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Alzheimer's - A Detailed Study On Causes, Symptoms, Remedies And Current Research Studies

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Abstract: *It is a chronic neurodegenerative disease that usually starts slowly gets worse over time and become incurable and the valid grounds of Alzheimer's disease [1] are poorly understood. About 70 % of the risk is believed to be genetic with many genes usually involved. Other risk factors include a history of head injuries, depression, or hypertension. Affected people increasingly rely on others for assistance, often placing a burden on the caregiver; the pressures can include social, psychological, physical, and economic elements. Exercise programs are beneficial with respect to activities of daily living and can potentially improve outcomes. The cause for most Alzheimer's cases is still mostly unknown except for 1 % to 5 % of cases where genetic differences have been identified. Symptoms can be treated with medication, but there is no cure. People who engage in intellectual activities such as reading, playing board games, crossword puzzles, musical instruments or regular social interaction and physical activity are also connected with a reduced risk of Alzheimer's disease despite usage of medications. Treatment may involve medications that are thought to decrease the rate of decline. Majority of patients will receive neuroimaging (CT, MRI) as a part of the diagnostic work. Genetic tests may be supportive in diagnosis but further studies are needed to confirm their reliability. No diagnostic test is definitive for Alzheimer's disease.*

Key words: *Dementia, Cholinergic hypothesis, Amyloid hypothesis, Tau hypothesis, Neurofibrillary tangle, Senile plaque, Genetics, Pathophysiology.*

I. Difference between Alzheimer's and Dementia

Alzheimer's disease (AD) also known as Alzheimer disease or just Alzheimer's accounts for up to 70 % of cases of dementia [2,3]. Alzheimer's is a variety of neurodegenerative disorder that is most usually seen in grown-up people. In other words, it can be said as a type of dementia that causes complications dealing with memory, thinking and behaviour. Dementia and Alzheimer's are not related. Dementia is said to be a type of neurological disorder that takes hold on the performance of the regular acts and communication, while Alzheimer's is a form of dementia that affects parts of brain which controls thought, memory and language. Dementia is a disorder of the brain that results in cognitive function [4] that is impaired to the point of affecting the ability to perform daily tasks and communication. Alzheimer's disease is the most common cause of dementia which is characterized by a gradual deterioration of the brain where in the brain cells die and is not replaced, leaving ever growing gaps in the brain matter.

1.1 History Of Alzheimer's Disease:

In 1906 a German neurologist and psychiatrist named Dr. Lois Alzheimer first noticed the symptoms of Alzheimer's in a 51 year old woman Auguste. D. The symptoms noticed in her are struggling or inability to speak, loss of memory, confusion, behavioral problems and delusions. After her death the brain tissue was analyzed and beta-amyloid plaques [5-7] and neurofibrillary tangles are observed. From 1910s -1940s a belief persisted that "senile dementia" [8] is a normal part of aging. In 1950s the structure of plaques and tangles are learned. In the 1960s Alzheimer's was documented as a distinct disease, but not a customary part of aging. In 1970s the volumes of Acetyl Choline, a neurotransmitter declines sharply in individuals with Alzheimer's disease. In 1980s, diagnostic principles for Alzheimer's disease are established. The development of beta-amyloid plaques and the uncharacteristic tau proteins in tangles are identified. In 1990s USFDA approved TACRINE (COGNEXe) for the treatment of Alzheimer's disease. In 2000s FDA approved some other drugs like Rivastigmine (Exelon®), Galantamine (Razadyne) Donepezil (Aricept®), and Memantine (Namenda®) for the treatment of Alzheimers disease. Pittsburgh Compound B (PiB) is developed, that aided the scientists to notice beta-amyloid plaques in the brains of living people. The study of vaccines for Alzheimer's disease began in 2000s.

1.2 Brain:

The brain of an adult weighs about 3 pounds and measures the size of a medium cauliflower. It directs numerous body functions, such as breathing, blood circulation, and digestion, exclusive of our realization or direction and also the functions those we carry out consciously. The brain is made of several nerve cells which are also termed as the neurons. About 100,000,000,000,000 (100 billion) neurons are estimated to be present in the brain and they work with the aid of the glial cells duly holding the neurons in locus and provide nourishment to them. They also play a key role in the elimination of cellular debris in the brain; make available insulation to neurons in the brain and spinal cord. It is predicted that the number of glial cells is that 10 times more than that of the number of neurons in the brain. The gaps between the neurons are called as synapses which are about 100,000,000,000,000 (100 trillion). The brain receives 20 percent of the total blood supply of the body through tiny blood vessels, known as capillaries which bring oxygen, glucose, nutrients, and hormone to the brain cells and also carry waste products. The number of capillaries in the brain amounts to 400,000,000,000 (400 billion). Glucose serves as the prime source of energy. Fig 1 shows a detailed description about the transverse section of brain.

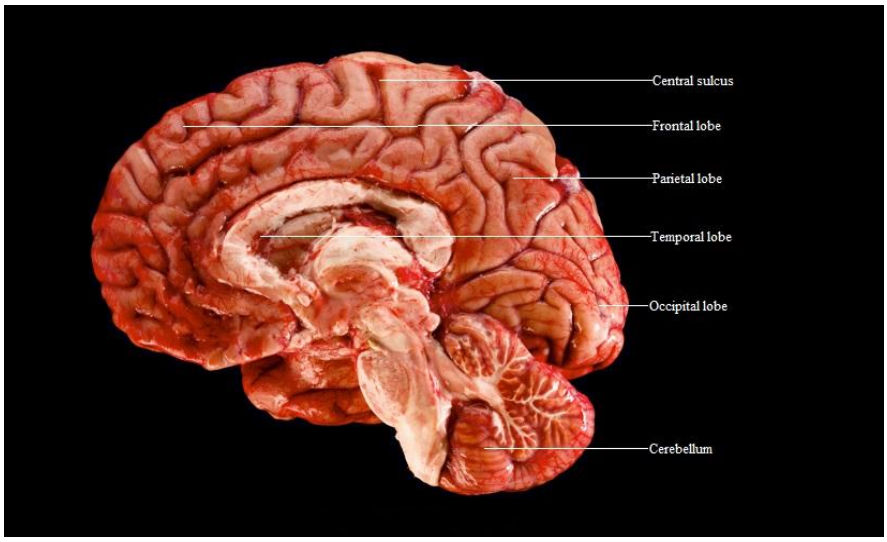

Figure 1. T.S of human brain.

