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Review Article

Alzheimer's Disease: A Comprehensive Review

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Abstract

Alzheimer's disease usually starts slowly and worsens over time and it is chronic neurodegenerative disease. In 60% - 70% cases of dementia, main cause is Alzheimer's disease. Difficulty in remembering recent events(short term memory loss) is most common early symptom of Alzheimer's disease. The symptoms of AD, stages, causes, neurology and pathogenesis are discussed in the article. There are many medicinal agents used for the treatment of Alzheimer's disease. In addition, the article describes advances in the treatment of AD by use of biomarkers, Positron emission tomography for diagnosis of Alzheimer's disease and highlights ongoing efforts to develop novel therapies.

Keywords: *Alzheimer's Disease; Dementia; Tangles; Plaques; Mild Cognitive Impairment*

Abbreviations

AD: Alzheimer's Disease; MCI: Mild Cognitive Impairment; EOAD: Embodiment of Alzheimer's Disease; LOAD: Late Onset Alzheimer's Disease; APP: Amyloid Precursor Protein

Introduction

Alzheimer's disease usually starts slowly and worsens over time and it is chronic neurodegenerative disease. Alzheimer's disease affects the brain because it is physical disease. 'Plaques' and 'tangles' are protein structures build up in the brain during the course of Alzheimer's disease. Loss of connection between nerve cells, and eventually to the death of nerve cells and loss of brain tissue occurs in Alzheimer's disease. Some of Alzheimer's patients also have a shortage of some chemical in their brain. The transmit of signals around the brain due to chemical messenger. These signals are not transmitted as effectively when there is shortage of these chemical messengers [1].

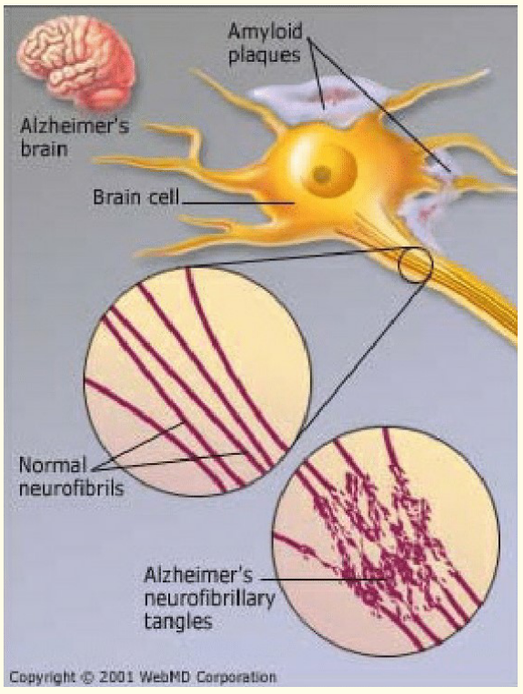

Figure 1: *Alzheimer's brain cell.*

Alois Alzheimer's described a 51 year patient who developed dementia with predominant language and behavioral changes in 1907. Auguste Deter, the patient who proved to have amyloid plaques and neurofibrillary tangles that have come to describe the neuropathol-

ogy in AD. Early onset dementia was the embodiment of AD (EOAD), with the much more common late onset (LOAD) with onset after age 65 which consider as senile dementia from normal aging. Blessed and colleagues showed in 1968 the patients who's brains affected with senile dementia and has plaques and tangles that were qualitatively the same as early onset forms. In 1976, Robert Katzman emphasized that AD and senile dementia were a single disease because of consolidation of these two age related forms. The definition of AD was transformed to the usual memory deficit presentation seen in LOAD, with the range of AD spanning onset from 40 - 90 years of age, by the NINCDS-ADRDA in 1984. Due to this point, many clinicians and investigators forgot the example of Auguste Deter and lessons to be learned from the non-amnestic subtypes of EOAD.

EOAD is an important clinical problem. Alzheimer's disease, which is the most common neurodegenerative dementia, is particularly devastating when it occurs at a young age. Beyond the psychological and medical toll, EOAD disproportionately impacts individuals during their most productive years, and the cost of treating patients with EOAD is significant. The few epidemiological studies on EOAD indicate an incidence rate of about 6.3/100,000 and a prevalence rate of about 24.2/100,000 in the 45- to 64-year-old age group or between 220,000 and 640,000 people in the United States. This compares to a 10 - 20 times greater incidence and prevalence rates for LOAD. In some specific populations such as U.S. veterans, the frequency of EOAD may be even higher. Finally, although the cut-off age of 65 years for EOAD is arbitrary and harkens back to the original AD vs. senile dementia distinction, it remains useful for distinguishing different AD syndromes. Many EOAD patients have non-amnestic syndromes infrequently present among those with LOAD.

Dementia: Dementia is a clinical syndrome (a group of co-occurring signs and symptoms) that involves progressive deterioration of intellectual function. Various cognitive abilities can be impaired with dementia, including memory, language, reasoning, decision making, visuospatial function, attention, and orientation. In individuals with dementia, cognitive impairments are often accompanied by changes in personality, emotional regulation, and social behaviors. Importantly, the cognitive and behavioral changes that occur with dementia interfere with work, social activities, and relationships and impair a person's ability to perform routine daily activities (e.g., driving, shopping, housekeeping, cooking, managing finances, and personal care) [2].

Pathogenesis of Alzheimer's Disease

Two microscopic features are characteristics of Alzheimer's disease which are as follows:

1. Extracellular amyloid plaques which consist of amorphous extracellular deposits of Aβ proteins.
2. Neurofibrillary tangles comprises of filaments of phosphorylated tau protein [3].

