# Alzheimer's disease: Causes & treatment of review

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**Abbreviations:** AD: Alzheimer's disease; NMDA: N-methyl-D- aspartate; WHO: World Health Organization; APOE4: Apolipo- protein 4; CI: Cholinesterase inhibitors, NPs: Neuritic plaques; NFTs: Neurofibrillary tangles; MI: Myocardial infarction; PSEN1: Presenilin-1; APP: Amyloid precursor protein; PSEN2: Preseni- lin-2; ApoE: Apolipoprotein E; PET: Positron emission tomog- raphy; MCI: Mild cognitive impairment; CT: Computed tomog- raphy; MRI: Magnetic resonance imaging; ACh: Acetylcholine; ADDLs: Aß-derived diffusible ligands; PHFs: Paired helical fila- ments; ADAS-cog: Alzheimer's Disease Assessment Scale-cogni- tive subscale; NICE: National Institute for Health and Care Excel- lence; BPSD: Behavioral and psychological symptoms related to dementia; SSRI: Selective serotonin reuptake inhibitors.

## ABSTRACT:

Alzheimer's disease is an unavoidable neurological dis- order in which the death of brain cells causes memory loss and cognitive decline and ultimate dementia. It is the most common cause of dementia in people of 65 years and older. It affects 10% of people over the age of 65 and 50% over the age of 85 years. Approximately 4million Alzheimer's pa- tients in the United States (**U.S.**) and the annual treatment costs = \$100 billion. It is the fourth leading cause of death in the United States and is becoming prevalent in many other countries. The total brain size shrinks with Alzheimer's - the tissue has progressively fewer nerve cells and connections. As such there is no known cure for Alzheimer's disease the death of brain cells in the dementia cannot be halted or re- versed. Along with an aim to improve research in to preven- tion and treatment, the goals of the plan also include mea- sures for present interventions. To help people suffering expand supports for people with Alzheimer's disease and their families, and enhance public awareness and engage- ment and expand your support towards them. Enhance care quality and efficiency. There are no disease-modifying drugs available for Alzheimer's disease but some options may reduce its symptoms and help improve quality of life and thereby help the patients to some extent. There are four drugs in a class called cholinesterase inhibitor approved for symptomatic relief in the US i.e., Donepezil (brand name Aricept), Alantamine (Reminyl), Rivastigmine and Tacrine (Cognex). A different kind of drug, memantine (Namenda), an N-methyl-D-aspartate (**NMDA**) receptor antagonist, may also be used, alone or in combination with a cholinesterase inhibitor. As with other types of dementia and neurodegen- erative disease, a major part of therapy for patients with Alzheimer's comes from the support given by healthcare workers to provide dementia quality-of-life care, which be- comes more important as needs increase with declining in-

dependence and increasing dependence.

## I. INTRODUCTION

The credit for first time describing a dementing condition, which later became known as Alzheimer's disease, goes to Ger- man physiatrist and neuropathologist Dr. Alois Alzheimer. Al- zheimer disease (AD) an aggressive form of dementia, manifest- ing in memory, language and behavioral deficits [1,2]. According to the World Health Organization (WHO) estimates, the over all projected prevalence in global population will quadruple in the next decades, reaching 114 million patients by 2050 [3]. Apart from having a great social impact, this would clearly lead to increased economic burden to healthcare systems worldwide [4,5]. It is currently estimated that 46.8 million people world- wide have dementia with an estimated global cost of dementia care at US\$818 billion in 2010 [6]. By 2030 it is estimated that there will be 74.7 million people with dementia, and the cost of caring for these individuals could rise to some US\$2 trillion. There are no effective options available at present for preven- tion and treatment of Alzheimer disease despite all scientific re- ports. Alzheimer's disease progresses gradually and can last for decades. There are three main stages