II. Types of Alzheimer's

There are three types of Alzheimer's namely:

2.1 Early – Onset Alzheimer's:

This form of Alzheimer's disease is diagnosed before 65 years of age and is not often seen. Not more than 10% of Alzheimer's patients have this type and people with Down syndrome [9] are particularly at risk. A type of muscle twitching and spasms are more commonly seen in this type of Alzheimer's. This condition is called myoclonus.

2.2 Late – Onset Alzheimer's:

This is the most common type of Alzheimer's and occurs beyond the age of 65. About 90 % of the patients are suffering from late onset Alzheimer's. It may or may not be hereditary. Late onset dementia is also 0called as Sporadic Alzheimer's disease.

2.3 Familial Alzheimer's Disease (FAD):

This type of Alzheimer's is extremely rare and accounts for only 1%. When affected by Alzheimer's disease, it leads to the damage of nerve cell death, causing shrinkage of the brain.

2.4 Pre Clinical Alzheimer's Disease:

Alzheimer's disease starts developing in the entorhinal cortex of the brain, a region near to the Hippocampus region [10,11]. The neurons present in the entorhinal region works less efficiently, loses communications with other neurons present in the brain and eventually dies. This progressively spreads to the hippocampus region, which plays a major role in converting the short - term memories to long -term memories. Scientists deem that the above changes occur 10 to 20 years before any clinically evident signs or symptoms of amnesia appear. Fig 2 shows a detailed view of brain in pre clinical alzheimers stage.

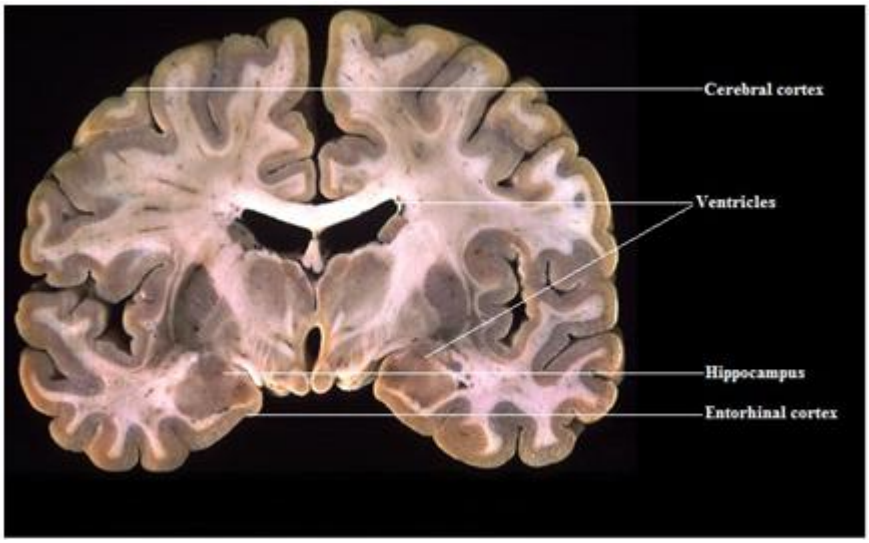

Figure 2. Brain in pre clinical alzheimers disease stage.

2.5 Mild Alzheimer's Disease:

With an increase in the spreading of Alzheimer's disease through the brain the number of plaques and tangles grows consequently the shrinkage of the brain progresses, as a result of which the cerebral cortex is affected to a greater extent. Fig 3 gives a view of brain in mild alzheimers disease stage.

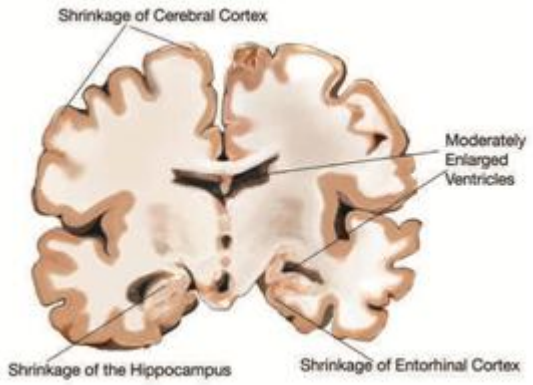

Figure 3. Brain in mild alzheimers disease stage.

2.5.1 Symptoms Of The Mild Alzheimer's Disease Are:

Memory loss, misperception about the whereabouts of familiar places, taking longer than before to complete normal diurnal tasks, difficulty in managing money and clearing bills, insignificant judgment leading to bad decisions, loss of spontaneity and sense of initiative, mood and personality changes, increased anxiety and or aggression.

The people suffering from mild Alzheimer's cannot realize that they are suffering with it and the only way they can realize is, unless and until they get informed about it by his or her family members and friends etc.

2.6 Moderate Alzheimer's Disease: In this stage, the disease spreads to the regions of the cerebral cortex, but there will be control over the language, reasoning, sensory processing, and conscious thought. Behavioral problems, like wandering and agitation, can occur.

2.6.1 Symptoms Of This Stage Include:

Mounting memory loss and confusion**,** reduced duration of attention**,** improper eruption of anger**,** troublesome in identifying friends and family members**,** problems with language and glitches with reading writing and working with numbers**,** difficulty in organizing thoughts and thinking**,** incapability to learn novel things, to cope with new or unexpected situations**,** restlessness, agitation, anxiety, tearfulness, wandering mostly in the late afternoon or at night**,** repeated statements or movements, unsystematic muscle twitches**,** delusions, suspiciousness or fear, irritability**,** loss of impulse control**,** and an incapability to accomplish events that involve a mixture of steps in series such as dressing, preparing coffee, or putting a table.

2.7 Severe Alzheimer's Disease:

This is the final stage and the severe stage of Alzheimer's disease. The plaques and tangles are widespread throughout the brain as a result of which major portion of the brain gets shrink and the ventricles also get more enlarged. Fig 4 shows extreme shrinkage of brain in severe alzheimers disease state.

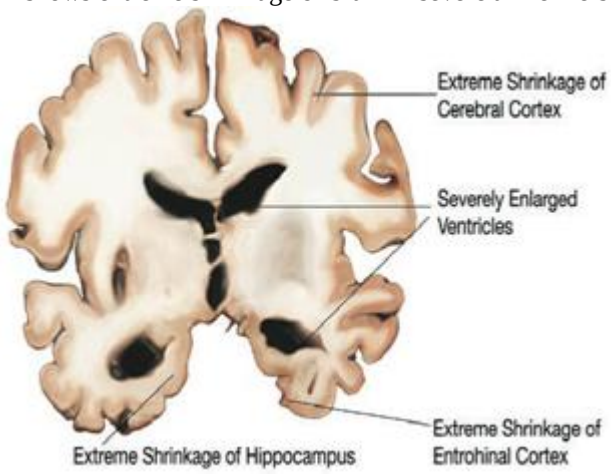

Figure 4. Brain with severe alzheimers disease.

