Understanding Alzheimer's disease: A Review

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ABSTRACT

Alzheimer Disease is a neurodegenerative disease characterized by cognitive decline leading to complete need for care within several years after clinical diagnosis. Alzheimer disease is characterized by deposition of amyloid plaques affecting memory, behaviour as well as cognition. Alzheimer's disease (AD) was discovered more than a hundred years ago. In spite all of this, the etiology and pathogenesis of the disease, as well as the occurence of the primary changes in the brain are still not fully understood. Pathophysiology changes due to AD involves loss of neurons, deposition of amyloid plaques, Neurofibrillary tangles, neurotransmitter changes such as cholinergic depletion, GABA, somatostatin, glutamate and corticotropin. Total Tau, Amyloid beta and phosphorylated Tau are the main biomarkers which act as a prospective tool in unfolding mysteries regarding mechanism as well as preventive measures towards occurrence of dementia. Certain animal models are also utilized for clinical studies of various anti-alzheimer drugs. Despite of pharmacological and non-pharmacological treatment, special care is needed to the patient. The main focus in AD research lies between underlying risk factors as well as newer therapies or treatment for delaying and preventing symptoms and onset of AD.

Keywords: *Alzheimer Disease; Total Tau; Phosphorylated Tau; Amyloid Beta*

Background: Alzheimer's disease (AD), as characterized by Alois Alzheimer in 1907, is a gradually progressive dementia occurs due to deposition of amyloid plaques in the Hippocampus affecting cognition, behavior, and functional status. AD profoundly affects the family as well as the patient. According to Alzheimer's association, there were 38 million people suffering from the disease worldwide in 2014. However possible risk factors, for AD include family history of AD, age, female gender, decreased reserve capacity of the brain (reduced brain size, low educational level, and reduced mental and physical activity in late life), head injury, and risk factors for vascular disease (hypercholesterolemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, and diabetes), inheritance of certain allelic forms of the gene. The need for supervision and assistance increases until the late stages of the disease, when AD patients become totally dependent on a family member, spouse, or other caregiver for all of their basic needs. These are the all-too-common experiences of the millions of people in the United States who care for someone with AD [1]. The exact pathophysiologic mechanisms underlying AD are not entirely known, and no cure exists. Although drugs may reduce AD symptoms for a time, the disease is eventually fatal.

Epidemiology: AD associated epidemiologic and economic development is a serious cause for concern as it indicates that AD will soon have a tremendous impact on society and could be considered as a modern epidemic. In 2005, prevalence and incidence rates in 14 regions had been estimated by group of experts. They concluded dementia in about 24.2 million people with possibility of about 4.6 million new cases [2][3]. North America (6.4%) and Western Europe (5.4%) held the highest prevalence rate of dementia at the age of 60 years which is followed by Latin America (4.9%), china and its western-pacific neighbours (4%). However, about 80-90% rise in dementia population is predicted in Europe, North America and the developed Western Pacific region between 2001-2040 whereas a steep increase is forecasted in Latin America, India, China, North Africa and the Middle Eastern Crescent. The prevalence rates for AD increases after 65 years of age. A study about prevalence rate of dementia suggested about 15 fold increase in AD risk among age group of 60-85 years [3]. The incidence of Alzheimer disease is higher in US as compared to Africa, Asia and Europe. However, prevalence rate for African-American and Hispanic populations living in the US will be higher as compared to Africans residing in their Homelands [3][4][5]. Another study revealed that prevalence rate for AD gets double after every 5 years of 60 years age [6].

Diagnosis: Method used to diagnose AD in CSF fluid involves Total Tau, Phospho-tau-181 and β- amyloid using ELISA technique. However, it is a great challenge to search for novel biomarkers in CSF and blood by

using modern potent methods, such as microarrays and mass spectrometry, and to optimize the handling of samples (e.g. collection, transport, processing, and storage), as well as the interpretation using bio-informatics. It seems likely that only a combined analysis of several biomarkers will define a patient-specific signature to diagnosis AD in the future. Alzheimer disease (AD) is characterized by dementia that typically begins with subtle and poorly recognized failure of memory and slowly becomes more severe and, eventually, incapacitating. Other common findings include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Occasionally, seizures, Parkinson features, increased muscle tone, myoclonus, incontinence, and mutism occur. Death usually results from general inanition, malnutrition, and pneumonia. Other abnormalities involves deposits of the protein fragment β-amyloid (plaques) and twisted strands of the protein tau (tangles) as well as evidence of nerve cell damage and death in the brain.