of the disease, each with its own challenges and symptoms. By identifying the current stage of the disease, physicians can predict what symptoms can be expected in the future and possible courses of treatment. Each case of AD presents with a unique set of symptoms, vary- ing in severity. Inheritance of certain genes is a risk factor for AD, with both familial and sporadic cases occurring. In sporadic AD, which is the more common form, there is a link with the apolipoprotein 4 (APOE4) allele, with the risk being greater in homozygotic situations [7,8]. Environmental factors, vascular factors and psychical factors contribute to the development of Alzheimer's disease. Currently, no drugs are available to halt the progression of neurodegeneration in Alzheimer disease; the nature of Alzheimer's disease treatment is symptomatic [9].For instance, cholinesterase inhibitors (CIs) that promote cho- linergic neurotransmission are used in mild to moderate cases of Alzheimer's disease. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is used in moderate to severe cas- es to prevent excitotoxicity, and antipsychotics and antidepres- sants are used in the treatment of neuropsychiatric symptoms [10,11]. Right now, there's no proven way to prevent Alzheim- er's disease. Research into prevention strategies is on going and is getting developed day by day. The strongest evidence so far suggests that you may be able to lower your risk of Alzheimer's disease by decreasing your risk of heart disease. Many of the same factors that tend to increase your risk of heart disease can also increase your risk of Alzheimer's disease and vascu- lar dementia. Important factors that may be involved include high blood pressure, high blood cholesterol, excess weight and diabetes. Alzheimer's disease is complex, and it is unlikely that any one drug or other intervention can successfully lead to its proper treatment. Current approaches focus on helping people maintain mental function, manage behavioral symptoms, and slow or delay the symptoms of disease. Researchers hope to develop therapies targeting specific genetic, molecular, and cel- lular mechanisms so that the actual underlying cause of the dis- ease can be stopped or prevented.

The future of treatment of Alzheimer's disease lies in the targeting of neuritic plaques (NPs) and neurofibrillary tangles (NFTs), which have the potential to delay neurodegeneration [12]. This review article will provide brief knowledge to Al- zheimer's disease and its diagnosis and causes. This article se- lectively reviews some of the highlights and emerging trends in Alzheimer disease treatments.

**Clinical Features**

The clinical diagnosis of Alzheimer's disease follows a logical sequence: the history should include information from an in- formant; a mental state assessment should include a validated cognitive function test; and the physical examination should fo- cus on vascular and neurological signs supplemented by inves- tigations. Assessment of dementia involves a two-step process. Firstly, it is important to distinguish dementia syndromes from other conditions that can mimic them, such as depression, de- lirium, and mild cognitive impairment. Secondly, once dementia syndrome is recognized, the diagnosis of a subtype is important because it may determine the kind of treatment possible. The progression of Alzheimer disease can be divided into a series of stages: pre-dementia, mild, moderate and severe. The pre-dementia stage is often unreliably distinguished from normal aging or stress-related issues [13,14]. One of the first signs is the deterioration of episodic memory. No decline in sensory or motor performance occurs at this stage, and other aspects such as executive, verbal and visuospatial functions are slightly im- paired at most. An individual remains independent and is not diagnosed as suffering from Alzheimer disease [14]. During mild stages of Alzheimer's disease, increased memory loss affects re- cent declarative memory more profoundly than other capaci- ties, such as short-term, declarative and implicit memories [15]. Recent memory continues to deteriorate in the moderate stage. Due to an inability to create new memories, Alzheimer's dis- ease patients seem to live in the past [16]. Patients are still able to manage basic ADLs, but help is required in certain areas such as grooming and dressing [15,16]. Insight into their disease is commonly lost by this stage, with patients becoming delusional. A longitudinal study conducted in 1993 showed that it is at this stage that cognitive decline, aggression, depression and incon-tinence in patients become predictive factors for placement in nursing homes [17]. In the severe stage, even early memories can be lost. Basic ADLs are now affected, declining gradually. Communication deteriorates further to single words or phrases, and language is thus significantly impaired [15,16]. Behavioral disturbances occur, causing disruptions to caregivers [15,18]. The most common cause of death in Alzheimer's disease pa-tients is pneumonia [19] followed by myocardial infarction (MI) and septicemia [15]. There are rare forms of inherited AD that show up routinely before 65 years of age, and regularly in the fifth