2.7.1 Symptoms Includes:

Weight loss, seizures, skin infections, complexity in swallowing, groaning, moaning, or grunting, increased sleeping and lack of bladder and bowel control.

III. Features of Alzheimer's disease

Alzheimer's disturbs the critical metabolic processes that keep neurons in good physical shape consequently the brain stops working, lose connections with other nerve cells, and finally die. There is no such a thing that Alzheimer's affect all the people in the same way. But the main symptom is the difficulty to remind new things. This occurs due to the death of the primary neurons that are mainly responsible in developing or creating memories. The death of the neurons leaves a peculiar condition to the individual leading to the situations such as, loss of memory that causes problems in day-to-day life, depression, difficulty in speaking, poor involvement in work or social activities, confusion and altered attitude and behavior.

3.1 Changes In The Brain That Is Associated With Alzheimer's Disease:

The brain of human being consists of nearly 100 billion neurons and 100 trillion synapses through which the information passes from brain to different organs in the body consequently enable to have memories, feelings, movements and skills. A protein called amyloid develops in the brain in the form of clumps which is likely responsible for causing Alzheimer's which is responsible to lose their memory, gets disoriented in space and time and other behavioral problems may happen. These protein clumps get accumulated outside of the neurons and prevents the transfer of information resulting in cell death, which occurs with advanced stages of Alzheimer's. Owing to dying neurons the cell death will become rapid and a lot of debris gets accumulated in the brain. The brain changes due to Alzheimer's may begin 20 or more years before symptoms appear. The time between the initial brain changes of Alzheimer's and the symptoms of advanced Alzheimer's is considered by scientists "continuum" of Alzheimer's and at its initial stage the individual is capable to function normally despite these brain changes. Further along the continuum, the brain can no longer compensate for the neuronal damage that has occurred, and the individual shows slight decline in cognitive function [12-14]. Later, the damage of neurons causes their death that is so significant that the individual shows noticeable cognitive decline, following symptoms such as memory loss or confusion as to time or place. Afterwards basic bodily functions such as swallowing are impaired. Fig 5 shows a brief view of neurons and dendrites in our brain and Fig 6 shows the formation of beta amyloid plaque from APP.

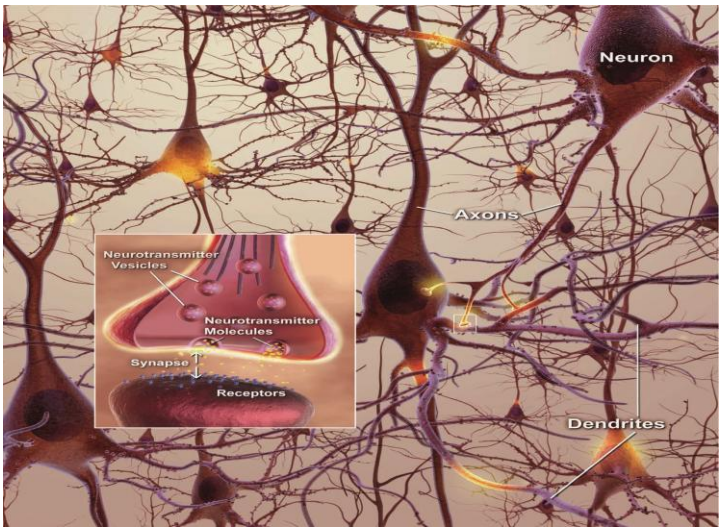

Figure 5. Network of neurons and dendrites in brain.

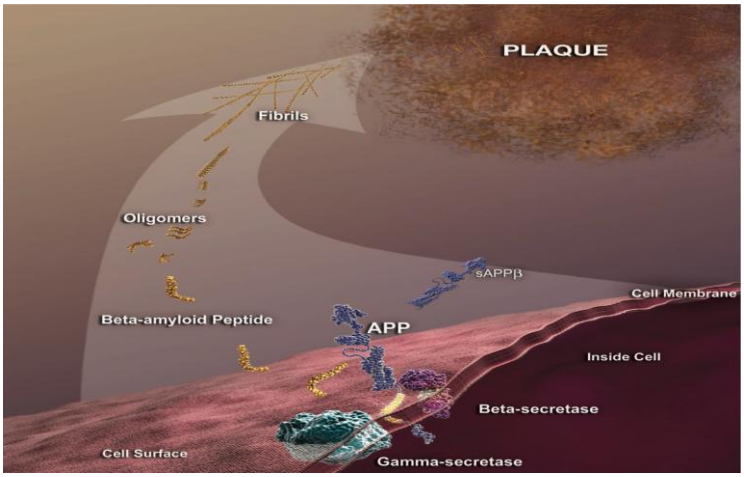

Figure 6. From APP to Beta-Amyloid Plaque.

3.1.1 Age:

The greatest known risk factor is increasing age and most individuals with the illness are 65 and older. After age 85 the risk reaches nearly 50 %.

3.1.2 Family History And Genetics:

Research has shown that those who have a parent or sibling with Alzheimer's are 2 to 3 times more likely to develop this disease than those who do not. Head injury and overall brain health are other risk factors. The Genetic, environmental and infectious etiologies have been explored as potential causes of Alzheimer's disease.

3.1.3 Genetics:

Almost all early onset cases of Alzheimer's disease can be attributed to alterations on chromosome number 1, 14 or 21. Approximately 5 % of the cases of Alzheimer's disease are early onset. The majority and most aggressive early onset cases are attributed to mutations of an Alzheimer's gene located on chromosome 14, which produces a protein called presenilin 1. Similar in structure to presenilin 1 is a protein produced by a gene on chromosome 1 called presenilin 2, which is responsible for early onset of Alzheimer's disease. Both presenilin 1 and presenilin 2 encode for membrane proteins that may be involved in amyloid precursor protein processing. It has been suggested that presenilins are actually gamma secretase or that presenilins affect gamma secretase activity. As a group, presenilins account for approximately 50 % of all early onset Alzheimer's disease cases. Amyloid Precursor Protein [APP] [15,16] is encoded on chromosome number 21. Only a small number of early onsets, familiar Alzheimer's disease cases have been associated with mutations in the Amyloid precursor protein gene, resulting in over production of beta amyloid protein. Genetic susceptibility to late onset Alzheimer's disease is thought to be primarily influenced by the apo lipoprotein [apo E] genotype. The gene

responsible for the production of apo E is located on chromosome number 19 in a region previously associated with late onset Alzheimer's disease. Three major subtypes or alleles of apo E occur and are termed apo E2, apo E3, and apo E4. The apo E4 allele is a risk factor for development of Alzheimer's disease. About 40% of patients with late onset Alzheimer's disease have at least one copy of apo E4.

