

## A Comprehensive Analysis on Different Types of Hypothesis, Diagnosis and Treatment of Alzheimers Disease

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**Abstract:** Alzheimer's disease was first identified more than 100 years ago, but 70 years passed before it was recognized as the most common cause of dementia and treated as killing instrument. Alzheimer's disease generally emerges in old age beyond 65 years and mostly in 85 years symbolising deterioration of cognitive functions such as remembering, reasoning, and planning and the like. Many scientists believe that Alzheimer's disease results from an increase in the production or accumulation of a specific protein (beta-amyloid protein) in the brain that leads to death of nerve cells. It slowly destroys reminiscence and thoughtful skills, the ability to carry out the simplest tasks. It progresses in triple stages an early, preclinical stage with no symptoms, a middle stage of mild cognitive impairment, and a final stage of Alzheimer's dementia. It commences little by little and gets worse gradually and at present, no cure for this dreadful ailment. Genetics / Familial Alzheimer's disease is a type of Alzheimer's which is very uncommon and 1 % may crop up. Alzheimer's disease is considered a major public health problem.

**Keywords:** Alzheimer's disease, cholinergic hypothesis, Amyloidal hypothesis, Tau hypothesis, neurofibrillary tangles, senile plaque.

### I. Introduction

**1.1 Alzheimer's and Dementia:** Alzheimer's is a degenerative disease of the brain, associated with the development of irregular tissues and protein deposits in the cerebral cortex and characterized by confusion, disorientation, memory failure, speech disturbances, loss of mental capacity. Symptoms of Alzheimer's, including early-onset of Alzheimer's, problems with memory, thinking and dementia will progress as the stages of Alzheimer's advance. It is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills, judgment and eventually the ability to carry out the simplest tasks. Symptoms can be treated with medication, but there is no cure.

Alzheimer's disease<sup>[1-8]</sup> is a neurological disease, the most common form of Dementia<sup>[9,10]</sup> and an irreparable, irreversible, progressive brain disorder that ultimately disables to accomplish the easy usual routine work with impairment of memory loss of mental ability interferes with normal daily routine life. It lasts for atleast 6 months, and it'll not be present from birth. Familial Alzheimer's disease refers to those small numbers of cases, in which there is a clear pattern of autosomal dominant inheritance. It is considered to be less than 5 % of all cases. Non-familial Alzheimer's disease, which constitutes at least 95 % of all cases, includes those cases where there is no clear familial pattern of inheritance. Early-onset Alzheimer's, problems like muscle twitching and spasms are seen. This condition is referred as myoclonus. Patients with Down syndrome are more prone to early-onset alzheimer's disease. However, some symptoms can be treated with medications, but there is no permanent cure at present. Communication ability, mood and personality also may be affected. Most people who have Alzheimer's disease die within eight years of their diagnosis. It is fourth leading cause of death in adults after heart disease, cancer and stroke. The likelihood of having Alzheimer's disease increases substantially after the age of 70 and may affect around 50 % of persons over the age of 85. Nonetheless, Alzheimer's disease is not a normal part of aging and is not something that inevitably happens in later life.

Dementia is a non-specific term used to describe a person having changes in brain function that obstruct the capability to function and do everyday normal activities. Loss of memory may lead to commencement of dementia. Numerous scientists consider that Alzheimer's disease outcomes from a raise in the excess production or build up of a particular protein called beta-amyloid protein<sup>[11-13]</sup> in the brain which leads to death of nerve cell. It is a term that has substituted a more outdated word, "senility", ( to demote cognitive changes with advancement of age where in the loss of cognitive performance like thinking, remembering, and reasoning and behavioural abilities to such an extent that it interferes with a person's daily life and routine activities. The person with dementia has problems in manifold functioning areas of the brain such as loss of memory, language, impulse control, ability to do things himself of his own, downgrading personality etc. Some of the common types of dementia are Alzheimer's disease, vascular dementia<sup>[14-16]</sup>, Lewy body dementia,

frontal-temporal dementia (FTD) <sup>[17-19]</sup> and mixed dementia (more than one type of dementia occurring in the same brain). Different types of dementia force the brain in diverse ways, with dissimilar symptoms causing changes in malformed abilities.

## **II. History & Its Risk Factors**

### **2.1 Archives Of Alzheimer's Disease:**

Dr. Lois Alzheimers a German neurologist and psychiatrist first noticed Alzheimer's disease as one of the most disabling and difficult health condition. Auguste Deter a 50-year-old woman was the first patient of Alois Alzheimer in 1902, and closely examined her case until she died in 1906 and first reported publicly on it. Thus, the disease is ultimately known as Alzheimer's disease. He noticed that she had memory problems and strong feelings of jealousy and was hiding objects, unable to remember her husband's name, the year, or how much time she was in hospital, could read but did not understand what she read, stressed the words unusually and became agitated and seemed to have irrational fears. After nearly 4years uninterrupted study on her case he detected changes in her brain tissue which was responsible for strange mental illness and released a public statement to that effect. The symptoms noticed by him from her are struggling or inability to speak, loss of memory, confusion, behavioural problems and delusions. After her death, he keenly examined her brain and found many strange clumps which afterwards called amyloid plaques and tangled bundles of fibers termed as neurofibrillary, or tau, tangles which in due course ultimately treated as most important chief characteristics features of Alzheimer's disease.