decade or earlier. These account for less than one percent of all cases of AD. The inheritance pattern typically exhibited by these forms is an autosomal dominant inheritance pattern which is related to mutations in genes that lead to alteration in beta-amyloid (Aβ) protein production or metabolism, includ-ing presenilin-1 (PSEN1), amyloid precursor protein (APP), and presenilin-2 (PSEN2). According to a meta-analysis with indi- vidual-level data on about 1307 patients with autosomal domi- nant AD, the mean age of symptom onset was found to be 46 years and was highly correlated with parental age of onset and mutation type [50]. Another analysis made was that patient's with PSEN1 mutations had the earliest median age of onset (43 years). The range of symptom onset across all mutation types is nonetheless fairly broad, with some presentations in the fourth decade and some mutations not manifesting symptoms until the seventh decade. Individuals suffering with Down syndrome, who have an additional APP gene dose due to trisomy of chro- mosome 21, unavoidably develop AD pathology, and symptoms start emerging at an earlier age, 10 to 20 years younger than the general population with AD [49].

## Risk Factors
**Age:** The single greatest risk factor for developing Alzheim- er's disease is age, one of the non-modifiable risk factors. Most cases of Alzheimer's disease are seen in older adults, ages 65 years or above. Between the ages of 65 and 74, approximately 5 percent of people have Alzheimer's disease. For those over 85, the risk increases to 50 percent [2]. Various studies show that aging can impair the body's self-repair mechanisms, including in the brain. And, many of the cardiovascular risk factors increase with age, such as high blood pressure, heart disease, and high cholesterol.

**Genetics:** In sporadic Alzheimer's disease, there is no ap- pearance of a genetic pattern of inheritance. A connection has been found between a gene called Apolipoprotein E (ApoE) and the development of Alzheimer's disease. This gene is sup- posed to be responsible for the protein that carries cholesterol in the blood vessels. One form of the gene, ApoE4, has been shown to increase the chances of developing the disease to a greater extent. However, the ApoE2 form protects from the disease [20,21]. In the cases occurring before age 65, a muta- tion of chromosomes can be responsible. This rare form of the disease is called Familial Alzheimer's disease and it affects less than 10 percent of Alzheimer's disease patients. It

is observed to be caused by mutations on chromosomes 1, 14, and 21. If one mutation on chromosome is inherited, the person has 50% risk of developing Alzheimer disease [22,23].The prevalence and incidence of AD in many cases strongly suggested that age is the most influential known risk factor. Indeed, AD prevalence increases significantly with age, and AD incidence increases from 2.8 per 1000 person years for people between 65 and 69 years to 56.1 per 1000 person years for people who are older than 90 years. Although it is also observed that the first-degree relatives of patients with late-onset disease have approximately twice the expected lifetime risk of the disease, the pattern of transmission is rarely consistent with Mendelian inheritance. Delusions and hallucinations are not typical observed signs but are believed to occur any time during the course of illness. Neu- rological symptoms that may occur later in the course of illness include seizures, hypertonia, myoclonus, incontinence, and mutism. Death commonly occurs from general inanition, mal- nutrition, and pneumonia which has been observed widely.

**Education:** It is observed that there is a connection between educational level and the risk of developing Alzheimer's disease. People with fewer years of education seem to be at a higher risk as they are unaware of the prevalent causes. The exact cause for this relationship is unknown, but it is theorized that a higher education level leads to the formation of more synaptic connec- tions in the brain. This creates a "synaptic reserve" in the brain, enabling patients to compensate for the loss of neurons as the disease progresses [1,20]. Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills, and eventually the ability to carry out the sim- plest tasks of day to day routine and ultimately leads to shrink- age of brain cells. In most people with Alzheimer's, symptoms first appear in their mid-60s. Scientists continue to expose the complex brain changes involved in the onset and progression of Alzheimer's disease. It is observed that damage to the brain starts a decade or more before memory and other cognitive problems appear. During this preclinical stage of Alzheimer's disease, people seem to be symptom-free, but toxic changes are taking place in the brain. Abnormal deposits of proteins and fats form amyloid plaques and tau tangles throughout the brain, and once-healthy neurons stop functioning completely and lose their ability to perform vital functions, lose connections with other neurons, and die. The damage initially appears to take place in the hippocampus, the part

of the brain essential in forming memories exclusively. As more neurons die, additional parts of the brain are affected, and they begin to shrink continu- ously. By the final stage of Alzheimer's, damage is widespread, and brain tissue has shrunk significantly.