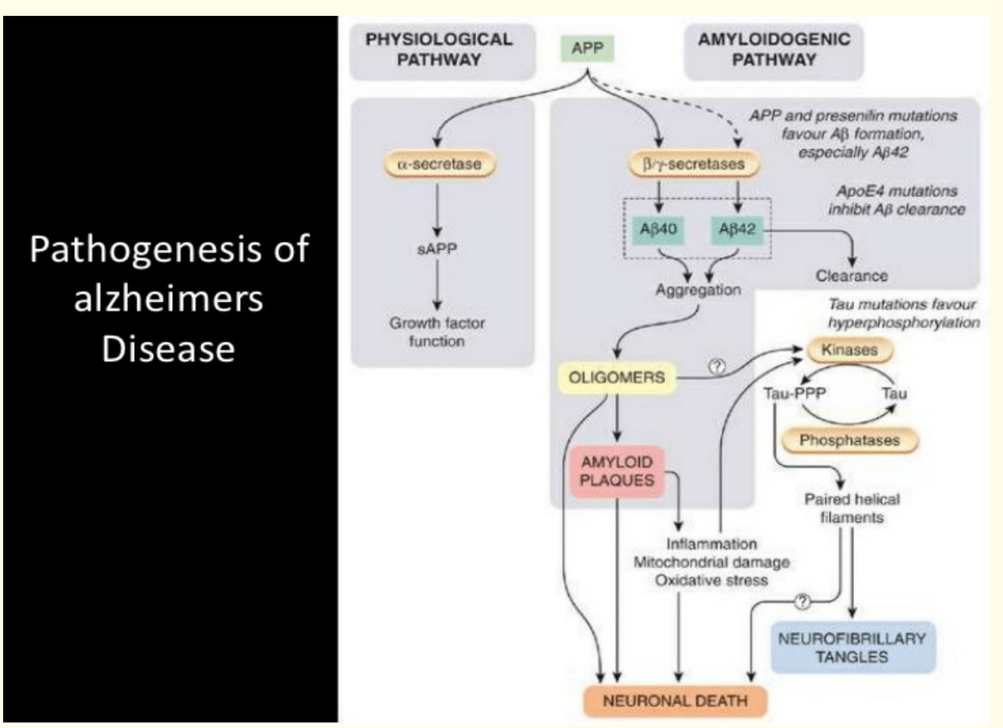

Figure 2: *Pathogenesis of Alzheimer's disease.*

Causes of Alzheimer's Disease

Alzheimer's disease is caused by brain cell death similar to all type of dementia. In the case of AD there is progressive brain cell death that happens over a course of time and it is chronic neurodegenerative disease. In the AD the size of brain shrinks, the tissue has progressively fewer nerve cells and connections. In the living brain affected by Alzheimer's disease they cannot be seen or tested. The tiny inclusion in the nerve tissues, called plaques and tangles will always observed in post-mortem or in autopsy.

- Plaques are found between the dying cells in the brain - from the build-up of a protein called β-amyloid.
- The tangles are within the brain neurons - from a disintegration of another protein, called tau [3,4].

Genetics cause

Ranges from 49% to 79% the genetic heritability of AD based on reviews of twin and family studies. The 0.1% cases of AD are familial forms of autosomal dominant inheritance, which have an onset before age 65 AD involve this form which is known as early onset familial Alzheimer's disease [5,6]. Amyloid precursor protein (APP), presenilns 1 and 2 are three genes, one of them how mutation. The main component of senile plaques is Aβ42 which is a small protein and its production is increases due to mutation in the APP and presenilins. The ratio between Aβ42 and the other major forms particularly Aβ40 may be alter because of mutation without increasing Aβ42 levels. AD involve many cases which do not exhibit autosomal dominant inheritance and are termed sporadic AD, in which risk factor are environmental and genetic difference. The inheritance of the ε4 allele of the apolipoprotein is best known genetic risk factor [7,8].

Cholinergic hypothesis

The current drug therapies are available on this cholinergic hypothesis .Due to the reduction in synthesis of the neurotransmitter acetylcholine AD can occurs. This hypothesis has not maintained widespread support because medication intended to treat acetylcholine deficiency have not been very effective. The other cholinergic effects have also seen proposed such as initiation of large scale aggregation of amyloid leading to generalised neuroinflammation [9,10].

Amyloid hypothesis

The extracellular amyloid beta (A_{β}) deposits are fundamental cause of the AD is postulated by amyloid hypothesis. Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit at least the earliest symptoms of AD by 40 years of age [11]. Also, a specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD. Breakdown of beta amyloid is enhanced by apolipoproteins. Some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid build up in the brain. Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits [12].

Tau hypothesis

The tau hypothesis proposes that tau protein abnormalities initiate the disease cascade. In this model, hyper-phosphorylated tau begins to pair with other threads of tau. Eventually, they form neuro-fibrillary tangles inside nerve cell bodies. When this occurs, the microtubules disintegrate, destroying the structure of the cell's cytoskeleton which collapses the neuron's transport system. This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells [13,14].

Symptoms of Alzheimer's Disease

At the any stage of Alzheimer's dementia symptoms can be diagnosed. After the initial diagnosis the progression through stages of the disease is monitored. Of course, the very nature of the symptoms can be confusing for both a patient and the people around them, with different levels of severity. The cognitive or behavioural symptoms is involves which shows a reduction from previous levels of the

'functioning and performing' and interfere with ability 'to function at work or at usual activities'. The cognitive decline is in at least TWO of the five symptom areas listed below:

Worsened ability to take in and remember new information, for example:

- Repetitive questions or conversations
- Misplacing personal belongings
- Forgetting events or appointments
- Getting lost on a familiar route.

Impairments to reasoning, complex tasking, exercising judgment:

- Poor understanding of safety risks.
- Inability to manage finances.
- Decision making ability is poor.
- Planning of complex or sequential activity not done properly.

Impaired visuospatial abilities (but not, for example, due to eye sight problems):

- Recognize faces, common objects or find object in direct view is not done properly.
- Problem in operating simple implements.
- Unable to wear clothes properly.