After wards followed by next five years, 11 related cases were reported with the name Alzheimers disease. Emil Kraepelin first explained that it has a distinctive disease duly naming presenile dementia, a subtype of senile dementia in 1910 after suppressing some of the clinical and pathological features contained in the original report of Auguste D. Between 1910 to 1940 a thought was prevailed that "senile dementia is a normal part of growing age. In 1950s the structure of plaques and tangles in the Alzheimer's are found and in1960 this was recognized as a different disease, but not a routine part of aging. In 1970s it was held proved that volumes of Acetyl Choline, a neurotransmitter deteriorates severely in Alzheimer's disease patients. Subsequent to 1977, the expressions modified when a meeting on AD concluded that the clinical and pathological symptoms of presenile and senile dementia were more or less alike, even if the authors also added that this did not exclude the likelihood that they had divergent causes. This situation finally guided to the diagnosis of Alzheimer's disease independently due to age factor. The name senile dementia of the Alzheimer type (SDAT) was applied a short time to describe the condition in those over 65, and with traditional Alzheimer's disease used for the younger. In 1980s diagnostic principles for Alzheimer's disease are established and the genetic links for early onset of Alzheimer's, the development of beta-amyloid plaques and the uncharacteristic tauproteins in tangles are identified for the treatment of Alzheimer's disease. In 2000 FDA approved some other drugs like Rivastigmine (Exelon), Galantamine (Razadyne), Donepezil (Aricept) and Memantine (Namenda) <sup>[20-22]</sup> for the treatment of Alzheimer's disease and intensive studies had been continued concentrating on vaccines. In Pittsburgh Compound B (Pib) was developed to see and examine beta-amyloid plaques in the brains of the surviving people. For most of the 20th century, the diagnosis of Alzheimer's disease was reserved for individuals between the ages of 45 and 65 who developed symptoms of dementia which eventually led to the diagnosis of Alzheimer's disease independently basing on age. The term senile dementia of the Alzheimer was used for certain time to describe the condition in those over 65, with traditional Alzheimer's disease being used for those younger. Then onwards the name Alzheimer's disease was properly adopted in medical field to describe individuals of all ages with identical common symptoms, guidelines, course of disease and neuropathy disorders. It was also found that the failure of connections between nerve cells known as neurons existed in the brain are responsible to convey messages between different parts of the brain, and in turn from the brain to muscles and all other organs in the body is one of the major ground for this disease.

### **2.2 The Brain And The Alzheimer's:**

To accomplish their task, brain cells operate like small factories. To continue everything to run perfectly, demands coordination as well as huge quantity of fuel and oxygen. Each nerve cell connects with many others to form communication networks. Groups of nerve cells share and perform different functions among thinking, learning and retention of information, seeing, hearing and smelling. They receive supplies, produce energy and dispose of waste. They also process and accumulate information and exchange with other cells. As damage spreads, cells lose their ability to carry out their works and, finally perish causing irreparable changes in the brain.

It seems likely that damage to the brain starts a decade or more before memory and other cognitive problems become evident. During this preclinical stage of Alzheimer's disease, people seem to be symptom-free, but toxic changes are taking place in the brain. The damage initially appears to take place in the hippocampus, one of the parts of the brain necessary in forming memories. Plaques are deposits of a protein

pieces called beta-amyloid that develop in the spaces between nerve cells. Tangles are entwined fibres of another protein entitled tau that builds up inside cells. It is due to unusual deposits of proteins form amyloid plaques and tau tangles throughout the brain, the healthy neurons stop functioning, lose connections with other neurons, and die resulting further parts of the brain are affected. By the final stage of Alzheimer's, damage is extensive, and brain tissue shrunk extensively.

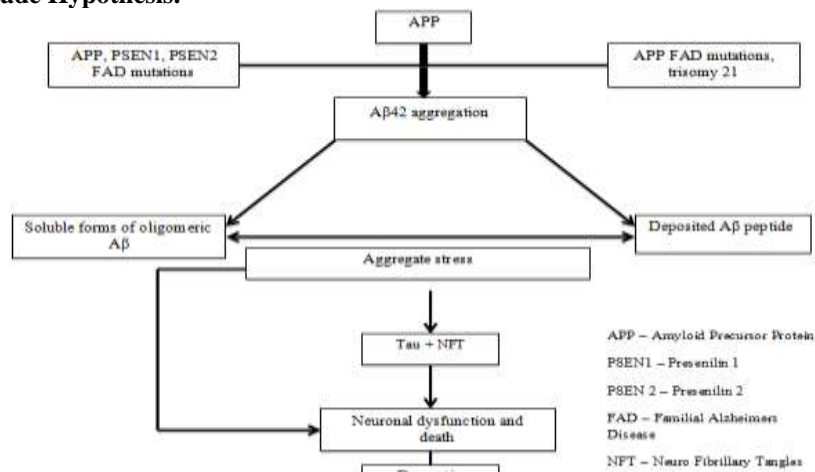
**2.3 A Brief Account On Human Brain:**

The brain is divided into three main parts the forebrain, midbrain, and hindbrain. The forebrain consists of the cerebrum, thalamus, and hypothalamus (part of the limbic system). The midbrain consists of the tectum and tegmentum. The hindbrain is made of the cerebellum, pons and medulla. The brain stem sits beneath the cerebrum and in front of the cerebellum. It connects of the remaining portion of the brain to the spinal cord, which runs downward up to the neck towards end of back. The brain consists of folds and wrinkles and their technical names are, higher ridges are called Gyri or Gyrus and the lower 'valleys' are called Sulci or Sulcus. The brain stem is in charge of all the functions. Major quantity of the human brain constitute the cerebral cortex, especially the frontal lobes, which are associated with executive functions such as self-control, planning, reasoning, and abstract thought. The area of the cerebral cortex devoted to vision, the visual cortex. The brain produces roughly 500 mL of cerebrospinal fluid per day. This fluid is constantly reabsorbed, out of 500mL only 100 -160 mL is present at any one time in the brain. The cerebrum or cortex is the largest part of the human brain, associated with higher brain function such as thought and action. The cerebrum is divided into four sections: frontal lobe, temporal lobe, parietal lobe, and occipital lobe. Each section has its own function.