Alzheimer's is the most common cause of dementia among older adults. Dementia is the loss of basic and day to day func- tioning thinking, remembering, and reasoning and behavioral abilities and verbal ability to such an extent that it interferes with a person's daily life including day to day activities and renders him incapable of doing anything. Dementia ranges in severity from the mildest stage, when it is just beginning to af- fect a person's functioning, to the most severe stage, when the person becomes dependent completely on others for basic ac- tivities of daily living.

The causes of dementia can vary to a greater extent, de- pending on the types of brain changes that may be taking place or that will change the behavior of the person and his attitude towards others. Other dementias include Lewy body dementia, frontotemporal disorders, and vascular dementia. It is common for people to have mixed dementia—a combination of two or more disorders normally, at least one of which is dementia. For example, some people have both Alzheimer's disease and vas- cular dementia and also many other linked diseases.

**Coexisting Health Problems:** It is observed that there is a strong link between cardiovascular health and brain health of an Alzheimer's patient. Having heart disease, high blood pres- sure or high cholesterol can increase the risk of developing Al- zheimer's disease to a greater extent. This is caused by damage to blood vessels in the brain, resulting in less blood flow and possible drastic brain tissue death. Type 2 diabetes may also in- crease the risk for Alzheimer's disease. Inefficiency of insulin to convert blood sugar to energy may cause higher levels of sugar in the brain, causing severe harm to the entire body. Symptoms such as forgetfulness and confusion are mild during the early stages of the disease as is observed in almost every case, but they gradually worsen as the disease progresses and damage to the brain becomes more severe and prominent. Some people with AD also have severe depression and don't know how to cope with a loss of cognitive and basic functions. The symptoms of depression may include:

• Insomnia
• Mood swings

• Less contact with the people around
• Difficulty in concentrating

The symptoms of depression can be similar to the general symptoms of AD as seen in many cases. This can make it difficult to determine whether your loved one is experiencing depres- sion or just the normal symptoms of AD which is normally diffi- cult to understand. Treatment options for depression in people with AD include attending support groups and speaking with a therapist to make him understand your condition. Speaking to others with AD can also be helpful to a greater extent. Getting regular exercise and participating in activities can also improve their mental outlook. In some cases, a doctor may recommend antidepressants to get relief from depression.

AD can also affect balance and coordination of the body to a greater extent. The risk of falling increases as the disease wors- ens. This can lead to head trauma and broken bones.

**Diagnosis**
**Diagnosis Criteria:** The clinical diagnosis of Alzheimer's dis- ease follows a logical sequence as is observed in many diseases: the history should include information from an informant i. e. the person related to the patient; a mental state assessment should include a validated cognitive function test; and the physical examination should focus on vascular and neurologi- cal signs supplemented by investigations and patient history. Assessment of dementia involves a two-step process in most cases. Firstly, it is important to distinguish dementia syndromes from other conditions that can mimic them, such as depression, delirium, and mild cognitive impairment as is observed in most cases, therefore these diseases need to be distinguished first. Secondly, once dementia syndrome is recognized, the diagnosis of a subtype is important because it may determine the kind of treatment possible. For cognitive screening in general practice, the clock test is popular because of its non-confrontational na- ture and because the normal drawing of a clock more or less excludes the presence of important cognitive impairment. How- ever, the rules for scoring the tests can be quite complex and using a solitary cognitive test to screen for the presence of a dementia syndrome does not do justice to the wide variety of symptoms and indications that make up the clinical syndrome of dementia. Activities of daily living are assessed alongside cognition, but there is less consistency in the assessment instru- ments used [21].
**Detection Methods:** Neuroimaging is a promising