Pathology: Pathological study of autopsy samples has resulted in better understanding of AD disease. Gross examination revealed atrophic brain with reduced weight. Deposition of senile or neuritic plaques and neurofibrially tangles are main characteristic symptoms seen in pathology of AD disease [7]. Changes in Amyloid plaques and neurofibrially tangles results in impaired cognition function. Neuritic and diffuse plaques are distributed in neo-cortex. Increased tangles and plaques results in neuronal death as well as reduced memory **[8,9,10].** Granulovacuolar degeneration occurs in AD which results in numerous lesions. Cerebral amyloid angiopathy leads to haemorrhage of vessels due to thickening and hyalinization. Presence of Hirano bodies has been correlated with memory impaired AD. However, Hirano bodies are also found in normal brains as well as other neurodegenerative disorders. Other characteristic pathological features involves decreased glucose consumption, mitochondrial and cytoskeleton dysfunction [11].

Risk factors: The exact etiology of AD is unknown, however possible risk factors for AD include family history, age and gender. Antecedent factors involves hypertension, smoking, obesity, Diabetes, Diet, Head injury, decreased reserve capacity of the brain (reduced brain size, low educational level, and reduced mental and physical activity in late life) and Cerebro-vascular disease [11, 12, 13]. Medical conditions which leads to Alzheimer disease are Huntington disease, Multiple sclerosis infections such as HIV/AIDS, Lyme disease, Parkinson disease, Pick disease, Progressive Supranuclear palsy. These risk factors act independently as well as agonistic to each other changing the outcomes from bad to worse.

a. **Gender:** In many studies, women appear to be at greater risk for AD. This finding has been suggested on the basis of hormonal difference between men and women, different lifelong environmental exposures, and differences in educational attainment.

b. **Education**: Some studies suggest that lack of education is a risk factor for dementia, probably for both AD and vascular dementia. One study showed that an uneducated person over the age of 75 is twice as likely to suffer dementia as is a person who has completed at least the eighth grade. However, the Framingham Study recently found that, after adjusting for age, low education attainment was not a significant risk factor for dementia in general or for AD; it was, however, associated with an increased risk of vascular dementia, perhaps related to smoking habits and other risk factor for stroke.

c. **Genetic:** AD is categorized into late-early onset as well as familial-sporadic forms [12,13]. Amyloid Precursor, Presenillin 1, Presenillin 2 and Apo E4 are the genes which are known to contribute a vital role in pathophysiology of AD. Chromosomes 1, 14 and 21 are related in early onset of AD. Mutations of chromosomes 1 and 14 results in production of Presenillin 1 and 2 proteins which are further involved in processing of amyloid precursor protein. Chromosome 19 results in production of Apo Lipoprotein E gene and its alleles Apo E2, E3 and E4. Mutation of Apo E4 results in onset of AD [11]. Amyloid precursor gene is responsible for the production of Amyloid precursor proteins (APP) which are utilized in formation of nerve cells as well as plasticity in neurons. Mutations of this gene result in formation of amyloid plaques which are characteristic of AD. Accumulation of such plaques results in neuronal death [14]. Presenillin 1 gene produces presenillin protein which plays a vital role in processing of Amyloid precursor protein, cell growth and maturation. Presenillin 1 gene and other enzymes helps in breaking Amyloid protein into smaller fragments (Peptides) such as soluble amyloid precursor protein (sAPP), amyloid beta peptide etc. Mutation in Presenillin gene results in defective protein formation and improper processing of APP. Presenillin 2 gene is almost the similar to presenillin gene 1 except for site of mutation. In presenillin 2, mutation occurs by replacing asparagine to isoleucine at position 141 and methionine to valine at position 239. Mutations in Presenillin 1 and 2 gene results in overproduction of amyloid beta protein and accumulation of amyloid plaques [12].