**2.4 Genetics**

The genetic heritability of Alzheimer's disease, range from 49 % to 79 %. Around 0.1 % of the cases are familial forms of autosomal dominant inheritance. It commences before age 65 which is known as early onset familial Alzheimer's disease. Most of autosomal dominant disorder can be passed down inherited through families and this familial AD can be tied up to mutations in one of three genes which are encoding amyloid precursor protein (APP) and presenilin 1 and 2. Majority of mutations in the APP and presenilin genes increase the production of a small protein called Aβ42, which is the main component of senile plaques causes the AD disease. Alzheimer's disease do not show signs of autosomal-dominant inheritance and are designated sporadic AD, in which ecological and genetic differences may perform as risk factors among which the inheritance of the ε4 allele of the apolipoprotein E (APOE)<sup>[23]</sup> is the prominent one. The APOEε4 allele enhances the menace of the disease by thrice in heterozygotes and by 15 times in homozygotes. Mutations in the TREM2 gene are come together with 3 to 5 times higher risk of developing Alzheimer's disease. If TREM 2 is mutated, white blood cells in the brain cannot control the sum of beta amyloid exist in the brain. Most people with Alzheimer's have the late beginning form of the disease, in which symptoms become apparent in their middle 60s. The apolipoprotein E (APOE) gene is involved in late-onset of Alzheimer's. This gene has several forms, one of them, APOE ε4, increases a person's risk of developing the disease and is also associated with an earlier age of disease arrival. Most cases are caused by an inherited change in one of three genes, resulting in a type known as early-onset familial Alzheimer's disease, or FAD. For others, the disease appears to develop without any specific, known cause, much as it does for people with late-onset of disorder. Figure 1 shows the amyloid cascade hypothesis.

**2.5 Amyloid Cascade Hypothesis.**



**Figure 1.** Amyloid Cascade Hypothesis

### **2.5.1 Cholinergic hypothesis**

The oldest cholinergic hypothesis suggests that AD is caused by reduced synthesis of the neurotransmitter acetylcholine which has no extensive support, since medications intended to treat acetylcholine deficiency have not proved very effective. Commencement of large-scale aggregation of amyloid, leading to generalised neuroinflammation is one of the proposed cholinergic effects among others.

### **2.5.2 Tau hypothesis**

In Alzheimer's disease, alterations in tau protein show the way to the breakdown of microtubules in the brain cells. In the tau hypothesis, tau protein abnormalities commence the disease power and, hyperphosphorylated tau begins to join up with other threads of tau ultimately they form neurofibrillary tangles inside nerve cells. Owing to this, the microtubules break up, demolishing the structure of the cell's cytoskeleton which cause fall down the neuron's transport system resulting in malfunctions in biochemical communication between neurons ultimately leads to death of the cells.

The tau hypothesis states that disproportionate or anomalous phosphorylation of tau products in the transformation of customary mature tau into PHF-tau (paired helical filament) and NFTs. Tau protein is an exceedingly solvable microtubule-associated protein (MAP). Through its isoforms and phosphorylation tau protein interrelates with tubulin to soothe microtubule assembly. Tau proteins comprise a family of six isoforms with the range from 352-441 amino acids. The lengthiest isoform in the CNS has four repeats (R1, R2, R3, and R4) and two inserts (441 amino acids total), whereas the smallest isoform has three repeats (R1, R3, and R4) and no insert (352 amino acids total). All of the six tau isoforms are contemporary in an often hyperphosphorylated state in paired helical filaments from AD. Mutations that amend function and isoform expression of tau lead to hyperphosphorylation. The route of tau aggregation in the nonattendance of mutations is not known but might consequence from augmented phosphorylation, protease action or exposure to polyanions. Hyper phosphorylated tau disassembles microtubules and sequesters normal tau, MAP 1 (microtubule associated protein1), MAP 2, and ubiquitin into tangles of PHFs. This unsolvable structure damages cytoplasmic tasks and interferes with axonal transference, which can lead to cell mortality.

### **2.5.3 Other hypothesis**

Reduced functioning of the blood brain barrier may be occupied in neurovascular hypothesis which state that Herpes simplex virus type 1 has to play a contributory role in people holding the susceptible reports of the gene. Added to this continual bacterial infection is also one of the potential risk factor. Another hypothesis asserts that the disease may be caused by age-related myelin (a fatty white substance that surrounds the axon of nerve cells) breakdown in the brain.

## **2.6 Typical forms of Alzheimer's disease: Posterior cortical atrophy (PCA)**

It occurs when there is harm to areas at the back and upper-rear of the brain which are parts that process visual information to deal with awareness. Logopenic aphasia entails damage to the areas in the left side of the brain which produce language. The speech of the patient becomes toiled with extensive breaks. Frontal variant Alzheimer's disease occupies damage to the lobes at the front of the brain. People having Down's syndrome are at scrupulous risk of developing Alzheimer's disease, due to discrimination in their genetic formation.