Impaired speaking, reading and writing:

- While speaking, problem in thinking of words.
- Errors in speech, spelling and writing.

Changes in personality and behaviour, for example:

- Out-of-character mood changes, including agitation; less interest, motivation or initiative; apathy; social withdrawal
- Empathy losses.
- Compulsive, obsessive or socially unacceptable behaviour [15-17].

Stages of Alzheimer's Disease

There are different stages of these diseases which are as follows:

Early stage Alzheimer's

- Not remembering episodes of forgetfulness.
- Forgets names of family or friends.
- Changes may only be noticed by close friends or relatives.
- Some confusion in situations outside the familiar.

Middle stage Alzheimer's

- Greater difficulty remembering recently learned information.
- Deepening confusion in many circumstances.
- Problems with sleep.
- Trouble knowing where they are.

Late stage Alzheimer's

- Poor ability to think.
- Problems speaking.
- Repeats same conversations.
- More abusive, anxious, or paranoid.

Early stage Alzheimer's

The definitive diagnosis is occur due to increasing impairment of learning and memory in patients of AD. In a small percentage, difficulties with language, executive functions, perception (agnosia), or execution of movements (apraxia) are more prominent than memory problems. AD does not affect all memory capacities equally. Older memories of the person's life (episodic memory), facts learned (semantic memory), and implicit memory (the memory of the body on how to do things, such as using a fork to eat or how to drink from a glass) are affected to a lesser degree than new facts or memories. Language problems are mainly characterised by a shrinking vocabulary and decreased word fluency, leading to a general impoverishment of oral and written language. In this stage, the person with Alzheimer's is usually capable of communicating basic ideas adequately. While performing fine motor tasks such as writing, drawing or dressing, certain movement coordination and planning difficulties (apraxia) may be present, but they are commonly unnoticed. As the disease progresses, people with AD can often continue to perform many tasks independently, but may need assistance or supervision with the most cognitively demanding activities [18].

Middle stage Alzheimer's

Progressive deterioration eventually hinders independence, with subjects being unable to perform most common activities of daily living. Speech difficulties become evident due to an inability to recall vocabulary, which leads to frequent incorrect word substitutions. Reading and writing skills are also progressively lost. Complex motor sequences become less coordinated as time passes and AD progresses, so the risk of falling increases. During this phase, memory problems worsen, and the person may fail to recognise close relatives. Long-term memory, which was previously intact, becomes impaired [19]. Behavioural and neuropsychiatric changes become more prevalent. Common manifestations are wandering, irritability and labile affect, leading to crying, outbursts of unpremeditated aggression, or resistance to care giving. Sun downing can also appear. Approximately 30% of people with AD develop illusionary misidentifications and other delusional symptoms. Subjects also lose insight of their disease process and limitations (anosognosia). Urinary incontinence can develop. These symptoms create stress for relatives and carers, which can be reduced by moving the person from home care to other long-term care facilities [20].

Late stage Alzheimer's

During the final stages, the patient is completely dependent upon caregivers. Language is reduced to simple phrases or even single words, eventually leading to complete loss of speech. Despite the loss of verbal language abilities, people can often understand and return emotional signals. Although aggressiveness can still be present, extreme apathy and exhaustion are much more common symptoms. The patients of AD will unable to perform very simplest task independently; muscle mass and mobility deteriorates to the point where

they are bedridden and unable to feed themselves. The cause of death is usually an external factor, such as infection of pressure ulcers or pneumonia, not the disease itself [21].

Neuropathology of Alzheimer's Disease

AD is a progressive neurodegenerative brain disorder that causes a significant disruption of normal brain structure and function. At the cellular level, AD is characterized by a progressive loss of cortical neurons, especially, pyramidal cells that mediate higher cognitive functions. Substantial evidence also suggests that AD causes synaptic dysfunction early in the disease process, disrupting communication within neural circuits important for memory and other cognitive functions. AD-related degeneration begins in the medial temporal lobe, specifically in the entorhinal cortex and hippocampus. Damage to these brain structures result in memory and learning deficits that are classically observed with early clinical manifestations of AD. The degeneration then spreads throughout the temporal association cortex and to parietal areas. As the disease progresses, degeneration can be seen in the frontal cortex and eventually throughout most of the remaining neocortex. Of note is the fact that AD causes pronounced damage to multiple components of the limbic system, including the hippocampal formation and the major fiber tracts that connect it to the cerebral cortex (fornix and cingulum), amygdala, cingulate gyrus, and thalamus. This widespread pattern of neuro degeneration, affecting both limbic and neocortical regions, correlates closely with the array of cognitive deficits and behavioral changes that AD patients exhibit. In addition to cognitive impairment across multiple domains (memory, language, reasoning, executive, and visuospatial function), patients with Ads how an impaired ability to perform activities of daily living and often experience psychiatric, emotional, and personality disturbances [22].

Medicinal Agents

In Alzheimer's disease there is no cure and drug therapy for the disease is still in its infancy. For the treatment of probable AD approved medications help to control the symptoms of AD but do not slow down the progression or reverse the course of the disease itself. The main stay of AD therapy is drugs that target neurotransmitter systems in the brain. Glutamate and acetylcholine producing neurons and their associated synapses primarily damages in AD and this damage correlate well with early cognitive symptoms of AD. A number of potential disease modifying AD drugs have been evaluated in clinical trials in recent years and many others are being evaluated in ongoing trials.

There are many compounds are available which are used to treat Alzheimer's disease. They are obtained from different source and acting on different target to treat disease.

