies are known to target symptoms not the cause of disease. To overcome these limitations of conventional therapies a large number of compounds have been validated and undergoing different phases of clinical trials. Various trials have been conducted for validating the use of new therapies in the treatment of Alzheimer's disease. However, only a few drugs clear these phases. For proper treatment of disease, it is essential to improve the quality of diagnosis. For this purpose, new diagnostic technologies including biomarkers are used. The Proper diagnosis helps in determining the progression and severity of the disease.

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