## **2.7 Unavoidable risk factors**

The confusion is more likely seen in older people, over-65-year-olds especially in more than 85years old<sup>[24]</sup>. Inheritance of genes having Alzheimer's in the family is connected with higher risk which is the second biggest risk factor after age.<sup>[25]</sup>

## **2.8 Likely avoidable or modifiable factors**

High cholesterol<sup>[26]</sup> and overweight<sup>[27]</sup> and high blood pressure<sup>[28]</sup> and Diabetes increase the risk of stroke, which can paves way to another type of dementia Lack of educational and occupational skills is also another factor; a severe traumatic brain injury may lead to dementia.

## **2.9 Alzheimer's patient has several cognitive disabilities<sup>[29, 30]</sup>**

The patient may be recurring with their questions or statements showing short term memory, may keep revolving between present and past, may not be able to carry out activities essential for daily living may be incapable to communicate himself due to language specifically in connection with all decision-making functions such as logical reasoning, conceptual thinking and judgement are affected at the opening, and at the later stages, the patient regularly needs support of others.

### **III. Symptoms, Stages Of Alzheimers & Diagnosis**

#### **3.1 Striking illustrations and symptom of Alzheimer's disease**

Asks the same question repeatedly with in the same conversation, puts wrist watch away other than usual place and forget soon, unable to remember word for wrist watch and then says in frustration, shy person becomes uncharacteristically outgoing or talkative at a family gathering, agrees to buy services or products the patient doesn't need and hard to balance account book or work out correct amount of money to pay whilst shopping, forgets to eat meals , or consume the unchanged food every meal etc.

#### **3.2 Stages of AD:**

##### **3.2.1 Pre-dementia**

The preclinical stage of the disease has also been termed mild cognitive impairment <sup>[31, 32]</sup> (MCI) the first symptoms are often mistakenly attributed to ageing or stress. Detailed neuropsychological testing can reveal mild cognitive difficulties up to eight years before short term memory loss with difficulty to remember recently learned facts and inability to acquire novel information

##### **3.2.2 Early stage Alzheimer's**

Not more than 10 % of Alzheimer's patients have this type of Alzheimer's disease and is diagnosed before 65 years of age that is not often perceived. In the early stages of AD, indication of controlled problems like lack of planning, attentiveness, flexibility, and abstract thinking, destruction in memory of meanings, relationships, symptoms of depression, reduced awareness memory difficulties and bad temperament can be observed where in certain sort of muscle trembling and seizures are more commonly occurred such condition is known Myoclonus. In the people with AD, the increasing impairment of learning and memory eventually leads to a perfect diagnosis <sup>[33]</sup>. Language problems are mainly characterised by a shrinking vocabulary and decreased word fluency, leading to a general impoverishment of oral and written language but usually capable of communicating basic ideas adequately. While performing movable tasks such as writing, drawing or dressing, certain movement coordination and planning difficulties may be present, while the AD progressing, yet the patient perform many tasks independently with the assistance and supervision.

##### **3.2.3 Middle/ Moderate stage of Alzheimer's**

Progressive deterioration eventually hinders independence, with subjects being unable to perform most common activities of daily living. Speech difficulties word substitutions losing reading and writing skills, Complex mobile sequences become less coordinated as AD progresses, deterioration of memory loss, prevalence of changes in Long-term memory, behaviour and neuropsychiatric are noticed. There appears Common manifestations such as wandering, irritability , outbursts of unpremeditated aggression, or resistance to care giving illusionary miss detections 1in 3 patients can be developed which leads to keep them from home care to other permanent care centres. The significant indications are bigger complexity to preserve recently studied information, profound uncertainty in numerous matters, sleeping problems, not remembering the staying place.

##### **3.2.4 Advanced/Late stage Alzheimer's**

At this advanced stage, the patient is utterly depending upon caretakers (persons who impart direct care); Poor ability to think, Problems of speaking, recurrence of same discussions, more abusive, anxious, and fearful features can be noticed. They condense language to easy phrases or even single words, finally resulting total loss of speech and verbal language abilities, patients can identify but can convey exciting signals. Aggressiveness, extreme apathy and feeling of exhaustion are most general warning signs. Alzheimer's disease will ultimately pave path to incapable to do petty tasks alone, declining muscle strength and cannot move even to the bed and not capable to eat themselves.

#### **3.3 Alzheimer's disease Diagnosis**

Any difference in thinking, memory, reasoning, attention, grooming, behaviour, or personality when interferes with the person's ability to maintain health and safety for him requires to look for medical care and examination. Alzheimer's disease is complicated to diagnose as there is no single test for it. For this reason, the first thing doctors do is to exclude other problems before confirming whether mental signs and symptoms are severe relating to any type of dementia or something else.

##### **3.3.1 Neuropsychological testing <sup>[34]</sup>**

It is the most accurate diagnosis method of pinpointing and documenting a person's cognitive problems and its aggressiveness, reasoning, conceptual thinking, and problem solving which could aid in treatment planning. In addition, he also illicit answers from the patient regarding appearance, mood, anxiety

stage, and experience of vision or illusions which clarify his cognitive abilities such as memory, awareness, use of language, and abilities to carry out various tasks and follow instructions.

### **3.3.2 Lab tests**

These include blood tests to rule out infections, blood disorders, chemical abnormalities, hormonal disorders and liver or kidney problems that could cause dementia symptoms.