d. **Hypertension**: Altered blood pressure serves as a vital contributor in late-life dementia. However, rise in dementia symptoms leads to reduced Blood pressure due to reduced body weight as well as stiffening of blood vessels. Studies assessing hypertensive old aged humans have concluded that

altered Blood pressure (high as well as low) is strongly associated with Dementia [15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34]

e. **Cerebrovascular Disease:** Cerebrovascular diseases are often correlated with AD. A cohort study conducted in hospitals showed frequency of about 7% new-onset dementia following first stroke [35]. Stroke results in dementia through amnestic syndrome such as thalamic strokes , Aβ destruction, destruction of brain parenchyma [1,36,37]. Cardiovascular disease acts as main risk factor for late life dementia in about 20% of patients. Various forms of cerebrovascular such as Macrovascular and Microvascular disease, infarction such as Single strategic, multiple bilateral as well as multiple lacunar, small vessel disease plays an important role in pathogenesis of AD [38].
f. **Smoking:** Risk of Dementia through smoking is well understood due to cholinergic metabolism. Smoking results in up-regulation of cholinergic nicotinic receptors in brain [39]. Improved attention and information processing occurs due to enhanced acetylcholine release mediated through increased nicotinic receptors. However, Acetylcholine release is opposed through smoking induced oxidative stress. It results in generation of free radicals as well as affecting immune system which activates phagocytes causing further oxidative damage [40,41,42]. AD is characterised by decreased acetylcholine and choline acetyl transferase. A study has concluded reduced risk for AD due to smoking [43].
g. **Body Weight:** Body Mass Index is an index for the growth and nutrition of a person. It can be defined as body mass (in kilograms) divided by individual's height in metre square. Lower BMI is co-related with AD and age related brain atrophy [44]. Another study concluded higher association between obesity and AD [45]. Other studies have showed strong association between altered body weight and AD.

Pathophysiology: AD is associated with numerous neurotransmitter changes. Severity of AD symptoms and cholinergic depletion are highly correlated. Other neurotransmitter dopamine, serotonin and norepinephrine are also altered in AD patients which results in various non-cognitive symptoms such as mood, motivation and executive function. GABA, glutamate, somatostatin and corticotropin releasing factors are also affected in AD (pathology paragraph). Neuritic plaques and neurofibrillary tangles are found in cortical and medial temporal area of brain. There are always higher levels of plaques and NFTs present in AD patient. These lesions results in neuronal loss as well as cortical atrophy [10,45,47]. NFTs are occasionally seen in hippocampus and Senile plaques are seen in neocortex. Neuritic plaques are extracellular lesions located in brain and cerebral vasculature which contains β-AP and APP which is coded by gene located on chromosome 21. Altered APP processing result in increased β-AP production which increases plaques. These plaques induce neurodegeneration and neuronal loss resulted in clinical dementia symptoms of AD [46,47]. NFTs consist of altered hyperphosphorylated tau protein which provides structural support to major constituent of cytoskeleton i.e. microtubules. Altered phosphorylation results in less effective binding and collapsed microtubules. Consequently, it will lead to improper cell functioning and cell death [9]. Loss of neurons in AD patient results in brain atrophy. Amyloid beta plays an important role in neuronal cell death. Neuronal loss is associated with depleted synapses and neuropil threads. Severity of symptoms of Dementia is highly correlated with neuropil threads and loss of synapse in AD [9,10]. Microglia and astrocytes releases pro-inflammatory substances in brain. Dystrophic neuritis with glial reaction in senile plaques occurs due to inflammatory response of neural degeneration in AD. Other inflammatory substances such as cytokines, nitric oxide, radical species and complement factors are also involved in AD. Levels of cytokines and chemokines levels are also elevated in AD and pro-inflammatory gene polymorphisms are associated with AD [46,47].