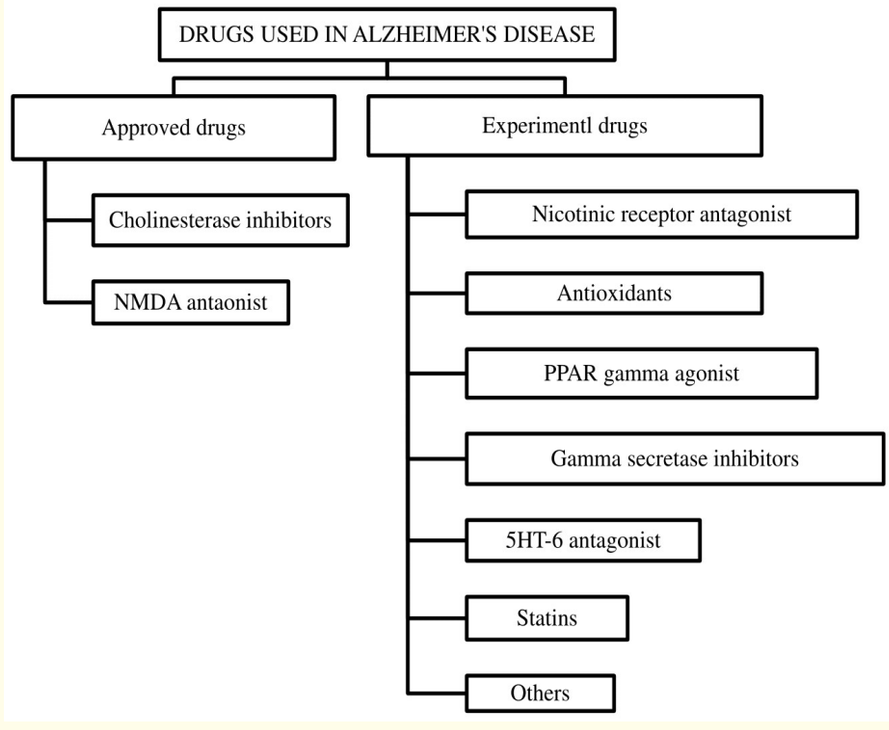

Figure 3: *Drugs used in Alzheimer's disease.*

1. Cholinesterase inhibitor. Eg. Donepezil, Rivastigmine, Galantamine
2. NMDA antagonist. Eg. Memantine
3. Nicotinic receptor agonist. Eg. 4-OH-GTS-21
4. Antioxidants. Eg. Ginkgo biloba, Vitamin E, Melatonin
5. PPAR gamma agonist. Eg. Pioglitazone
6. Gamma secretase inhibitors. Eg. Semagacestat
7. 5HT-6 antagonist. Eg. SB-271046
8. Statins. Eg. Simvastatin, Pravastatin
9. Others. Eg. Estrogens

Donepezil

Aricept is a trade name of Donepezil and is a medication used in the palliative treatment of Alzheimer's disease. Donepezil does not slow the progression of or cure the disease ad used to improve cognition and behaviour of people with Alzheimer's. Loss of appetite, gastrointestinal upset, diarrhea, difficulty sleeping, vomiting or muscle cramping are common side effects. It was developed by Eisai and Pfizer and is sold as a generic by multiple suppliers. This drug acts as a centrally acting reversible acetylcholinesterase inhibitor because it binds and reversibly inactivates the cholinesterase, thus inhibiting hydrolysis of acetylcholine. This results in an increased acetylcholine concentration at cholinergic synapses. The precise mechanism of action of Donepezil in patients with Alzheimer's disease is not fully understood. AD involves a loss of the elements of the cholinergic system and the symptoms of AD's are related to this cholinergic deficit, particularly in the cerebral cortex and other areas of the brain [23,24].

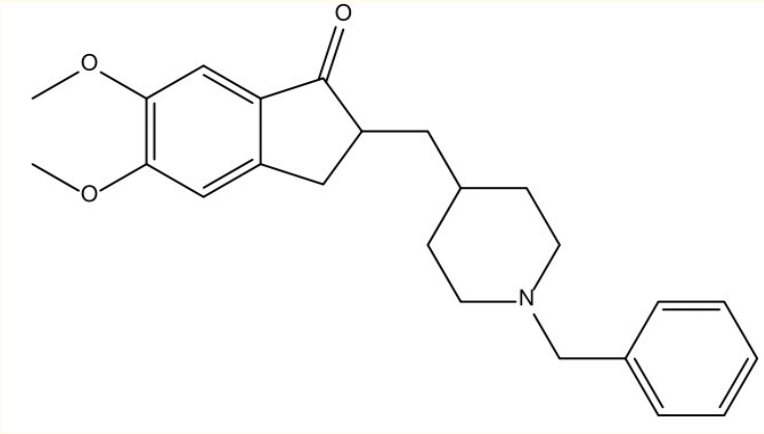

Figure 4: *Donepezil.*

Rivastigmine

Rivastigmine is a para sympathomimetic or cholinergic agent for the treatment of mild to moderate dementia of the Alzheimer's type and dementia due to Parkinson's disease. Oral formulations or transdermal patch are used and latter form reduces the prevalence of the side effects which include nausea and vomiting. This drug eliminated through the urine and has some drug-drug interactions. Rivastigmine capsules, liquid solution and patches are used for the treatment of mild to moderate dementia of the Alzheimer's type and for mild

to moderate dementia related to Parkinson's disease. Rivastigmine has demonstrated treatment effects on the cognitive, functional and behavioural problems commonly associated with Alzheimer's and Parkinson's disease dementias. Main side effects include nausea and vomiting, decreased appetite and weight loss [25,26].