3.1.4 Environmental Factors:

A number of environmental factors have been associated with increased risk of Alzheimer's disease apart from stroke, alcohol abuse, small head circumference, repeated or severe head trauma, and lower levels of education. In particular, traumatic head injury in combination with the apo E4 genotype has been associated with an increased risk of Alzheimer's disease.

Only one percent or less Alzheimer cases are due to genetic mutations. This involves the genes for the amyloid precursor protein and the genes for the presenilin 1 and presenilin 2 proteins.

IV. Diagnosis

There are no specific tests in the present day for the detection of Alzheimer's. But at present various approaches that are being adopted to confirm the disease are: The doctors may ask for the medical and family history, psychiatric history of the individual. A brief input of the patient is taken from a family member who is close to the patient. In addition, the physician conducts cognitive tests and physical and neurologic examinations and may request that the individual undergo magnetic resonance imaging (MRI) scans. MRI scans can help identify brain changes, such as the presence of a tumor or evidence of a stroke that could explain the individual's symptom. Computerized tomography (CT) and Positron emission tomography (PET) [17] are the other methods that are used to diagnose Alzheimer's.

4.1 Treatment:

4.1.1 Pharmacologic Treatment:

These are treatments [18] in which medication is administered to slow or stop an illness or treat its symptoms. None of the treatments available now - a - days for Alzheimer's disease slows or stops the malfunction and death of neurons in the brain that cause Alzheimer's symptoms and eventually make the disease fatal. However, several drugs and therapies aimed at slowing or stopping neuronal malfunction and death are being studied by the scientists around the world, out of which five drugs have been approved by the U.S. Food and Drug Administration that temporarily improve symptoms of Alzheimer's disease by increasing the amount of chemicals called neurotransmitters in the brain. The effectiveness of these drugs varies from person to person.

4.1.1.1 Management:

Despite lack of disease-modifying therapies, studies have consistently shown that active management of Alzheimer's and other dementias can improve quality of life through all stages the individuals with dementia and their caregivers.

4.1.1.2 Active Management Includes:

Appropriate use of available treatment options is: Co-ordination of care among physicians, other health care professionals and arranged caregivers, and participation in activities or adult day care programs and in support groups and support services.

4.1.2 Non-Pharmacologic Therapy:

Non-pharmacologic therapies are those that take up approach other than medication, such as physical therapy and reminiscence therapy (therapy in which photos and other familiar items may be used to bring out recall). As with pharmacologic therapies, non-pharmacologic therapies have not been shown to alter the course of Alzheimer's disease. Rather than altering the disease course, non-pharmacologic therapies are often used with the aim of maintaining cognitive function or helping the brain to compensate for impairments. Non-pharmacologic therapies are also used with the objective of improving quality of life or reducing behavioral symptoms such as depression, apathy, wandering, sleep disturbances, agitation and aggression.

A wide range of non-pharmacologic interventions have been proposed or studied. of the 25 categories of non-pharmacologic therapies reviewed in the Cochrane Database, only cognitive stimulation had findings that suggested a beneficial effect. A different systematic review found that there were too few high-quality studies to show that non-pharmacologic therapy for dementia was effective. Inspite of review of the high-quality studies, cognitive training, cognitive stimulation and training in activities of daily living appeared most successful in reaching the aims of the interventions. A metaanalysis, which combines results from many studies, found the most successful non-pharmacological interventions for neuropsychiatric symptoms of dementia were

multicomponent, adapted to the needs of the caregiver and person with dementia, and delivered at home with periodic follow up.

4.2 Recent Five Therapeutic Approaches For The Management Of Alzheimer's Are: [19]

Cholinergic hypothesis, Hormone replacement approaches, Anti inflammatory approaches, Neurotrophic approaches and approach to inhibit formation of amyloid and neurofibrillary tangles.

4.2.1 Cholinergic Hypothesis:

of cholinergic innervations of the hippocampus and cerebral cortex combines with the loss of cholinergic neurons in the basal fore brain. Hence this detection lead to treatment for memory loss in Alzheimer's disease had been focused centralized on cholinergic hypothesis

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4.2.1.1 Three Different Approaches Of Enhancing Cholinergic Function Are:

Increase the acetyl choline levels using acetyl cholinesterase inhibitors, dispensation of acetyl choline precursors or acetyl choline releasing agents and inhibition of acetyl choline degradation duly stimulating cholinergic receptors directly using cholinomimetics

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4.2.2 Acetyl Cholinesterase Inhibitors:

The improvement of the central cholinergic function has been considered as one of the trust worthiest approaches for the treatment of Alzheimer's disease with acetyl cholinesterase inhibitors. Recent studies proved that acetyl cholinesterase inhibitors interact with both peripheral as well as active site of enzyme and also act as prospective inhibitor for formation of beta amyloid. Over the last decade several research groups gave authorized reports on compounds that inhibit acetyl cholinesterase as approaches to treat Alzheimer's disease. Tacrine [Tetra hydro amino acridine] was found to be a potent acetyl cholinesterase inhibitor and its derivatives namely Velnacrine and Surnacrine have been reported as acetyl cholinesterase inhibitor in the treatment of Alzheimer's disease.

4.2.2.1 Dosage:

Initially 10 mg q.i.d followed by 20-40 mg q.i.d for 4-6 weeks. Possible side effects are Hepato toxicity, Otto toxicity, Gastro intestinal upset, Nausea and Vomiting.

Later a number of compounds like 4-amino pyridine, 4-aminoquinoline, tetra hydro acridine and 9-(N-n-butyl amino) 1, 2, 3, 4-tetra acridine have been examined in this connection. The ultimate results reveal that 4-amino pyridine and 4- aminoquinoline have been found very weak of acetyl cholinesterase activity although their basicities were almost equal to that of tacrine. The N- butyl derivatives were not particularly active with the butyl chain hindering the interaction of the compound with the enzyme, but tetra hydro acridine a much weak base was found to be as active as tacrine.