Other Neurotransmitter involved: Numerous neuronal pathways are affected in AD due to cell destruction resulting in neurotransmitter deficiencies, altered cholinergic levels being the prominent [8,9,10,11,48,49]. Loss of Cholinergic cells has been associated with reduced memory and cognitive impairment in AD. Pathology of AD also concluded loss of cholinergic neurons, serotonergic neurons of raphe nuclei and noradrenergic cells of locus cerulus. However, increased levels of Monoamine oxidase B (MAO-B) is found in brain and platelets which is also responsible for metabolising dopamine. Altered glutamate pathways were also reported in cortex as well as limbic structures in AD (reference). Glutamate exerts its toxic effects through elevated intracellular calcium and deposition of intracellular free radicals. Elevated Glutamate levels acts on NMDA receptor through overstimulation of receptors which results in APP processing to produce β-amyloid [50,51]. Elevated glutamate level may be due to oxidative modification in their major pathways. Glutamate transporter helps in transporting glutamate to glial cells. The main glutamate transporter which is oxidatively modified in AD is GLT-1 which binds to lipid peroxidation 4-hydroxy nonenal (HNE) generated by β-amyloid [52]. In AD, decreased glutamine

synthetase and glutamate transport inhibition results in increased concentration of glutamate which leads to stimulation of NMDA receptors, calcium accumulation and cell death [53]. Glutamate is converted into inhibitory neurotransmitter GABA through Glutamate decarboxylase. Study has concluded association of messenger RNA for Glutamate decarboxylase in AD patients. Elevated concentration of GABA acts on presynaptic $GABA_A$ receptors and causes dystrophy and cholinergic depolarising block which lead to differentiation and degeneration of neuronal system.

Animal models: Animal models have played an important role in understanding mechanism as well as molecular pathways associated with development and progression of AD. These models have led to improvements and various modifications in treatment of AD. Most commonly used pharmacological model for AD is scopolamine-induced amnesia [54,55], which explains association of cholinergic system in cognition and helps in screening of various cholinomimetic agents [56,57,58] and muscarinic receptor 1 agonists [59]. Few chemical induced animal models have been modified to study brain inflammation, neurodegeneration as well as impaired glucose/energy metabolism. Endotoxins and pro-inflammatory cytokines can induce brain inflammation [60,61]. Altered mitochondrial metabolic pathways as well as neuronal insulin signal transduction results in disruption of brain metabolism [62,63]. However, the nature of these models is also much debatable due to conflicting results arising due to various factors which in turn influence the outcomes such as, different species or strain, physiopathological characteristics, maintenance, protocol, location and extent of lesion, lesion-inducing agent, type and concentration of drugs, morphological, histochemical, biochemical and cognitive methods associated with animal models [64]. Memory-deficit models can be generated by lesioning particular area of brain or area of brain related to memory and learning [65,66,67,68]. Such models are also useful in understanding neural mechanism, pathology, identifying more pathways and new target sites for curing AD. Animal model has played an important role in preclinical studies for better understanding of disease as well as new drug discovery. These models contribute equally with human clinical studies in the discovery and development of new drugs.

Biomarkers: Widely used biomarkers for diagnosing AD are Aβ (1-42), total tau and phospho-tau-181. These biomarkers are very useful in diagnosing sporadic AD having sensitivity of >95% and a specificity of >85%. Amyloid Beta is one of the main biomarker which gets cleaved from APP through secretases and their processing yields a 42-amino acid peptide. These peptides gets accumulated in brain under stress conditions such as acidosis, metals etc. it has been suggested that elevated plaque deposition and reduced clearance of a-beta results in depleted levels of Aβ in Cerebrospinal fluid. Total tau is also another biomarker whose level increases with age in normal human beings. However, their levels are remarkably increased in AD as compared to healthy individual. Levels of total tau also serve as a parameter in determining conversion rate from MCI to AD. Except in cases of stable MCI, higher CSF tau level was found in about 90% of MCI cases which later progressed to AD. Elevated level of phosphorylated tau was found in AD as compared to controls. Hyperphosphorylation of tau results in functional loss as well as axonal transport dysfunction. Three variants of apoE gene are ApoE2, E3 and E4. Population homozygous to E4 allele suffers from AD 10 to 20 years earlier as compared to those having E2 or E3 alleles. However, patients heterozygous to E4 suffers from AD 5 to 10 years earlier as compared to E2 or E3 [69]. E4 allele serves as an important risk factor for AD which binds to β-amyloid and neurofibrillary tangles [70]. In CSF, elevated levels of conjugated and free ubiquitin were found in patients with MCI progressing to AD [71].