and widely expanding area of research for detecting Alzheimer's disease. There are multiple brain imaging procedures that can be used to identify abnormalities in the brain, including PET, MRI, and CT scans which are considered to be preliminary tests for the detection of disease. Each scan involves a unique technique and detects specific structures and abnormalities in the brain and associated parts. Brain imaging is not currently a standard part of Alzheimer's disease testing, however current clinical studies have shown promising results that may change the procedure used by physicians to diagnose the disease. Despite many years of intensive and effective research, no effective treatment cur-rently exists for Alzheimer's disease, which is the most common form of dementia. It has become increasingly clear that, if the disease is to be treated successfully, it must be detected as early as possible, perhaps even before symptoms are evident. Thus, there is a great need for reliable diagnostic methods so that treatment to slow or prevent the disease can begin as early as possible to treat the disease in proper way.

A characteristic, pathological sign of Alzheimer's disease is the formation of insoluble amyloid plaques that accumulate in the brain and neurons. The presence of these plaques can be measured in the brain using positron emission tomography (PET camera) to visualize radioactive tracer molecules that bind to the amyloid plaques. Amyloid levels can also be measured in spinal fluid. While amyloid accumulates in the brain in Al- zheimer's disease, research has shown that levels of amyloid in the spinal fluid instead reduced. In the current study, research- ers compared the amyloid-PET measurements in the brain with amyloid-$\beta$42 in the spinal fluid to see how well they align. The investigations were performed at seven European memory clin- ics on 230 patients who were examined for memory disorders and dementia. Patients received various diagnoses, such as mild cognitive impairment (MCI), Alzheimer's disease and various types of dementia.

**PET:** Positron emission tomography (PET) uses radiation sig- nals to create a three-dimensional color image of the human body [24]. The patient is injected with a radiotracer, composed of a radioactive medicine bound to a naturally occurring chemi-cal. For the study of the Alzheimer's disease chemical is usually glucose and is used widely. The radiotracer travels to the organs that use that specific molecule for energy. As the compound is metabolized, positrons are emitted. The energy from these pos-itrons is detected by the PET scan, which converts the input to an image on the output screen. This image shows the function of the patient's body by showing how effectively the radio tracer is broken down. The amount of positron energy emitted creates a variety of colors and intensities, which reflects the extent of brain activity. A PET scan has the capacity to detect changes in metabolism, blood flow, and cellular communication processes in the brain and other activities taking place inside the brain (24). A study published in the 1996 Journal of Clinical Psychiatry described the method of using a PET scan to detect the changes in glucose metabolism in the brain of an Alzheimer's disease patient. It is observed that in the parietal, temporal, and pos- terior cortices, an abnormally low metabolic rate of glucose is seen. The rate was further decreased in patients who had an advanced stage of the disease and affected more locations in the brain [25]. Small and his colleagues discovered that a PET scan could be used to detect the changes in glucose metabolism well before the clinical presentation of symptoms. In addition to diagnosis, a PET image could also be implemented in determin-ing the effectiveness of Alzheimer's disease treatments [26].

**CT:** A computed tomography (**CT**) scan takes a series of cross- sectional images of the body [27]. With the help of a computer, the individual scans are integrated and incorporated into one detailed image. The CT scan provides the physician with infor- mation about the density of tissues in the body and in various parts of the brain. For improved clarity, a contrast dye may be injected to provide a distinction between similar tissues [28].

**MRI:** Magnetic resonance imaging (**MRI**) techniques, first used in 1977, create two or three-dimensional images of the body that can be used to diagnose injury and illness. The es- sential component of the MRI system is the super conducting magnet, which produces a large and stable magnetic field [29]. There are smaller gradient magnets that create weaker magnet- ic fields. These magnets allow for different parts of the body to be scanned. The human body is composed of billions of atoms. However, it is the hydrogen atoms that are altered by the mag- netic field. Hydrogen atoms are each randomly spinning around an axis, but inside the magnetic field of the MRI, the molecules are lined up with the direction of the field. Half of the atoms point towards the patient's head, and half point toward the feet, cancelling each other out. A few atoms out of every million are not cancelled out. The machine then emits a radio frequency pulse specific to hydrogen, which causes these protons to spin in a different