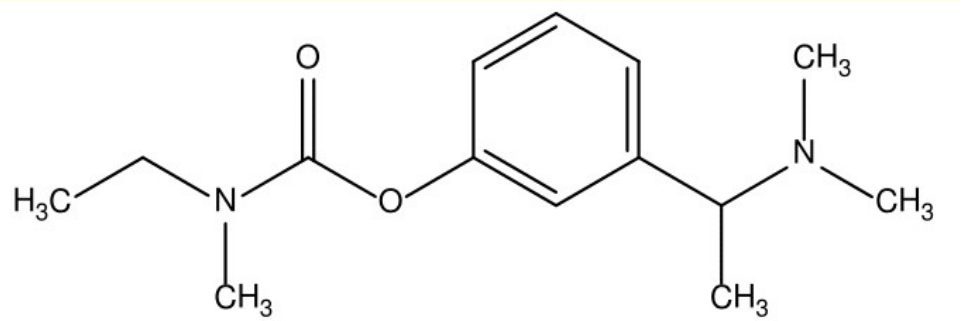

Figure 5: *Rivastigmine.*

Galantamine

Galantamine is used for the treatment of various memory impairments, in particular those of vascular origin and in mild to moderate Alzheimer's disease. It is isolated from the bulbs and flowers of *Galanthus caucasicus* (Caucasian snowdrop), *Galanthus woronowii* (Voronov's snowdrop) and some other members of the family Amaryllidaceae such as Narcissus (daffodil), *Leucojum aestivum* (snowflake), and *Lycoris* including *Lycoris radiata* (red spider lily). It can be produced ny synthetic way. Galantamine is a potent allosteric potentiating ligand of human nicotinic acetylcholine receptors (nAChRs) $\alpha_4\beta_2$, $\alpha_3\beta_4$, and $\alpha_6\beta_4$, and chicken/mouse nAChRs α_7/5-HT_3 in certain areas of the brain. By binding to the allosteric site of the nAChRs, a conformational change occurs which increases the receptors response to acetylcholine. This modulation of the nicotinic cholinergic receptors on cholinergic neurons in turn causes an increase in the amount of acetylcholine released. This drug also acts as a weak competitive and reversible cholinesterase inhibitor in all areas of the body. The side effect of this drug is very similar to that of other cholinesterase inhibitors, with gastrointestinal symptoms being the most notable and most commonly observed [27,28].

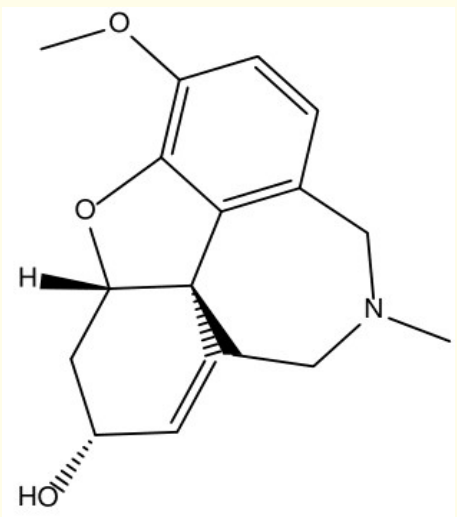

Figure 6: *Galantamine.*

Memantine

Memantine is used for the treatment of moderate to severe Alzheimer's disease and act on the glutamatergic system by blocking NMDA receptors. This drug was first synthesized by Eli Lilly and company in 1968 as a potential drug; the NMDA activity was discovered in the 1980s. Memantine is marketed under the brands Namenda or Auxura or Ebixa and Memory among others. Memantine especially used for people who are intolerant of or have a contraindication to acetylcholinesterase inhibitors [29]. Moderate decrease in clinical deterioration with small positive effect on cognition, mood, behaviour and the ability to perform daily activities in moderate to severe AD cause due to Memantine. Adverse drug reaction include confusion, dizziness, drowsiness, headache, insomnia, agitation, hallucination whereas less adverse effects include vomiting, anxiety, hypertonia, cystitis and increased libido [30].

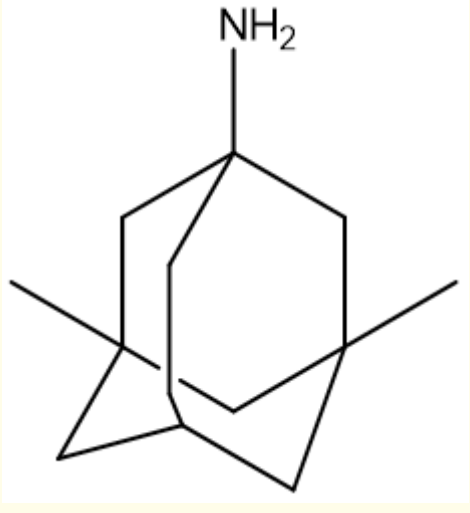

Figure 7: *Memantine.*

4-OH-GTS-21

α4 β2 and α7 nicotinic receptor types localized in areas of brain associated with dementia and memory loss. α7 nicotinic receptor agonist are 4-OH-GTS-21 which shows protective action on cholinergic neurons. This drug shows anti-amnestic effect in Alzheimer's disease type amnesia [31].

Ginkgo biloba

Ginkgo biloba is most commonly known as gingko or ginkgo. The cognitive function in people without known cognitive problems can enhance by extract of *Ginkgo biloba* leaf as dietary supplement. Ginkgo tree or maidenhair tree which is the only living species in the division *Ginkgo* phyta. Studies have failed to find such effects on memory or attention in healthy people. Undesirable effects may have especially for patient with blood circulation disorders and those taking anticoagulant drug such as Aspirin or Warfarin. Recent studies have found that Ginkgo has little or no effect on the anticoagulant properties or pharmacodynamics of Warfarin in healthy subjects [32,33].