Current treatment available: Current pharmacotherapy for the disease neither cures nor arrests the pathophysiology rather it focuses on impacting three domains, namely: cognition, behavioral and psychiatric symptoms, and functional ability. Nondrug therapy and social support for the patient and family are the primary treatment interventions for AD [72]. However, use of various drugs have shown to improve the behavioural symptoms of AD.

1. **Pharmacological treatment**

a. **Cholinesterase Inhibitors:** Cholinesterase inhibitors and memantine are used to treat cognitive symptoms of AD. Newer cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, showed similar efficacy and adverse event profiles to one another and are generally well tolerated. The most frequent adverse effects associated with these agents are mild to moderate gastrointestinal symptoms (nausea, vomiting, and diarrhea) [73]. The mechanism of action differs slightly between drugs in this class [74]. Donepezil specifically and reversibly inhibits acetylcholinesterase. Rivastigmine inhibits both butyrylcholinesterase and acetylcholinesterase. Galantamine is a selective, competitive, reversible acetylcholinesterase inhibitor and also enhances the action of acetylcholine on nicotinic receptors. Other cholinergic side effects are generally dose-related and include urinary incontinence, dizziness, headache, syncope, bradycardia, muscle weakness, salivation, and sweating. Other medications have been suggested to be beneficial because of their potential preventive or cognitive effects [75].

Among antiglutaminergics, memantine is the only NMDA antagonist currently available. By blocking NMDA receptors, exitotoxic reactions which ultimately lead to cell death, may be prevented. The most common adverse events associated with it include constipation, confusion, dizziness, headache, hallucinations, coughing, and hypertension. Other cerebroactive drugs like: piracetam, pyrithioxine, dihydroergotoxine, piribedil etc. are also used in the treatment of AD. Piracetam selectively improves efficiency of higher telencephalic integrative activities putatively by: enhancement of learning and memory; facilitation of synaptic transmission; and increased tonic cortical control on subcortical areas. Pyrithioxine has been raised for: sequelae of cerebrovascular accidents, head injury, prolonged anesthesia; childern with developmental disorders of CNS, delayed syndromes: and concentration and memory defects. Dihydroergotomine is believed to act by protecting altered brain metabolism. Piribedil being a dopaminergic agonist is claimed to improve memory, concentration, vigilance, giddiness and tinnitus in the elderly.

b. **Vitamin E**: Vitamin E antagonizes inflammatory effects of plaques. It also improves cognitive function in Dementia. It also helps in countering B-amyloid deposition. However, it is not advised in other CNS disease such as Parkinsonism.
c. **Non-steroidal anti-Inflammatory Drugs (NSAIDs):** B-amyloid plaques mediated inflammation makes up the pathogenesis of AD [76]. Studies have suggested low risk of AD on concomitant use of NSAIDs. A meta-analysis concluded Alzheimer patient treated with NSAIDs were at lower risk as compared to non-NSAIDs treated. However, some studies have antagonistic view regarding use of NSAIDs in the treatment of AD [77,78]. Aspirin was also reported to reduce upto 13% risk for AD (). However, another study showed that NSAIDs such as prednisolone, Diclofenac/misoprostol, nimesulide, naproxen, ibuprofen, indomethacin, tarenflurbil, and celecoxib, rofecoxib were proved less effective in cognition improvement in AD patients [79].
d. **Statins:** Synthesis of cholesterol takes place in brain and liver only. Cholesterol metabolism has been associated with accumulation of B-amyloid plaques and occurrence of AD. The cholesterol levels are associated with food and dietary factors. Statins are used primarily for reduction of LDL cholesterol levels [80,81,82,83,84,85,86]. Neural cholesterol levels can be reduced through lipophilic statins. Highly lipophilic statins crosses blood brain barrier easily [78,87]. During a 5-year follow up study, low risk of dementia has been associated with use of statins [88]. Statins has been reported to reduce about 20-30% of cardiovascular disorders [80,81,82,83,84]. Other action of statins prior to cholesterol reduction involves treatment of dementia via improved cognitive functioning [85,89,90,91]. However, risk reduction effect of statins on dementia has been less consistent [91]. In-vitro and in-vivo cerebral AB generation is cholesterol dependent [78,92,93]. Cell culture and animal studies suggested reduced AB levels with cholesterol reducing drugs. Study has concluded relatively same levels of AB in simvastatin treated as well as untreated controlled mice. Simvastatin improved learning and memory but it is thought to be due to signalling pathway modulation in memory formation [94].
e. **Ginkgo Biloba:** Ginkgo Biloba has been used in treatment of AD by improving cognitive functioning. However, evidence does not support significant role of gingko biloba in AD patients [78,95,96]. According to Cochrane library, there were inconsistent evidence on use of gingko biloba and reduced risk of AD [97].