direction. When the spinning ceases, the protons release energy, which is interpreted by the system. Using a con-trast dye, each type of tissue responds differently and appears as a unique shade of gray when the image is created [24]. Know-ing how the system works, researchers are able to determine if an MRI can effectively detect the structural changes and cellular death seen in the brain of an Alzheimer's disease patient. Atro- phy of the hippocampus is often seen in Alzheimer's disease, even before the appearance of clinical symptoms [23]. The Nun Study, conducted in 2002, collected post mortem MRI scans of 56 participants with varying degrees of cognitive impairment. The MRI was used to detect the hippocampal volume and deter- mine its significance as an indicator of AD neuropathology [30]. The results indicated that the scans could be used to identify non-demented elderly with Alzheimer's disease neuropathol- ogy who have not yet presented with memory impairment. By identifying the risk for these patients to develop Alzheimer's dis- ease well before the appearance of symptoms, physicians may be able to administer treatment to slow the progression of the disease. A more recent study conducted in 2009 by the Depart- ments of Radiology and Neurology at the University of Penn- sylvania investigated the use of sodium magnetic resonance imaging in the detection of Alzheimer's disease. This imaging technique uses the same principle as discussed above. However, instead of measuring the hydrogen atoms, this technique uses naturally abundant sodium, 23Na. This ion was chosen because of the ability of sodium in the brain to detect tumors and track cell death [31]. The participants included five healthy elderly adults and five who had a probable diagnosis of Alzheimer's disease. When neuronal death occurs, the intracellular space is decreased. Therefore, there is an increased concentration of sodium in the extracellular space, causing stronger signal inten- sity from the MRI for patients who have Alzheimer's disease. Though this technique is not yet perfected, studies are being conducted to determine if the increased signal intensity is caused by a change in ion concentration or a change in volume [26].

## Causes

At first, increasing forgetfulness or mild confusion may be the only symptoms of Alzheimer's disease that are noticeable. But over time, the disease robs you of more of your memory, especially recent memories. The rate at which symptoms wors- en varies from person to person also depending on the age of the person.

If you have Alzheimer's, you may be the first to notice that you're having unusual difficulty remembering things and orga- nizing your thoughts. Or you may not recognize that anything is wrong, even when changes are noticeable to your family mem- bers, close friends or co-workers and colleagues.

The causes of Alzheimer's disease can be explained with the help of three hypotheses.

**Cholinergic hypothesis:** The cholinergic hypothesis of Al- zheimer's disease came about due to the combined observa- tions of deficits in choline acetyltransferase and acetylcho- line (ACh) and the fact that ACh is important in memory and learning. It was thought that reduction in cholinergic neurons as well as cholinergic neuro transmission led to the decline in cognitive and noncognitive functions. Cholinergic function loss correlated to cognitive decline, but no causal relationship was established (32,33). Moreover, the use of cholinesterase inhibi-tors (CIs) does not have a significant effect in more than half of Alzheimer's disease patients receiving treatment, indicating the presence of other important processes in the progression of the disease[33].

**Amyloid hypothesis:** Amyloidosis is the abnormal deposition of amyloid proteins in tissues, with the altered amyloid proteins forming an insoluble ß-pleated sheet. Reduced tissue and cel- lular clearance is observed in amyloid protein deposits. The membrane protein amyloid-ß precursor protein (APP) is prote- olysed to form Aß, and it is the amyloid form of A that makes up the amyloid plaques (neuritic plaques) found in the brains of Alzheimer's disease sufferers [34]. According to the amyloid hy- pothesis, the basis of Alzheimer's disease is the presence of Aß production in the brain [32]. Evidence for the amyloid hypoth- esis was compelling, as gene mutations encoding the amyloid-ß precursor protein (APP) was found to cause familial Alzheimer's disease with sites of major mutations found in secretase and APP (34). Aß is derived from APP by proteolysis in the amyloido- genic pathway, mediated by ß secretase (BACE1) and secretase, in the extracellular and transmembrane region, respectively. Cleavage by ß-secretase produces APPsß and C99. C99 is fur- ther cleaved by secretase to form either Aß1-40 or the more hydrophobic, aggregation-prone Aß1-42 [35]. Aß40 is more pre- dominant in cerebral vasculature [2] APP can also be cleaved by secretase in the non-amyloid genic pathway, producing Appam C83. Further evidence came from an