Figure 8: *Ginkgo biloba plant.*

Vitamin E

Tocopherols and tocotrienols are refers as a group of compound of Vitamin E. γ-tocopherol is most common form of vitamin E which is commonly found in North American diet. Corn oil, soybean oil, margarine and dressings are common source of γ-tocopherol. Most biologically active form of vitamin E is α-tocopherol which is second most common form of vitamin E in diet. Wheat germ oil, sunflower oil, safflower oil is other source of vitamin E. As a fat-soluble antioxidant, it interrupts the propagation of reactive oxygen species that spread through biological membranes or through a fat when its lipid content undergoes oxidation by reacting with more-reactive lipid radicals to form more stable products [34]. As an enzymatic activity regulator, for instance, protein kinase C (PKC), which plays a role in smooth muscle growth, can be inhibited by α-tocopherol. α-Tocopherol has a stimulatory effect on the dephosphorylation enzyme, protein phosphatase 2A, which in turn, cleaves phosphate groups from PKC, leading to its deactivation, bringing the smooth muscle growth to a halt. In eye, neurological functions, inhibition of platelet coagulation, protection of lipids and prevent the oxidation of polyunsaturated fatty acids, vitamin E plays important role [35].

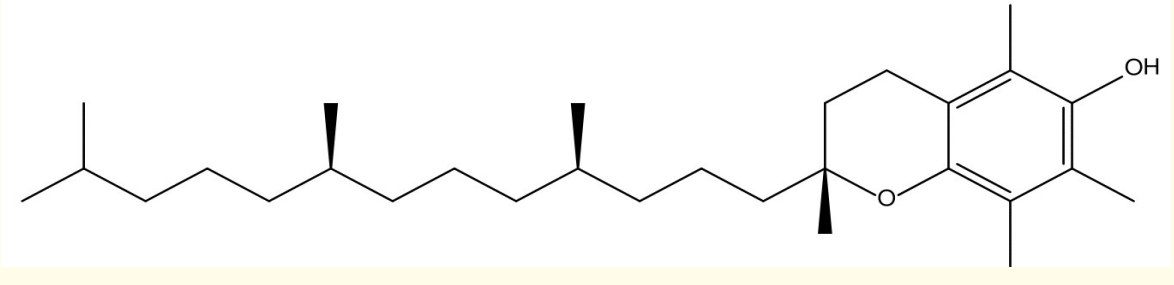

Figure 9: *Vitamin E.*

Melatonin

Melatonin is a hormone produced by pineal gland animal and regulates sleep and wakefulness and it is also produced in plants where it acts as first line of defence against oxidative stress. It is used for treatment of insomnia. In the United states, Canada and some European countries Melatonin is sold over the counter. It may require prescription or it may be unavailable in other countries. Side effects involve nausea, next day grogginess and irritability. It can cause reduced blood flow and hypothermia in elder patients. Melatonin supplementation may exacerbate symptoms due to immunomodulation in autoimmune disorders [36].

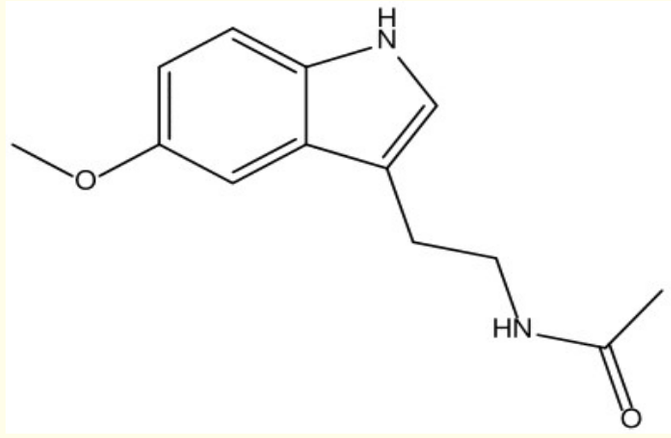

Figure 10: *Melatonin.*

Pioglitazone

Pioglitazone is marketed under Actos which is prescription drug of thiazolidinedione class with hypoglycaemic action to treat diabetes. While pioglitazone does decrease blood sugar levels, studies on the main cardiovascular outcomes have not yielded statistically significant results [37]. Pioglitazone is used to lower blood glucose levels in the treatment of diabetes mellitus type 2 (T2DM) either alone or in combination with a sulfonylurea, metformin, or insulin. The main study that looked at the medication, however, found no statistically significant difference in the main cardiovascular outcomes that were looked at. The secondary outcome of death from all causes, myocardial infarction, and stroke were lower. Pioglitazone has also been used to treat non-alcoholic steatohepatitis (fatty liver), but this use is presently considered experimental. Pioglitazone can cause fluid retention and peripheral edema. As a result, it may precipitate congestive heart failure . Anaemia may be occur due to this drug [38].

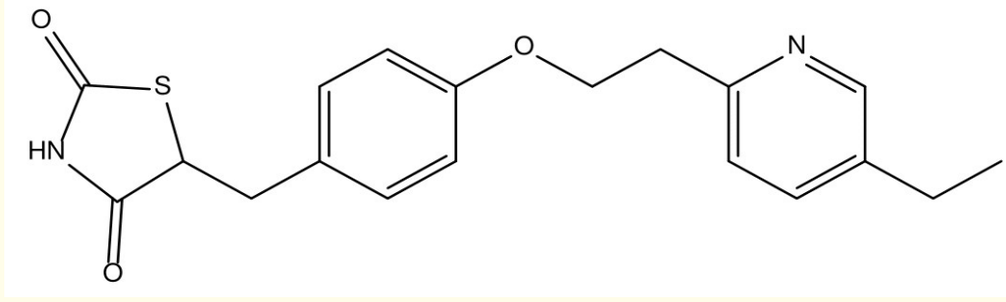

Figure 11: *Pioglitazone.*

Semagacestat

A candidate drug Semagacestat was used against Alzheimer's disease. It was developed by Eli Lilly and Elan and the clinical trials were conducted by Eli Lilly. B-amyloid is a peptide linkage of 39 to 43 amino acids. Main constituents of amyloid plaques in the brain of Al-

zheimer's disease patients are isoform of this drug with 40 - 42 amino acids. By proteolysis of amyloid precursor protein (APP) β-amyloid is formed. Soluble form of this peptide is a causative agent in the development of Alzheimer as suggested due to research on laboratory rats. The enzyme γ-secretase is responsible for APP proteolysis gets blocks due to Semagacestat [39].