2. **Non-Pharmacological treatment:** Lifestyle modification, good nutrition, regular physical activity as well as social interaction are some non-pharmacological methods used to ameliorates/reduce risk of AD. However, calm, safe and structured environment also helps in reducing risk of AD. Non-pharmacological treatment also involves cognitive training, behaviour training, kinesiotherapy, Music therapy, pet therapy, Reality Orientation therapy, validation therapy, self-preservation therapy.

a. **Music Therapy:** Music has a very strong impact on human's health/state of mind and is an important tool in management of AD [98]. It helps in reducing incidence of shouting, agitation as well as restlessness [99]. Moreover, it helps in restoring/improving mental and physical abilities of AD patients/suffering from AD. It provides calming effects to patient. White noise is also an important part of this therapy. It utilizes/comprises of different sound frequencies which combines with natural calming sounds. Therapy involves listening to music or white noise for 30-35 minutes in a quiet and lone room which helps in providing peace to mind. Various studies have concluded positive association between music therapy and improved conditions of Dementia **[100,101].**
b. **Cognitive therapy**: AD is characterized by impaired and deficient cognitive function such as decreased memory and attention, impaired visuospatial functioning and decreased social interaction **[102].** Pharmacological treatment has shown mixed result to improve cognitive functioning **[103,104,105].** However, cognitive training, a part of Non-pharmacological treatment has shown positive association and results during mild to moderate stages of AD. Cognitive training aims at

improving memory as well as attention. These strategies can be categorized into restorative and compensatory **[106,107].** Compensatory strategies aim at utilizing internal as well as external strategies to improve cognitive functioning. Internal techniques involves use of visualizing information questionnaires and attention whereas external techniques involves use of calenders, notebooks etc. **[108,109,110**]. Restorative strategies aim at restoring/ returning functioning of AD patients to premorbid levels. It involves restorative techniques, orientation therapy, reminiscence, vanishing cues etc. **[108,109,110,111,112**]. A meta-analysis study concluded promising/positive association between cognitive therapy and reduced risk of AD. Another study concludes cognitive training to be more effective in improving attention, cognitive functioning and decision making **[113]**.

c. **Reality orientation therapy**: AD often results in increased disorientation and lack of socialism (alone feeling/cutoff from world). Therefore, reality orientation therapy can be utilized to improve social behavior and self-belief. This therapy involves repetitive reorientation of person towards environment through continuous stimulation [114]. AD patients can be re-orientated by continuously reminding them about the past (things). ROT is a continuous type in which patient is oriented in reality based communication system. Studies have suggested beneficial effect of ROT in improving cognition and behavior in AD patients [114,115,116,117]. Randomised clinical trial concludes ROT acting as agonist for Donepezil for improving cognition in AD [118].

d. **Miscellanous non-pharmacological therapy**: There are other various non-pharmacological therapies which are gaining recognition and proving helpful in the treatment and management of AD. Such therapies involves pet therapy, touch therapy, simulated presence