experiment in the 1990s whereby transgenic mice expressing three different isoforms of mutant APP were found to have characteristic Alzheimer's disease neuropathologies[36]. Despite widespread support of Aß fibrils being the main cause of pathology seen in AD, it was sug- gested that oligomerization of Aß1-42 plays a more important role. Oligomerization of Aß1- 42 produces soluble Aßoligomers, which are known as Aß-derived diffusible ligands (**ADDLs**). Ex- periments showed that these ADDLs are potentially more toxic than Aß fibrils as they target synaptic spines and disrupt synap- tic plasticity, thus affecting cognitive function. Their toxicity lies in toxin receptors on cell surfaces and in Fyn, a tyrosine kinase receptor over expressed in Alzheimer's disease [37,38].

**Tau hypothesis:** The Tau hypothesis revolves around the presence of neurofibrillary tangles (**NFTs**) in Alzheimer's dis- ease. As a result of increased phosphorylation of Tau (originally bound to microtubules), there is an increase in free tau accom- panied by loss of functioning microtubules [39]. Phosphorylated Tau are subunits of paired helical filaments (**PHFs**), which form NFTs. The impaired microtubules affect axonal transport of pro-teins and eventually cause neuronal death [40].

**Treatments**

**Drug Therapy:** There are two types of medication used to treat Alzheimer's disease: acetylcholinesterase inhibitors and N-methyl D-aspartate antagonists. The two types work in dif- ferent ways.

**Cholinesterase Inhibitors:** There are lower levels of a chemi- cal called acetylcholine in the brain of a person with Alzheimer's disease. Acetylcholine performs the function of sending mes- sages between nerve cells. Cholinesterase inhibitors (**CI**) aim to increase acetylcholine availability in synaptic neurotransmis- sion in order to treat memory disturbances. Currently, three CIs are being used as the first-line treatment in mild to moderate Alzheimer's disease: donepezil, rivastigmine and galantamine [32]. While donepezil and rivastigmine are both selective inhibi- tors, galantamine inhibits both ACh and butyrylcholinesterase. A meta-analysis collaborating 13 randomized, double blind tri- als that were designed to evaluate the effectiveness and safety of CIs showed no improvement in ADL and behavior. In addition, donepezil and rivastigmine showed no significant difference in their impact on cognitive functions, ADLs and behavior. Overall, similar benefits were observed across all three drugs [41]. It is known that CIs are unable to halt disease progression, but

theyhave been found to have effects for a substantial period of time. As seen in a randomized double-blind trial, patients undergoing long-term treatment with donepezil showed no beneficial loss for up to two years [42]. In addition, there may be some added benefits to increased doses of CIs given. In a randomized, double blind, parallel-group, 48-week study conducted to determine the efficacy and safety of a rivastigmine patch of a higher dose, deterioration of ADLs was significantly reduced and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) was improved in patients treated with higher doses [31]. Side effectsas a result of CIs are minimal and are usually limited to gas-trointestinal symptoms such as diarrhea, nausea and vomiting [8]. The National Institute for Health and Care Excellence (NICE) has issued guidelines on the use of these drugs. NICE review drugs and decides whether they represent well enough value for money to be available as part of NHS treatment.

**NMDA Receptor Antagonists:** Memantine is a non-compet- itive NMDA receptor antagonist effective in the treatment of moderate-to-severe Alzheimer's disease. The modulation of NMDA receptors results in reduced glutamate-induced excito- toxicity. Its benefits were proven in a 28-week, double blind, parallel-group study, which showed that treatment significantly, reduced deterioration in patients. Most adverse reactions to the drug were not severe and were considered to be unrelated to the drug. The positive effect on cognitive function translates to behavioral improvements: patients were less agitated and required less assistance from caregivers Improvement of the behavioral and psychological symptoms related to dementia (BPSD) was also highlighted by a meta-analysis of 6 studies in-volving memantine treatment [44]. The NICE guidance [2011] recommends use of memantine as part of NHS care for severe Alzheimer's disease. NICE also recommends memantine for people with moderate Alzheimer's disease who cannot take the cholinesterase inhibitor drugs because of side effects.