### **3.3.3 Imaging studies**

A scan usually is necessary to rule out other conditions such as brain tumors and stroke that can also cause dementia since brain scans cannot detect Alzheimer's disease. MRI or CT scan of the brain may be done to prohibit other brain conditions. When the diagnosis of Alzheimer's disease is especially uncertain, Single-photon emission computed tomography (SPECT) <sup>[35]</sup> scan is used in certain cases for confirmation as it is especially good at identifying certain less common causes of dementia. Genetic testing for apolipoproteins is employed in research studies of Alzheimer's disease. Spinal tap (lumbar puncture) is a process of obtaining a sample of cerebrospinal fluid may be done to discount certain other brain conditions that can cause dementia. EEG is also held to compute the electrical activity of the brain to discard other conditions.

## **IV. Treatment & Statistical Data**

### **4.1 Alzheimer's disease treatment**

The administration of Alzheimer's disease consists of drug and non-medication based treatments. There is no permanent cure for Alzheimer's disease and the existing treatments suggest somewhat small symptomatic benefit. Present treatments can be divided into three type's namely pharmaceutical, psychosocial and providing proper care. These treatments centralise on relieving and slowing down the advancement of the symptoms, behaviour modifications, and other problems <sup>[36]</sup>. An AD patient should always be under medical care handled by family caretakers. Medical care should focus on optimizing the individual's health, safety, and quality of life coupled with medications and nondrug treatments like behaviour therapy.

#### **4.1.1 Drug treatment** <sup>[37]</sup>

Symptoms of Alzheimer's disease include agitation, depression, anxiety, hallucinations, disorders, wandering and aggression . However, frequently these symptoms are so rigorous that it becomes not possible for caregivers to take care of the patient, and treatment with medication to control these symptoms become indispensable Standard psychiatric drugs are widely used to treat these symptoms although none of these drugs have been specifically approved by the FDA for treating these symptoms in patients with Alzheimer's disease.

There is no recognized healing aids for Alzheimer's disease as the death of brain cells in the dementia cannot be arrested or reversed but there available remedial methods to facilitate Alzheimer's patients amicably to slow the development of symptoms which improve functions significantly. Alzheimer's disease is highly intricate, and any one drug or other intervention cannot effectively treat it. Current approaches concentrated on aiding patients to keep up mental function, control behavioural symptoms, and slow or delay the signs of disease. Treatments without medications may yield better relief when mixed with drug treatment. There is a virtual lack of a brain chemical neurotransmitter called acetylcholine in Alzheimer's patients. These neurotransmitters are the chemical messengers generated by nerves which ultimately communicate with each other so as to carry out their functions including formation of new memories. The cholinesterase inhibitors (ChEIs) block the rupture of acetylcholine; consequently, more acetylcholine will be present in the brain, and easily enables to form new memories. Glutamate is the major excitatory neurotransmitter in the brain but excessive glutamate may not be good for the brain and cause deterioration of nerve cells. Memantine (Namenda) works by partially decreasing the effect of glutamate to activate nerve cells.

There are no disease-modifying drugs available for Alzheimer's disease but some of them may reduce its symptoms and aid to pick up quality of life. The symptoms of AD can occasionally be relieved temporarily, by drug treatment. Two different classes of pharmaceuticals are approved by the FDA for treating Alzheimer's disease: cholinesterase inhibitors and partial glutamate antagonists. These drugs regulate neurotransmitters which are chemicals that transmit messages between neurons and assist to uphold thinking, memory, and communication skills, and aid with certain behavioural problems, conversely these drugs don't modify the original disease progression. The best so far available drug is the cholinesterase inhibitors. This is an enzyme that breaks down acetylcholine a chemical in the brain which acts as chief messaging structure in the brain and this enzyme stop the breakdown of this neurotransmitter causing increase the quantity of acetylcholine and build up brain function. Cholinesterase inhibitors not only improve cognitive functions but also have helpful effects on activities of daily living but the effects are provisional, as these drugs do not alter the fundamental cause of the dementia.

The following cholinesterase inhibitors and Memantine have been approved by the US Food and Drug Administration (FDA) exclusively for Alzheimer's disease for symptomatic relief. The drugs that most frequently prescribed from each class are: Cholinesterase inhibitors namely Donepezil<sup>[38]</sup> (Aricept brand), Rivastigmine (Exelon brand), and Galantamine (Reminyl) Alantamine (Reminyl brand). These new branded drugs have replaced an old drug by name Tacrine (Cognex brand). Another drug, Memantine (Namenda) is NMDA receptor antagonist, is showing promise in Alzheimer's disease. This new drug works by blocking brain damage caused by another brain. Certain Examinations reveal that the progression of symptoms of AD patients with the treatment of Cholinesterase inhibitors appears to stabilise for six to 12 months, but unavoidably development restarts for a second time. Memantine ER (extended release) is at present marketed by name Namenda XR, which is used to treat moderate to severe Alzheimer's. These widely used cholinesterase inhibitors (ChEIs) Rivastigmine and Galantamine drugs are only approved by the FDA for mild to moderate Alzheimer's disease, while Donepezil is commended for mild, moderate, and severe Alzheimer's disease. Most of the patients can endure ChEIs therapeutic doses. The most important side effects of ChEIs associate with the gastrointestinal system and include nausea, vomiting, cramping, and diarrhoea which can be controlled with change in amount or timing of the dosage or consuming with a small quantity of food. An unchanging-dose combination of Memantine hydrochloride extended-release (an NMDA receptor antagonist) and Donepezil hydrochloride (an acetylcholinesterase inhibitor) drugs may assist to improve memory problems, enhance concentration and motivation, and help with aspects of daily living such as cooking, shopping or hobbies.