Physostigmine has been reported to have memory enhancing effect in Alzheimer's disease with short half-life, variable bioavailability and narrow therapeutic index. Heptyl Physostigmine a more lipophilic analogue is reported to be less toxic than Physostigmine while retaining its invitro acetyl cholinesterase inhibiting potency. 8-carbaphysostigmine has greater potency and reduced toxicity compared to physostigmine. Galantamine is a reversible inhibitor of cholinesterase and an allosteric modulator of nicotinic acetylcholine receptor, which is well tolerated during long term treatment and is useful for clinical evaluation for the treatment of Alzheimer's disease. Dosage: 4 mg b.i.d followed by 8-16 mg b.i.d for 4 weeks. Possible side effects are nausea, vomiting and diarrhoea.

Sugimoto et al. reported that N-benzyl –4-[2-(N-benzoyl amino)-ethyl] piperidine, 1- benzyl 4-1[2-(N-phthalimido ethyl)] piperidine, 1- benzyl – [5, 6-dimethoxy-1-indanon-2-yl) methyl] piperidine Hcl (Donpezil) have the controlling capacity over the acetyl cholinesterase inhibitory activity.

Huperin, originally obtained from the Chinese herb and Huperiza serrata, is a reversible inhibitor of acetyl cholinesterase, reported to have under clinical trials for alleviation of Alzheimer's disease. A compound by name huperine has been reported as a more potent acetyl cholinesterase inhibitor, with 40 fold more potent than donepezil and 180 fold potent than Huperine A.

Donepezil and Rivastigmine have been marketed recently for the treatment of the cognitive symptoms of Alzheimer's disease. Dose of Donepezil: 5 mg q. i. d followed by 5-10 mg q.i.d for 4-6 weeks. Dose of Rivastigmine: 1.5 mg b.i.d followed by 3-6 mg b.i.d for 2 weeks. Side effects include nausea, vomiting, diarrhoea, decrease in weight and anorexia. Use of acetyl cholinesterase inhibitors in combination with vitamin E is generally considered for earlier stage of the disease since vitamin E enhances the brain catecholamine and reduces the oxidative damage to neurons thus reduces the progress of Alzheimer's disease.

In the recent past, a hexa hydro chromeno [4, 3-b] pyrrole derivative has been reported as acetyl cholinesterase inhibitor activity. An amino pyridazine analogue, minaprine has been reported to have acetyl

cholinesterase inhibitory activity in homogenized rat striatum. An in vivo injection of minaprine to rats significantly increases acetylcholine level in the hippocampus and striatum. Further studies and optimization of minaprine led to the identification of 3-[2-(1-benzyl piperidin -4yl) ethyl amino] pyridoxine and 3-[2-(1-benzyl piperidin 4-yl) ethyl amino] methyl -6- phenyl pyridoxine. The 3-[2-(1-benzyl piperidin -4-yl) ethyl amino] pyridoxine, representing a 5000-fold increase in potency compared to minaprine.

Recently a study on a series omega [N- methyl –N-(3- alkyl carbamoyl –o-phenyl)methyl] amino alkoxy aryl derivative an azoxanthone derivative reported an acetyl cholinesterase inhibitors which are more potent than tacrine but less than donepezil and showed acetyl cholinesterase inhibitory activity in rat cortex.

4.2.3 Cholinergic Agents:

The cholinomimetic effect of these compounds is based on increase in the quantity of Acetylcholine precursor. Compounds that have such a cognition stimulating mechanism include exogenous choline, lecithin and phosphatidyl choline. Gliatilin and acetyl-L-carnitine (ALCAR) have been reported for the treatment of Alzheimer's disease from this class.

4.2.4 Acetylcholine Release Modulators:

Acetylcholine release modulator, linopyridine enhances the potassium evoked acetylcholine release from the rat cortex, hippocampus and caudate nucleus in-vitro. Another mechanism of the stimulation of the acetylcholine is realized via antagonist of H3 histamine receptors. H3-histamine receptors, a subtype of histamine receptor are localized on pre synaptic terminals of histaminergic and non-histaminergic neurons in the central and peripheral nervous system. Two drugs namely clobenpropit and thioperamide have been reported for the treatment of Alzheimer's disease. Clobenpropit is H3 histamine receptor antagonist whereas thioperamide is H3 histamine receptor agonist which belongs to 4- substituted imidazole derivatives.

A stimulation of acetyl choline release via the increase of the pre synaptic uptake of endogenous choline, created due to the acetyl cholinesterase catalyzed enzymatic degradation of acetyl choline considered to be an alternative to the receptor regulated acetyl choline release. MKC-231 has been started for Alzheimer's disease from this class. It is an activator of the high affinity choline uptake the important component of acetylcholine re-synthesis.

4.2.5 Muscarinic Agonists:

Cholinergic agonist acting directly on muscarinic receptor may improve the cholinergic dysfunction seen in Alzheimer's disease. In Alzheimer's disease the basal fore brain muscarinic neurons that predominantly express the pre synaptic M2 receptors have been found in atrophy. However mainly the pre synaptic M1 receptors are highly concentrated in the cortex and hippocampus and their density is reported to be unaltered in Alzheimer's disease. A preferential involvement of the M1 receptor in memory has been proposed which suggest that M1 selective agonist may be useful.

4.3 Hormone Replacement Approaches:

Estrogen replacement therapy in post menopausal women resulted in 40 - 50 % reduction in the risk of developing Alzheimer's disease. 17 β - estradiols protect neurons against oxidative damage [20,21] induced by beta amyloid as well as other oxidants such as hydrogen peroxide and glutamate. Animal studies have shown that the administration of estrogen to estrogen deficient laboratory animal restores the number of neural synapsis causing beta amyloid to be more soluble. It also induces and increases the activity of choline acetyl transferase, the rate-limiting enzyme for acetylcholine synthesis in both the basal fore brain and target area of cholinergic neurons.

4.4 Anti Inflammatory Approaches:

Prostaglandins are implicated in the pathology of the Alzheimer's disease. The neural damage in Alzheimer's disease may be due to the inflammatory reaction with consequent free radical and protease release than to the presence of amyloid precursor protein, consequently inhibition of inflammation may delay or even about the loss of neurons consequent on amyloid deposition. Recently, it has been reported that NSAIDS alleviate inflammatory changes in the brain with Alzheimer's patients. Although NSAIDS would not be expected to modify the abnormal metabolism of beta amyloid, yet they could reduce the response of microglia to the protein. The existing reports reveal that ibuprofen and naproxen reduce the severity of Alzheimer's disease.