- **Simulated Presence therapy**: This therapy is helpful in reducing stress and disturbance. This therapy involves audiotapes, videotapes, telephonic messages or voice mails of family events and functions. This therapy helps in improving behaviour as well as cognition [101].
- **Pet therapy**: Pet therapy has suggested positive result in reducing depression as well as dementia in patients [119].
- **Exercise**: Various exercises helps in management of AD such as walking, jogging etc. Exercise helps in refreshing mind as well as elevating self-esteem. Exercise helps in boosting confidence in patient.
- **Touch therapy**: Massage helps in reducing aggressive behaviour, anxiety and stress conditions [120,121].
- **Cognitive activities**: Various activities and games helps in improving cognition in dementia patients. Bingo can be utilized in managing AD patients [122]. Other activities involves reading books or magazines, playing block games and sorting games also proves useful in improving cognition in AD patients. Rocking chair intervention is also used to reduce depression as well as anxiety in dementia patient's [123].

3. **Vaccination:** Vaccination plays an important role in reducing amyloid clogs present in brain. It was also concluded that vaccines such as tetanus or diphtheria, poliomyelitis, influenza provides resistance against development of AD [124]. In AD mouse model, peptide immunization of Abeta 1-42 had shown reduced levels of amyloid beta in brains of treated mice which further improves memory functions [125,126,127]. However, another clinical trial performed on Abeta 1-42 had resulted in occurrence of encephalitis in 6% of the total participants due to inflammatory T cell response against Amyloid beta levels [128,129,130]. An alternative approach utilises DNA encoded Abeta immunization and avoids peptide administration to eliminate risk of encephalitis. Abeta 42 immunization provides Th2 cellular mediated immune response [131,132,133,134]. Another approach utilises humanised antibodies which provides passive immunization to the host body. Except Bapineuzumab, other antibodies such as Bapineuzemab, Solanezumab, Gantenerumab, Crenezumab etc had shown better and significant results in AD [135,136,137,138,139,140].

Care and Management: Proper care is needed in the management of AD. Separate areas for patients, home-assisted and other care giving facilities are always helpful in the management and treatment of AD. Care-taker or family of the patient always plays a vital role in the management of AD. Proper directions should be followed by care-taker or families in order to get better results. Pharmacological and non-pharmacological therapy should be properly maintained by care-takers or families. There are various strategies which can prove helpful for better results in management of AD. Maintaining proper independence in daily activities will boost a confidence as well as self-esteem in the patients. Regular follow-up between doctor and patient is necessary in which care-taker or families play a vital role. Requests or demands of the patient should be made simple and clear. Avoid confrontation as well as complex tasks which could lead to frustration. Calm, firm and supportive environment should be maintained around the patient. Frequent reminders, explanations and orientation cues should be made to the patient in such a way that patient will not get upset, confused, demotivated or frustrated. Patient should be emotionally as well as socially supported through counselling and orientation. Behavioural management can

also help in alleviating behavioural disturbances and provides comfort or reduces stress from care-givers. Sometimes, it becomes difficult for the patient to follow up proper treatment and care which makes the role of care givers a lot more valuable. It becomes the responsibility of the care givers to motivate patient as well as to boost confidence to stand against given conditions.

Conclusions and Future Directions: The prevalence of AD has been increasing in both developed as well as developing countries. Better understanding of this disease is still debatable in many countries. Identification of people who are at risk of suffering with AD is still difficult which alleviates probabilities of better management and treatment. Proper counselling, orientation and awareness about the disease should be done so as to take necessary precautions. Patient should be motivated for various life-style modifications such as weight-loss, physical activities, healthy food habits etc. these modifications will prove a vital tool in providing resistance against diseases and maintaining quality of life. Long-term studies on pharmacological as well as non-pharmacological treatment and reduction of risk of AD should be performed for better care and management. Earlier, prevalence of risk factors among patients was one of the main focused branch of research which has been shifted towards preventive approach to prevent or delay the onset of Alzheimer.

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