Agitation is universal, particularly in middle and later stages of Alzheimer's disease, to suppress it antipsychotics, mood-stabilizing anticonvulsants, Trazodone (Desyrel), anxiolytics, and beta-blockers are prescribed by the specialist doctors. Antipsychotic drugs are: Haloperidol (Haldol), Risperidone (Risperdal), Quetiapine (Seroquel, Depakote), Gabapentin (Neurontin), Lamotrigine (Lamictal). It was presumed that new anti-psychotic agents namely Clozapine (Clozaril), Risperidone (Risperdal), Olanzapine (Zyprexa, Zydis), Quetiapine (Seroquel) and Ziprasidone (Geodon) may comprise certain benefits more than the older antipsychotic agents due to smaller amount severe side effects and the patients' ability to enduring capability by the patients. A few researches explain that these newer antipsychotics may be associated with increased risk of stroke or sudden death than the older antipsychotics but this hypothesis has to be technically proved.

#### **4.1.2 Mood stabilizing or Anti-depressant drugs frequently relieve troublesome or psychotic as well as anger. Antidepressants / anxiolytics drugs are**

Fluoxetine (Prozac), Sertraline (Zoloft), Paroxetine (Paxil), Citalopram (Celexa), Olanzapine (Zyprexa), Lithium (Eskalith, Lithobid), Valproic acid (Depakote). Lack of interest and trouble in concentrating happen in several AD patients so that they should not be dealt with antidepressant medications. But the patients suffering with other symptoms of depression with continued feelings of unhappiness or incapacity to enjoy their customary activities may get advantage with antidepressant medications like selective serotonin reuptake inhibitors (SSRIs), such as Sertraline (Zoloft), Citalopram (Celexa), or Fluoxetine (Prozac), being important agents for treating depression in AD. Complications in sleeping known as insomnia crops up in several patients during the existence of Alzheimer's disease for that specialist Doctors opt to prefer the use of sedating ant-depressants like Trazodone (Desyrel) apart from Sleep improvement measures. Anxiety is one of the symptoms in Alzheimer's disease that need to be treated. Benzodiazepines anxiolytics such as Diazepam (Valium) Or lorazepam (Ativan) Buspirone (Buspar) or SSRIs may be utilised to reduce confusion and memory destruction. Anti-inflammatory drugs also may be attempted on the ground that inflammation is one of the causes of senile plaques and neurofibrillary tangles. Long-standing usage of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced likelihood of developing AD. Evidence also supports the notion that NSAIDs can reduce inflammation related to amyloid plaques. Although cardiovascular risk factors, such as hypertension, hypercholesterolaemia, hypertension, diabetes, and smoking, are associated with a higher risk of beginning of AD, statins, which are cholesterol lowering drugs, are not effective in averting the disease.

#### **4.2 Side effects**

All drugs create side effects but the chief objective in prescribing the medications is that the advantages of the drug prevail over its side effects. Most probably elders are especially likely to prone drug side effects. Dementia patients particularly in elders who are utilising these drugs must be examined frequently to ensure that if any side effects take place, they do not cause serious troubles. Side effects may occur not only due to one particular drug, but also combinations of various drugs since they may interact with each other or with other drugs. The most common side effects are nausea and vomiting, both of which are associated to cholinergic excess. These side effects arise in about 10–20 % of users, are mild to modest and can be managed by slowly adjusting medication doses. Contemporary studies suggest that estrogens should not be prescribed to post-menopausal women on the plea of decreasing the risk of Alzheimer's disease.

### **4.3 Role of vitamins in the Alzheimer's**

The antioxidant tocopherol (vitamin E) is believed by some to counteract damage in brain cells, which may be responsible for Alzheimer's disease or its growth. Elevated levels of brain shrinkage are connected with the amino acid homocysteine. Mostly vitamin B<sub>6</sub> and B<sub>12</sub> are useful to inhibit brain shrinkage correlated with Alzheimer's disease. B vitamins are aiding agents to prevent the body from producing homocysteine. Vitamin B<sup>is</sup> necessary for proper digestion, regulating mood, relieving depression and anxiety, improving memory, and reducing the risk of heart disease.

#### **4.3.1 Herbal treatment**

Curcumin, a potent polyphenolic antioxidant has broad history as a food additive and herbal medicine in India. Turmeric Curcumin is an herbal supplement that contains curcumin, which has antioxidant activity with powerful antioxidant effects that helps neutralize free radicals. It neutralizes free radicals itself, with one-two punch against free radicals duly stimulating the body's own antioxidant enzymes. Curcumin also boosts the activity of the body's own antioxidant enzymes. It is strongly anti-inflammatory and the chemicals in turmeric might decrease swelling (inflammation). Curcumin blocks NF-kB, a molecule that travels into the nuclei of cells and turns on genes related to inflammation. NF-kB is believed to play a major role in many chronic diseases like heart disease, cancer, metabolic syndrome, Alzheimer's and various degenerative conditions. It is known that, curcumin has beneficial effects on both inflammation and oxidative damage play a role in Alzheimer's disease. Studies proved that curcumin can help empty a build-up of protein tangles called Amyloid plaques which is a major cause of Alzheimer's disease. It boosts levels of the brain hormone BDNF (Brain-Derived Neurotrophic Factor) which improves the growth of new neurons and fights numerous degenerative processes in the brain by delaying or even reversing many brain sicknesses and age-related diminished brain function. Decline in the activity of the cholinergic neurons are a familiar feature of Alzheimer's disease. Acetylcholinesterase inhibitors are used to lessens the rate at which acetylcholine (ACh) is stopped, thereby increasing the absorption of ACh in the brain and struggling the loss of ACh caused by the death of cholinergic neurons.