4.5 Agents That Stimulate Neurotrophic Effects:

Compounds namely propentofyline, citicoline, anapests and AIT - 082 have a neuroprotective and cognition-stimulating activity via stimulation of neurotrophic function in central nervous system. The foremost

effect of propentofyline is the inhibition of the adenosine re-uptake system leading to the accumulation of adenosine in CNS and consequent activation of adenosine receptors. Citicoline is an endogenous intermediate in the biosynthesis of structural membrane phospholipids and brain acetylcholine, which may develop memory through its neurotrophic effect. AIT-082 acts at the site of hemi oxygenase and generate carbon monoxide and by activation of guanylyl cyclase brings a cascade of biochemical reaction through the second messenger system leading to the production of mRNA neurotrophins, but this is at present in phase-III clinical trials.

4.6 Inhibition Of Amyloid Formation And Neurofibrillary Tangles: [22, 23]

The proteolysis of the membrane APP results in the generation of the beta amyloid peptide is believed to be caused for the pathology and succeeding cognitive decline in Alzheimer's disease. The amyloid approaches suggest that the agents decrease amyloid protein level in vivo would have hopeful therapeutic advantage in Alzheimer's disease. Amino acid derivatives, amine and urea analogues and hydroxyl –hexanamide acts as derivative function to inhibit amyloid protein synthesis or its release. Apo lipoprotein E4 is found in both senile plaques and neurofibrillary tangles which interact duly precipitating with beta amyloid protein. The oxygen mediated complex formation is involved which denotes that anti-oxidant may have therapeutic potential in Alzheimer's disease.

A foremost part of neurofibrillary tangles is tau, a family of microtubule related protein, which is imperative for the maintenance of the neuronal cytoskeleton. Neurofibrillary tangle associated tau is excessively phosphorylated which may result from neural calcium dysregulation. Before incorporation in neurofibrillary tangles, the abnormal phosphorylation of tau may lead to microtubules destabilization and cytoskeleton distraction resulting in impaired neuronal function and survival. Glycogen synthase kinase -3 (GSK-3)[24] has been proposed as a possible phosphorylation enzyme for tau. Much recent report indicated that GSK-3 inhibitors viz. 3-anilino -4-aryl maleimides, 6-aryl-pyrazolo [3,4-b] pyridines, 6-hetero aryl pyrazolo [3,4-b] pyridines, 5-aryl-pyrazolo-[3,4-b]pyridazines, 1-(4-amino furazan -3-yl)-5-dialkyl amino methyl -1H-[1,2,3]triazols-4-carboxylic acid derivatives, pyrazolo pyramidines derivatives and 3-(7-azaindolyl)-4-aryl maleimides have therapeutic potential for treating Alzheimer's disease by protecting neuron from death induced by reduced PI-3 kinase path way activity. Statin derivatives such as simvastatin, atorvastatin and some other statins have also shows potential anti-alzheimer activity that would be based on their ability to reduce a lipoprotein oxidation, decrease inflammation, production of radical oxygen species and diminish the cerebral beta amyloid level.

V. Care and management

The following causes may lead to frustration to the Alzheimer's patient.

Denial of requests and conflict with the alzheimer's patient should be avoided otherwise it creates disturbance and irritation to him. If the patient become disturb, better to be calm and cool, duly rendering help required by the patient. Maintain a dependable calm atmosphere suited to him duly averting avoidable changes. Provide regular reminders, explanations and orientation indications. Be acquainted with deterioration in his capabilities and provide adjustments to regain patient's performance. Be cautious and alert to identify declines in his functions and appearance of new symptoms to professional thought. There are independent neighbourhoods for alzheimer's patients such as nursing homes, supported living residences and additional care taking facilities duly providing special programs suitable to the needs of the patients.

5.1 Vaccine For Alzheimer's Disease:

A team of researchers led by Dale schenk at Elancorp tried to trick the immune system of mice to identify amyloid proteins as a foreign substance that should be attacked. The vaccine appears to protect against clogging and even reduce the brain clogging deposits that are characteristics of the disease. Aqueous extract of DSS were examined on physically aged mice to investigate the pharmacological basis for its therapeutic usefulness on senile dementia in particular alzheimer's disease. The results explained that DSS significantly prolonged latency in a step through test and increased brain index so as to improve impaired cognitive function of aged mice after oral administration at doses of 250 &500mg/kg for three months. Using high performance liquid chromatographic technique with electrochemical detection, it was found that DSS has enhanced the content of monoamine neurotransmitters such as nor epinephrine, dopamine, and 5-hydroxy tryptamine in the brains of aged mice. If the same phenomenon can be applied in human beings it will have a very vital impact.

Investigators discover that people who drink fruit and vegetable juices three or more times per week can face a lower risk of developing alzheimer's disease since it reduces the threat of developing alzheimer's ailment by 76 percent. Researchers at Cardiff University produced an antibody, which is able of blocking the production of beta amyloid, and are useful as preventive treatment for the public having family history of Alzheimer's.

5.2 Various Drugs That Are Being Utilized For The Treatment Of Alzheimer's Disease Are Detailed In The Following Statement: [25-27]

DRUG NAME	DRUG TYPE AND USE	HOW IT WORKS	COMMON SIDE EFFECTS	MANUFACTURER'S RECOMMENDED DOSAGE
Donepezil (Aricept®)	Cholinesterase inhibitor prescribed to treat symptoms of mild, moderate and severe Alzheimer's.	Prevents the breakdown of acetylcholine in the brain.	Nausea, vomiting, diarrhea, muscle cramps, fatigue, weight loss.	• Tablet: Initial dose of 5 mg once a day. • May increase dose to 10 mg/day after 4-6 weeks if well tolerated, then to 23 mg/day after at least 3 months. • Orally disintegrating tablet: Same dosage as above. • 23 mg dose available as brand-name tablet only.
Rivastigmine (Exelon®)	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's (patch is also for severe Alzheimer's).	Prevents the breakdown of acetylcholine & butyrylcholine (a brain chemical similar to acetylcholine) in the brain.	Nausea, vomiting, diarrhoea, weight loss, decreased appetite, muscle weakness	• Capsule: Initial dose of 3 mg/day (1.5 mg twice a day). • May increase dose to 6 mg/day (3 mg twice a day), 9 mg (4.5 mg twice a day), and 12 mg/day (6 mg twice a day) at minimum 2-week intervals if well tolerated. • Patch: Initial dose of 4.6 mg once a day; may increase dose to 9.5 mg once a day and 13.3 mg once a day at minimum 4-week intervals if well tolerated. • Oral solution: Same dosage as capsule.
Memantine (Namenda®)	N-methyl D-aspartate (NMDA) antagonist prescribed to treat symptoms of moderate to severe Alzheimer's.	Blocks the toxic effects associated with excess glutamate & regulate glutamate activation.	Dizziness, headache, diarrhoea, constipation, confusion.	• Tablet: Initial dose of 5 mg once a day. • May increase dose to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day) at minimum 1-week intervals if well tolerated. • Oral solution: Same dosage as above. • Extended-release capsule: Initial dose of 7 mg once a day; may increase dose to 14 mg/day, 21mg/day, and 28 mg/day at minimum 1-week intervals if well tolerated.
Memantine extended-release & donepezil (Namzaric)	NMDA antagonist and cholinesterase inhibitor prescribed to treat symptoms of moderate to severe Alzheimer's.	Blocks the toxic effects associated with excess glutamate and prevent the breakdown of acetylcholine in the brain.	Headache, nausea, vomiting, diarrhoea, dizziness, decreased appetite.	• Capsule: 28 mg Memantine extended-release + 10 mg Donepezil once a day. • 14 mg memantine extended-release + 10 mg donepezil once a day (for patients with severe renal impairment).
Galantamine Razadyne®	Cholinesterase inhibitor prescribed to treat symptoms of mild to moderate Alzheimer's.	Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain.	Nausea, vomiting, diarrhea, weight loss, decreased appetite.	• Tablet: Initial dose of 8 mg/day (4 mg twice a day) • May increase dose to 16 mg/day (8 mg twice a day) and 24 mg/day (12 mg twice a day) at minimum 4-week intervals if well tolerated. • Oral solution: Same dosage as above. •Extended-release capsule: Same dosage as above but taken once a day.