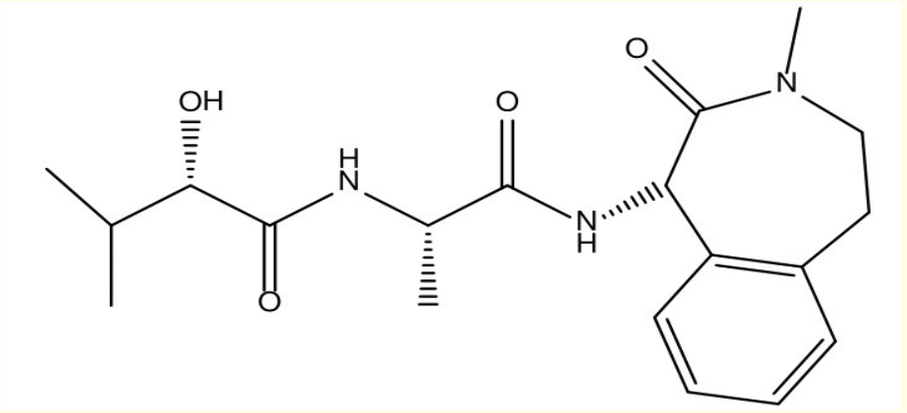

Figure 12: *Semagacestat.*

Simvastatin

Simvastatin is a lipid lowering medication marketed under the trade name Zocor. It is taken by oral route. The risk of heart problems is decreased because of its use. Main side effects are constipation, headache and nausea. Serious side effects may include muscle breakdown, liver problems and increased blood sugar levels. In people with kidney problems lower dose is used. This drug is not used by those who are breast feeding and there is also evidence of harm to unborn babies when taken during pregnancy. It is in the statin class of medications and works by decreasing the manufacture of cholesterol by the liver. Simvastatin primarily used to treat dyslipidemia and to prevent atherosclerosis-related complications such as stroke and heart attacks in those who are at high risk. In low cholesterol diet, it is recommended to be used [40,41].

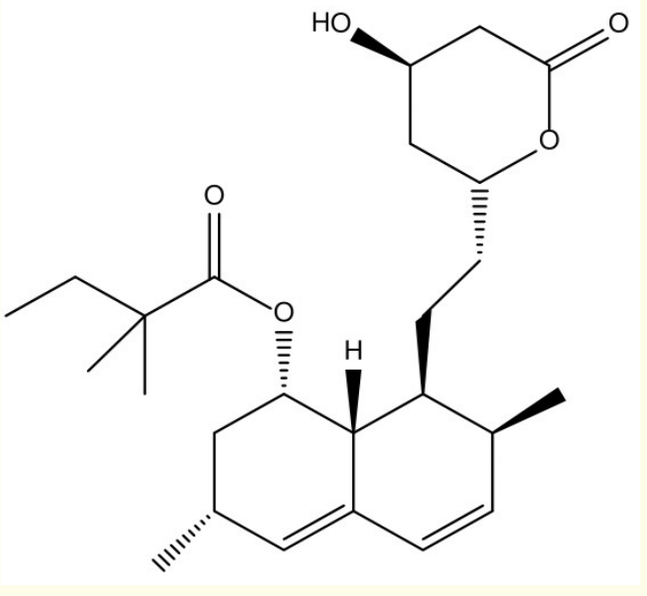

Figure 13: *Simvastatin.*

Estrogen

Estrogen (American English) or Oestrogen (British English) is used as medication which is primary female sex hormone. In all vertebrates as well as in some insects it can be synthesized. Estrogenic sex hormone has an ancient evolutionary history because of its of estrogen and presence in both vertebrates and insects. Estrone (E1), estradiol (E2) and estriol (E3) are three major occurring forms of estrogen. Estetrol (E4) is another type of estrogen which is produced only during pregnancy. Exogenous administration estrogen-like substances results into hyper-estrogenism or it may be result of physiologic condition such as pregnancy. Increase in the risk of thrombosis due to the hyper-estrogenism. Due to lowered metabolic function of the liver, which metabolises estrogen, it causes the liver cirrhosis and leading to spider angioma, palmar erythema, gynecomastia and testicular atrophy in some male patient's [42,43].

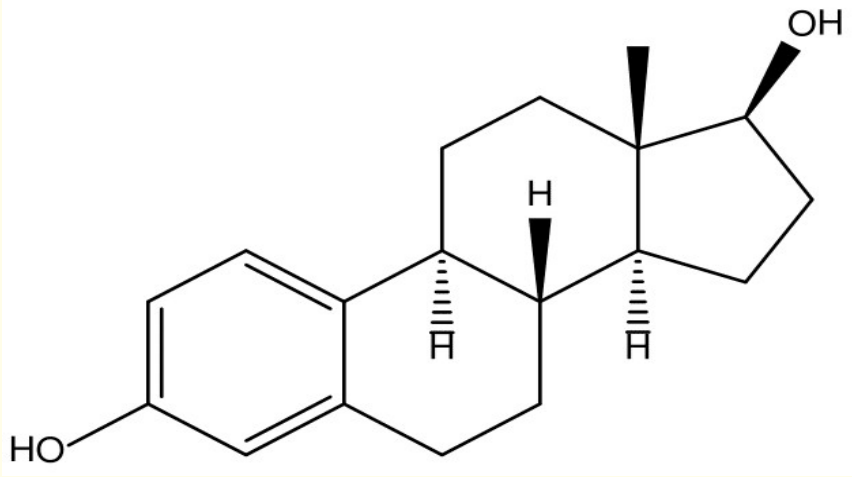

Figure 14: *Estrogen.*

Literature Survey

The literature survey was done to take into account the current research work reports on Alzheimer's disease:

1. Daoqiang Zhang, Yaping Wang, Luping Zhou, Hong Yuan and co-workers reported multimodal classification of Ad and MCI. They also reported that for the diagnosis of AD and MCI, structural MR imaging, brain atrophy measurement. Functional imaging for hypo-metabolism quantification multiple biomarker have shown sensitive effect. Only a single modality of biomarkers is used for diagnosis of AD and MCI is observed through existing research. Recent studies shown that different biomarker may provide complementary information for diagnosis of AD and MCI. MRI, FDG-PET and CSF biomarkers are three modalities of biomarker which are used to distinguish between AD and healthy control by using kernel combination method [44].

2. Patrick L. McGeer, Michael Schulzer and Edith G. McGeer worked on protective factor of AD such as arthritis and anti-inflammatory agents. By the presence of numerous inflammatory proteins lesions of AD can be characterized. Brain inflammation is a cause of neuronal injury in AD and for protection anti-inflammatory drugs my act as protective agents. From nine different countries seventeen epidemiologic studies have published in which risk factor for AD is consider as arthritis, us of anti-inflammatory drugs [45].

3. Nhi Ha Trinh, Jennifer Hoblyn, Subhanjoy Mohanty, Kristine Yaffe., *et al*. reported on treatment of neuropsychiatric symptoms and functional impairment in Alzheimer's disease meta-analysis and for these efficacy of cholinesterase inhibitors. Cholinesterase inhibitors have a modest beneficial impact on neuropsychiatric and functional outcomes for AD's patients. Future research should focus on how such improvements translate into long-term outcomes such as patient quality of life, institutionalization, and caregiver burden [46].

4. Benjamin Wolozin, Wendy Kellman; Paul Ruosseau., *et al.* have worked on decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme a reductase inhibitors. The pathophysiology of Alzheimer disease (AD) has many connections with cholesterol metabolism. Epidemiological studies show that patients with elevated cholesterol levels have an increased risk of AD. One of the major risk factors for AD, is apolipoprotein E type 4 (APOE4), which is a cholesterol transport protein. A second putative risk factor for AD, α_2-macroglobulin, binds to the same receptor as does APOE4. This receptor, the lipoprotein receptor–related protein, is important for cellular uptake of cholesterol [7]. Cholesterol also affects the biology of β-amyloid (Aβ). β-α amyloid is a protein that accumulates in the affected brains of patients with AD and is thought to cause the neuro-degeneration underlying AD. Production of the Aβ peptide is increased by cholesterol in some cells. These multiple links suggest a potentially important relation between cholesterol and AD [47].

5. Richard A Hansen, Gerald , Aaron P Webb,Laura C Morgan, Charity G Moore, and Daniel E Jonas reported on efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: A systematic review and meta-analysis. Alzheimer's disease is an age-associated neurodegenerative disorder, affecting approximately 24 million individuals worldwide. Primary manifestations of Alzheimer's disease include cognitive impairment, alterations in behaviour and reduced ability to perform activities of daily living. Nonpharmacologic and pharmacologic interventions are available, although none prevents or cures the disease. Non-pharmacologic interventions primarily address behavioural disturbances (e.g. task simplification, environmental modification, minimal excess stimulation, etc) and other sources of cognitive impairment (e.g. treating comorbid medical conditions, minimizing or eliminating drugs with deleterious cognitive side effects). Pharmacologic therapies are intended to slow the progression of disease and improve symptoms. Drugs currently approved for Alzheimer's include cholinesterase inhibitors [48].

6. Melanie-Jayne R. Howes, Rui Fang, Peter J. Houghton worked on effect of Chinese herbal medicine on Alzheimer's disease. Alzheimer's disease (ad) is reaching epidemic proportions yet treatment strategies are limited and are restricted to providing symptomatic relief for the cognitive and behavioural and psychological symptoms of dementia (BPSD). Chinese herbal medicine (CHM) has been a valuable source of medicines for centuries and research has burgeoned in recent years to understand the scientific basis for their use. Some plants have been used in CHM for AD symptoms (e.g. *Polygala tenuifolia*), while others are CHMs for different conditions, but they show mechanistic effects relevant to AD (e.g., *Salvia miltiorrhiza*). Some CHMs (e.g. *Ginkgo biloba* extract and huperzine A from *Huperzia serrata*) show pharmacological activities relevant to AD, and promising effects on cognitive functions in clinical trials. Other CHMs show effects relevant to BPSD (e.g. *Crocus sativus*) [49].

Conclusion

Now there is no complete treatment and cure for AD. However, one group of drugs called cholinergic drugs appears to be providing some temporary improvement in cognitive functioning for some people with mild to moderate Alzheimer's disease. Drugs can also be prescribed for secondary symptoms such as restlessness or depression or to help the person with dementia sleep better. Community support is available for the person with Alzheimer's disease, their families and well-wishers. This support can make a positive difference to managing dementia.

Mild cognitive impairment (MCI), biomarkers of AD and MCI, positron emission tomography, magnetic resonance imaging, fluid biomarkers are advancements used in treatment of Alzheimer's disease. Substantial advances have been made in characterizing pre-demen-

tia stages of AD, such as MCI, and improving the diagnostic and therapeutic options available for managing AD. Recognizing the urgent need to develop clinically useful neuro-imaging and other biomarkers for the early detection of AD, the NIA sponsored the ongoing Alzheimer's disease Neuro-imaging Initiative (ADNI) beginning in 2004.

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Conflict of Interest

The authors declare no conflict of interest.

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