#### **4.3.2 Psychosocial intervention**

Psychosocial involvements are used as an addition to pharmaceutical treatment and can be categorized within behaviour, emotion, cognition or stimulation-oriented approaches. Behavioural interventions attempt to identify and reduce the antecedents and consequences of problem behaviours. This approach has not proved success in improving overall functioning, but can assist to reduce some specific problem behaviours, such as incontinence but there is no high eminence data on the effectiveness of these techniques. Emotion-oriented involvements consist of Supportive psychotherapy which has no prescribed scientific study, but it may help in gently impaired ailing persons. Reminiscence (recollection) therapy concerned with the conversation of earlier period occurrences with the support of photographs, pictures, and films, music and sound video recordings, domestic things, or other recognizable items from the ancient time which may be beneficial for cognition and mood. Simulated presence therapy (SPT) is centred on attachment theories connected with voice recording play with the nearby relatives who are already associated with Alzheimer's disease music and pet therapies, exercise, art and any other sort of amusement activities. But there is no full proof supporting that SPT may decrease Alzheimer's behaviours. The validation therapy is related to recognition of the actuality and personal facts of experience other persons by the patient. A specifically designed room for sensory integration therapy is also called snoezelen. An emotion-oriented psychosocial intervention for people with dementia is necessary. Sensory integration therapy is concerned with exercises aimed to inspire senses. Even though these therapies are being adopted there is no real confirmation to hold up the total utility of these therapies.

The aim of cognition-oriented treatments, include reality orientation and is the reduction of cognitive drawbacks. Reality orientation consists in the presentation of information regarding time, place or person and about its surroundings. Cognitive retraining attempts to enhance mentally impaired capacities but these treatments often yield adverse effects like frustration, irritation etc.

#### **4.3.3 Other Therapies**

As same with other types of dementia and neurodegenerative disease<sup>[39]</sup>, a most important portion of therapy for patients with Alzheimer's comes from the assistance rendered by healthcare members to provide quality life connected with dementia with utmost care, which becomes most imperative since the required needs increase with diminishing self-determination of the patient. According to researchers from the Rowan University School of Osteopathic Medicine, an antibody test that can accurately detect the existence of Alzheimer's disease even before symptoms become visible which will give physicians a chance to get involved at the early treatable point. The innovation of small heat shock proteins prevents uncontrolled protein clumping known as beta-amyloid, facilitate the opportunity of developing appropriate drugs basing on new study by



revealing how small heat shock proteins interact with beta-amyloid to prevent clumping. Throughout the initial stages of Alzheimer's disease, when the persons appear to be free of symptoms, toxic changes occurred in the brain apart from loss of synapse, Scientists recently detected how cell connections in the brain are extinguished in the early stages of the disease.

#### **4.3.4 Mind diet in Alzheimer's**

The eating plan is called the MIND diet: The ideal daily wise food selections might lesser the possibility of getting Alzheimer's disease, Researchers find that people who habituated to a diet that included foods like leafy greens, and fish berries and Whole grains has a prime reduce in peoples risk for the memory-sapping disease, which affects beyond age 65. But the MIND diet foods specifically include foods and nutrients that medical literature prove to be the best of all for the brain

#### **4.3.5 Brain-Friendly Foods**

MIND stands for Mediterranean-DASH (The Mediterranean diet is a heart-healthy eating plan that emphasizes fruits, vegetables, whole grains, beans, nuts and seeds, and healthy fats.) The need of intervention for Neurodegenerative Delay which is similar to two other healthy meal plans, namely the DASH diet and the Mediterranean diet is necessary. <sup>[40]</sup>

#### **4.3.6 Daily Care measures**

People with Alzheimer's disease eventually need help with their extreme personal tasks. It's not always easy to communicate with a person who has Alzheimer's disease. Management of complications of Alzheimer's patients time and again begins with memory loss coupled with unpredictable behaviour, but as the disease gets worse, it can cause many other mental, emotional, and physical problems and it is tough job to deal with them for the caregiver.

Most the patients with Alzheimer's disease will live with the disease for 8-12 years, but Alzheimer's ailments have no cure and little by little worsen up to the death of patient. Based on the core causes of the disease, a little dementia cases nearly 20 % can be treated and even may be cured. But all dementia cases relevant to Alzheimer's, disease are not curable.

### **4.4 Statistical data**

Generally, occurrence of AD ranges between 1.9 to 5.8 cases per 100 population aged 65 and over. Moreover, its prevalence is likely to amplify in the next 20 years as a consequence of current demographic trends. The prevalence ratio for AD increases sharply with the age and is elevated in females <sup>[41]</sup>. An incidence of 2.4 cases per 100,000 populations per annum between ages 40 and 60, and 127 cases per 100,000 populations beyond age of 60 have been stated. The aged suffering from various form of dementia amplifies with age, with 2 % of those aged 65 to 69.5 % of those aged 75 to 79, and over 20 % of those aged 85 to 90 experiencing symptoms and one third of 90 and older experience modest to severe dementia. Table 2 shows the coverage, by region with respect to size of elderly population.