Out of the drugs detailed above, Donepzil, Rivastigmine, Galantamine are being prescribed to treat the symptoms mild to moderate Alzheimer 's disease. Donepzil drug was of late approved to treat severe Alzheimer's disease. The latest approved drug called Memantine for the treatment of Alzheimer's is being prescribed to treat moderate to severe Alzheimer's disease symptoms since it normalizes the levels of glutamate, a neurotransmitter involved in memory function. These drugs are cholinesterase inhibitors and proceed by obstructing or decelerating the action of acetyl cholinesterase, an enzyme that breaks down acetylcholine. They help in sustaining higher levels of acetylcholine in brain and render aid in enhancing abilities to accomplish activities of daily living, thinking, memory, or speaking skills, and can facilitate with certain behavioral symptoms. However they cannot stall the original progression of Alzheimer 's disease but assists to gain certain relief merely for months to not many years. The faster rates of disease spreading can be delayed or slowed down, but the complete cure of the disease is not yet known.

VI. Brief details about Alzheimer's disease

In 2010, there existed 21 to 35 million people with AD all over the world. It is estimated that at present 24.3 million people comprise dementia with 4.6 million new cases every year with one new case every 7 seconds. The number of people affected with this disease will become double for every 20 years comes to 81·1 million by 2040. In the developing countries dementia disease has been rising with upward trend from 60 % in 2001 to 71 % by 2040. It is also estimated that in developed countries this disease increased by 100 % between 2001 and 2040, but by more than 300 % in India, China and South Asia. The expectation indicated a significant increase in the number of demented elderly people from 25 million in the year 2000 shoot up to 63 million by 2030 and the majority of demented elders live in less developed regions. More or less half of the demented persons i.e., 46 % lived in Asia. In 2006, the universal prevalence of Alzheimer's disease was 26.6 million. By 2050, the occurrence will be four times by that time 1 in 85 persons will be living with the disease at universal level.

Most often this disease starts in people over 65 years of age, although 4 % to 5 % of cases are early-onset Alzheimer's which commence before this. It affects about 6 % of people 65 years and older. In 2010, dementia resulted in about 486,000 deaths. For each 67 seconds somebody in USA is facing Alzheimer's disease and around 500,000 people are dying due to this disease every year. Out of people suffering from Alzheimer's disease 2/3rd are women who are about 3.2 million. 1 out of 3 seniors are dying in America owing to Alzheimer's or some sort of dementia. In the year 2013, 15.5 million care givers dedicated about 17.7 billion hours of unpaid care which valued at more than $ 220 billion. It is estimated that in the USA alone in excess of 5 million people are staying alive with Alzheimer's. Among all the elder Americans 1 in 9 has been suffering from Alzheimer's disease. In America Alzheimer's is the 6th foremost ground of death and the 5th leading cause of death for those aged 65 and beyond in America. Those who have been diagnosed with the Alzheimer's disease only 33 % out of them are aware of the fact that they are suffering from it. Deaths due to Alzheimer's in America has fast increasing with 71 % from 2000 to 2013 when compared with the deaths owing to other most important diseases like heart disease, stroke, breast and prostate cancer, and HIV/AIDS. In 2015, it is estimated 700,000 people in the United States age 65 and older will die with Alzheimer's. Among people age 70, 61 % of those with Alzheimer's are expected to die before age 80 when compared with 30 % of people without Alzheimer's. Cost of medicines for other ailing persons in the age group of 65 and more is $ 47,752 per person and for those with dementia is $ 15,115 per person. By 2050, the number of people aging 65 and older with Alzheimer's disease may reach nearly three times from 5.1 million to an anticipated 13.8 million. In 2015, about 2 million people who have Alzheimer's disease are age 85 or older, which is 38 % of all people with Alzheimer's. By 2050, as many as 7 million people age 85 and older may have Alzheimer's disease, accounting for half (51 %) of all people 65 and older with Alzheimer's. It is only cause of death in the top 10 America that can't be prevented, cured or slowed. In USA almost two thirds of Americans Alzheimer's disease are women. One in three seniors dies with alzheimer's or other dementia. Alzheimer's disease is the 6th leading cause death in the US. In 2015 alzheimer's disease will cost the nation $ 226 billion. By 2050 the costs would rise as high as $ 1.1 trillion.

In India there has been a quick increase in the number of elderly persons between 1991 and 2001 and it has been anticipated that by the year 2050, the number of elderly people would rise nearly 324 million thus the India treated "an aging nation" with 7.7 % of its population being more than 60 years old. The occurrence ratio for AD ranges between 1.9 and 5.8 cases per 100 population aged 65 and above. Moreover, its prevalence is liable to increase in the next twenty years due to prevailing modern demographic fashions. In accordance with the information of 60th NSSO, the ratio of aged persons who unable to move and detained to their beds or home ranges from 77 per 1000 in urban regions and 84 per 1000 in rural localities.