**Antidepressants and Antipsychotics:** BPSD is a common oc- currence in Alzheimer's disease and a major source of burden on caregivers. CIs and memantine help to control these symp- toms to a certain extent, but as patients continue to deteriorate, control by these drugs becomes insufficient. Depression is very common, especially in the early and late courses of the disease. Antidepressants such as: selective serotonin reuptake inhibitors (SSRI: citalopram, fluoxetine, paroxetine, sertraline, trazodone), tricyclic agents and combined

serotonergic and noradrenergic inhibitors may be used to counter this. Discontinuation of anti-depressants in demented patients in a double blinded, random- ized, parallel-group placebo controlled trial showed significant increases in depression when compared to those who contin-ued treatment. These results are indicative of the beneficial effects of antidepressants [45]. A typical antipsychotic used in Alzheimer's disease include olanzapine, quetiapine and risperi- done, which are used to treat psychosis and agitation. However, the use of such drugs appears to be controversial, with patients showing significant declines in cognitive function with antipsy- chotic drugs administration when compared to patients receiv- ing the placebo [46].

**Disease modifying treatments:** While symptomatic treat- ments have proven helpful, it is the finding of a cure that is most vital. Since the amyloid hypo- thesis indicates that Aß generation and deposition from overexpressed APP cleavage make up the fundamental basis of Alzheimer's disease, inter- est centers on anti-amyloid therapies. These therapies result in decreased production of Aß, increased clearance of Aß and the prevention of Aß aggregation into amyloid plaques [34,47]. Immunotherapy has also been an area of interest as it targets the clearing of Aß peptides, which can either directly or indi- rectly impact cognitive decline [48]. Focusing on decreasing Aß generation, several methods can be employed to achieve this, mainly by targeting the amyloidogenic and nonamyloidogenic pathways. ß and secretases both compete for APP, with ß- and Y-secretase processing ultimately resulting in amyloid deposi- tion and Y-secretase generating soluble APPSC. 2Inhibiting ß- and Y-secretases while simultaneously potentiating Y-secretase action would thus reduce Aß generation and deposition overall. Scientists believe that for most people, Alzheimer's disease is caused by a combination of genetic, lifestyle and environmental factors that affect the brain over time and eventually lead to damage of brain cells.

Less than 5 percent of the time, Alzheimer's is caused by specific genetic changes that virtually guarantee a person will tend to develop the disease. Although the causes of Alzheimer's aren't yet fully understood, its effect on the brain is clear lead- ing to damage and shrinkage of brain cells. Alzheimer's disease damages and kills brain cells to a large extent. A brain affected by Alzheimer's disease has many fewer cells and many fewer connections among surviving cells than does a healthy brain. As more and more brain cells die, Alzheimer's disease leads to significant brain shrinkage and hence to memory loss.

## II. CONCLUSION

In this article, Alzheimer disease and its clinical features have been briefly discussed. There are four stages of Alzheimer dis- ease in series i.e., predementia, mild, moderate and severe. Pneumonia is the most common cause of death in Alzheimer disease, followed by myocardial infarction and septicaemia. Various risks factors like age, genetics, education etc. are asso- ciated with Alzheimer disease. In addition, environmental fac- tors, vascular factors and psychosocial factors also contribute to Alzheimer disease. Positron emission toronography, Com- puted toronography and Magnetic resonance imaging are the techniques available for detection of Alzheimer's disease in patients. The cause of Alzheimer disease can be explained on Amyloid hypothesis and Cholinergic hypothesis. Cholinesterase inhibitors and N-methyl D-Aspartate antagonists are the class of compounds used for treatment of Alzheimer disease. The delay in neurodegeneration by targeting neuritic plaques (NPs and Neurofibrillary (**NFTs**) is future potential mechanism for treat- ment of Alzheimer disease.

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