**Table 2.** Coverage, by region, with respect to size of elderly population.

Region	Over 60-year-old population	Number of eligible dementia prevalence studies (additional studies since WAR 2009)	Number of studies/ 10 million population	Total population studied	Total population studied/ million population
ASIA	485.83	144 (71)	3.0	420143	865
Australia	5.80	4(0)	6.9	2223	383
Asia Pacific, High Income	52.21	30(8)	5.7	46843	897
Asia, Central	7.43	0(0)	0.0	0	0
Asia, East	218.18	89.55	4.1	342231	1569
Asia, South	139.85	14(7)	10	19673	141
Asia, Southeast	61.72	6(1)	1.0	7144	116
Oceania	0.64	1(0)	15.6	2029	3170
Europe	176.61	78(17)	4.4	106909	605
Europe, Western	107.89	71(15)	6.6	104447	968
Europe, Central	26.92	6(2)	2.2	2462	91
Europe, Eastern	41.80	1(0)	0.2	-	-
THE AMERICAS	145.51	34(6)	2.3	94875	643

North America	74.88	15(2)	2.0	42361	548
Caribbean	5.78	5(1)	8.7	24525	4260
LA, Andean	5.51	3(0)	5.4	3465	629
LA, Southern	9.88	1(0)	1.0	4689	475
LA, Tropical	24.82	4(1)	1.6	7070	285
Africa	87.19	17(12)	1.9	18126	208
North Africa/ Middle East	38.93	6(4)	1.5	8371	215
SSA, Central	4.78	4(4)	8.4	3020	632
SSA, East	19.86	1(1)	0.5	1198	60
SSA, Southern	6.06	1(0)	1.7	150	25
SSA, West	17.56	5(3)	2.8	5387	307
World	896.14	273(106)	3.0	640053	715

#### **4.4.1 AD all over the world**

It is estimated that 24.3 million people have dementia today, with 4.6 million new cases of dementia every year with one new case every 7 seconds. The number of people affected will double every 20 years to 81.1 million by 2040. Most people with dementia live in developing countries rising from 60 % in 2001, to 71 % by 2040.

It is estimated that rates of raise in developed countries increased by 100 % between 2001 and 2040, but by more than 300% in India, China, and south Asia. The forecast indicated a considerable increase in the number of demented elderly from 25 million in the year 2000 to 63 million in 2030 and most demented elders live in less developed regions. Half of the demented persons i.e. 46 % lived in Asia. In 2006, the universal predominance of Alzheimer's disease was 26.6 million. By 2050, the frequency will be fourfold by which time 1 in 85 persons worldwide will be living with the disease and about 43 % of prevalent cases require a high level of care on par with a nursing home.

Presently, about 33.9 million people worldwide have been suffering from Alzheimer's disease and prevalence is expected to threefold over the next 40 years. The harshness of possible changeable risk factors for this ailment is diabetes, midlife hypertension and obesity, smoking, depression, cognitive inactivity or short educational achievement, and physical idleness. One half of the Alzheimer's cases all over the world nearly 17.2 million can be likely ascribed to these traits and the number of AD cases that can be averted by reducing the risk factors up to 10 % in the entire globe. A decrease of 10 to 25 % in all the said seven risk factors could be potentially prevented up to 3.0 million cases worldwide.

#### **4.4.2 A.D. in India**

There has been a sharp increase in the number of elderly persons between 1991 and 2001 and it has been projected that by the year 2050, the number of elderly people would rise to about 324 million. India has thus acquired the brand of "an ageing nation" with 7.7 % of its population being more than 60 years old. The incidence ratio for AD ranges between 1.9 and 5.8 cases per 100 inhabitants aged 65 and over. Moreover, its prevalence is likely to increase in the next twenty years as a consequence of current demographic trends. The occurrence ratio for AD increases steeply with age and is higher in females. It is reported that Annual incidence rates of 2.4 cases per 100,000 population between ages 40 and 60, and 127 cases per 100,000 populations after age 60 have been reported. At present, most of the geriatric outpatient department (OPD) services are available at tertiary (third level) care hospitals. Also, most of the government facilities such as day old age residential homes, care centres, and counselling and recreational facilities are all located in towns or cities 75 % of the elderly people reside in rural areas alone. The district hospitals, sub-district, and medium-size private hospitals consists of secondary level health facilities. India has about 12,000 hospitals with 7 lakh beds largely of them are under the public sector. According to the report of 60<sup>th</sup> NSSO, the proportions of aged persons who cannot move and confined to their beds or home are ranges from 77 per 1000 in urban areas and 84 per 1000 in rural areas. However, current statistics for the elderly in India gives a prelude to a new set of medical, social, and economic problems that could arise if a timely initiative in this direction is not taken by the program executers and policy makers.

## **V. Conclusion**

As the population grow old, Alzheimer's disease will become an enormous public health problem. The fast increase of Alzheimer's disease year by year shows a distinct burden on the health care systems, as well as on families and caretakers. Current trends in demographics coupled with rapid urbanization and lifestyle changes have led to an emergence of a numerous problems faced by the elderly. Therefore the health and health-related sectors must take constant concerted efforts to improve the quality of life of the aged connected with healing measures of their body, mind, spirit, and emotions to upkeep their best health and wellness. There is a need to highlight the medical and socio-economic problems that are being faced by the elderly people, and

strategies for bringing about an improvement in their quality of life also need to be explored. Certain omissions in the field of research on gerontology which is the study of the social, psychological, cognitive and biological aspects of aging have been identified, such as the lack of attention paid towards the aged people, failure to view elderly people as active participants in the economy, the perception of older persons as being mere recipients of social welfare services, and a lack of focus on policy recommendations, unless these gaps are not fulfilled expected results cannot be achieved. Regarding elderly patients from the poor and low income groups, facilities should be made available with free or reasonably priced treatment through public-private partnership and available voluntary organisations.

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