6.1 Hope For Future Drugs:

At present, there are 5 FDA approved AD drugs that treat symptoms of AD. But these medications do not treat the underlying causes of Alzheimer's. Inspite of increasing momentum in Alzheimer's research, there are main obstacles to overcome. For Alzheimer's research forward volunteers are needed for clinical trials. Volunteering to participate in a study is greatest ways someone can help move Alzheimer's research forward. Secondly federal research funding should be increased and roundtable members explore a broad range of Alzheimer's cutting edge science topics, including:

- New data and technologies that may progress the diagnosis of Alzheimer's disease, mainly in its earliest and mildest stages.
- Neuropsychological testing, genetic factors, and biochemical and neuroimaging biomarkers that could contribute to an earlier and more exact Alzheimer's diagnosis.
- Lessons learned about clinical trial design that may aid shape future clinical trials of drugs aimed at slowing or stopping the progression of Alzheimer's.
- The pros and cons of different scales as outcomes measures of clinical trials.

6.2 Targets For Future Drugs:

Over the last thirty years, researchers have made outstanding progress in understanding healthy brain function and what goes wrong in Alzheimer's disease. The following are examples of promising targets for next-generation drug therapies under investigation in current research studies:

Beta-amyloid is the main component of plaques, one hallmark Alzheimer's brain [28] abnormality. Scientists currently have a detailed understanding of how this protein fragment is clipped from its parent compound amyloid precursor protein (APP) by two enzymes beta-secretase and gamma-secretase. Researchers have been developing medications aimed at virtually every aspect in amyloid processing. This includes stopping activity of beta-secretase enzyme; preventing the beta-amyloid fragments from clumping into plaques; and even using antibodies against beta-amyloid to clear it from the brain.

6.3 Recent Drug In Research That Targets Beta-Amyloid: SOLANEZUMAB

Solanezumab is a monoclonal antibody designed to lower the level of beta-amyloid in the brain. These antibodies attach to beta-amyloid, stopping the formation of plaques; solanezumab may also aid carry excess beta-amyloid away from the brain. Numerous studies of this drug are under way with the goal determining if solanezumab improves participants cognition (thinking and memory) and functioning. Some participants will undergo a brain scan called positron emission tomography (PET) to estimate the levels of beta-amyloid in the brain. (Drug is still in research, which is in available to the public).

Beta-secretase (BACE) is one of the enzymes that clips APP and makes it possible for beta-amyloid to form. Therapies that interrupt this process may decrease the amount of beta-amyloid in the brain and ultimately intervene in the development of Alzheimer's disease.

6.4 Recenet Drug In Research That Targets Beta - Secretase: MK-8931

MK-8931 is a BACE [29,30] inhibitor. It inhibits the ability of the beta-secretase enzyme to make beta-amyloid. At the Alzheimer's Association International Conference® 2013 (AAIC®), researchers reported that the drug significantly lowered beta-amyloid levels in people with mild-to-moderate Alzheimer's. MK-8931 is being tested in phase 3 clinical trials. (Drug is still in research; not available to the public). Tau protein [31] is the main component of tangles, the other hallmark brain abnormality of Alzheimer's. Tau protein aids maintain the structure of a neuron, including tiny tube like structures called microtubules that deliver nutrients throughout the neuron. Researchers have been investigating mechanisms to stop tau protein from collapsing and twisting into tangles, a process that destroys microtubules and ultimately the neuron itself.

6.5 Recent Drug In Research That Targets Tau Protein: Aadvac1

AADvac1 is a vaccine that stimulates the body's immune system to attack an abnormal form of tau protein that destabilizes the structure of neurons. If successful, it has the possible to aid the progression of Alzheimer's disease. At AAIC 2015, researchers reported that AADvac1 was safe and well tolerated by participants in a phase 1 clinical trial. (Drug is still in research; not available to the public).

Inflammation is another key to Alzheimer's brain abnormality. Both beta-amyloid plaques and tau tangles cause an immune response in the brain. Microglia are cells that act as the first form of immune defense in the brain. While microglia help clear beta-amyloid in the brain, they may become overactive in the presence of beta-amyloid and produce compounds that damage nearby cells.

6.6 Recent Drug In Research That Targets Inflammation: CSP-1103

CSP-1103 is a microglial modulator that aims to decrease inflammation in the brain. At AAIC 2013, researchers presented the results of a 90-week trial in which people who had mild cognitive impairment (MCI) were given CSP-1103. Preliminary studies showed that CSP-1103 stopped beta-amyloid from being deposited on neurons and forming plaques. It also decreased problems with thinking and memory (cognition). The cognitive tests of people who had participated for at least 64 weeks showed statistically significant improvements in participants cognitive abilities. (Drug is still in research; not available to the public).

Insulin resistance in the brain is another regular feature of Alzheimer's disease. For reasons researchers do not completely understand, the brain becomes resistant to the normal effects of insulin, as well as the conversion of glucose to energy that brain cells can utilize to fuel cell functioning. Some research suggests that beta-amyloid reduces the body's ability to utilize insulin. Other research has found decrease levels of insulin in the brain.

6.7 Recent Drug In Research That Targets Insulin Resistance: INTRANASAL INSULIN [32,33]

Intranasal insulin is a therapy being tested in multiple studies for its effects on memory, thinking and daily functioning in people with MCI and mild-to-moderate Alzheimer's disease. There is growing evidence that

insulin plays a vital role in keeping the brain healthy. Intranasal administration of insulin may aid by increasing insulin signaling in the brain. (Drug is still in research; not available to the public).

VII. Conclusion

Deposits in the brain of a sticky protein called amyloid are one of the characteristics of Alzheimer's disease. Alzheimer's disease is usually diagnosed based on the person's medical history, history from relatives, and behavioral observations and various advanced medical lab tests. At present, there is no perfect evidence to support that any scrupulous measure is effective in preventing AD. It is indeed needed to conduct constant discoveries to find out the exact causes and apt remedies who have at the menace of Alzheimer's disease and who are at risk of disease much earlier. People who are suffering with Alzheimer's disease, the most immediate imperative need to be provided is to control the cognitive loss as well as problem behaviors, such as aggression, agitation, wandering, depression, hallucinations, delusions and sleep disturbances. Global studies of evaluation to prevent or delay the commencement of AD have often produced inconsistent results. Only further continual intensive investigations including clinical trials will reveal what precise factors can aid to prevent AD. Most of the Alzheimer's Associations are committed to connect with scientific, academic, government and industry thought leaders and key stakeholders worldwide. It is a believe that the value of collaboration and is a catalyst toward the time when we will have disease modifying treatments, preventive strategies and gold-standard care for all people affected by Alzheimer's disease. Infact lack of volunteers for alzheimer's clinical trials is one of the utmost obstacles slowing the progress of possible novel treatments.

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