An Updated Review on the Approved and Potential Drugs for the treatment of Alzheimer's Disease

By
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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
BRAC University
October, 2024

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis titled "An Updated Review on the Approved and Potential Drugs for Alzheimer's Disease" submitted by Rifah Nanjiba (20146056) of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract:

Alzheimer's disease (AD) is one of the most complex and prevalent neurodegenerative disease, and over 55 million people around the world are suffering from it. There are only three groups of drugs such as acetylcholinesterase inhibitors, NMDA antagonist, and anti-amyloid antibodies that are clinically approved for the treatment of AD. Among these three groups of drugs only anti-amyloid antibodies are disease modifying medicines and the rest two groups of drugs only treat the symptoms of AD. Hence, there is a dire need of sufficiently potent drugs and treatment strategies to manage this disease. Although the exact etiology of this progressive neurodegenerative disease is still unknown, factors like genetic, environmental, and lifestyle, might play a significant role. Meanwhile, extensive research is continuously being performed for developing potential/novel drugs for AD such as beta-secretase enzyme inhibitor, tau protein targeted inhibitors, genetic factors like ApoE4 gene and immunotherapies, emphasizing the multifaceted pathophysiology of the disease. Despite of certain challenges in novel drug development for AD, results obtained from recent clinical trials and preclinical studies, suggest that a large number of compounds has the potential to be used in the future therapeutic strategies for AD.

Keywords: Alzheimer's disease, neurodegenerative pathways, neuroinflammation, approved drugs, disease-modifying therapies, novel therapeutics.

Dedication

I want to dedicate this work to my parents and friends stood by me and showed their support and encouragement throughout my entire journey.

Acknowledgement

First and foremost, I would like to express my utmost gratitude to the Most Merciful Allah for blessing me with strength and ability to complete this journey. I would like to express my deepest gratitude to my supervisor, Assistant Professor Dr. Nishat Zareen Khair, for her invaluable guidance, insightful feedback and expertise throughout the course of this thesis. Her directions have been instrumental in shaping my ideas and enhancing the quality of this work.

Finally, I would also like to extend my love and appreciation to my family and friends who had belief in me and helped me to stay focused and dedicated towards my work.

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List of Acronyms

AD: Alzheimer's disease

APP: Amyloid precursor protein

Aβ: Amyloid beta

NFT: Neurofibrillary tangles

MAP: Microtubule associated protein

ApoE: Apolipoprotein E

ROS: Reactive oxygen species

IL-1β: Interleukin-1β

TNF-α: Tumor necrosis factor-alpha

GSK-3: Glycogen synthase kinase-3

CDK5: Cyclin-dependent protein kinase 5

BACE1: Beta-site APP cleaving enzyme

NMDA: N-methyl-D-aspartate

NMDAR: N-methyl-D-aspartate receptor

ACh: Acetylcholine

AChE: Acetylcholinesterase enzyme

BuChE: Butyrylcholinesterase enzyme

IC_{50}: 50% Inhibitory Concentration

nAChR: Nicotinic acetylcholinesterase receptor

mABs: Monoclonal antibodies

ARIA: Amyloid related imaging abnormalities

CFT: Carboxyl terminal fragment

AICD: APP intracellular domain

Chapter 1

Introduction

1.1 What is Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disease that gradually progresses and causes decline in cognitive function, improper formation of recent memory, eventual impairment of all intellectual functions, and lead to complete dependence on external support for basic daily functions, and premature death (Jack et al., 2018). When diagnosing a 51-year-old woman with behavioural problems in 1901, Alois Alzheimer made the discovery that she had the pre-senile form of the disorder. After the patient's death, he discovered that her brain was filled with the characteristic protein plaques and neurofibril tangles of AD (Alzheimer et al., 1995). So, the neuropathological hallmark of AD includes widespread amyloid plaques in the brain formed in the brain extracellularly, surrounded by intraneuronal neurofibrillary tangles and dystrophic neurites (dendrites or axon that protrudes from the cell body of neuron). Although, the exact cause of Alzheimer's disease is still not known different abnormal genetic and environmental factors might play a significant role (Mayeux & Stern, 2012). Amyloid beta protein clumps can form if there is any mutation in the cleaving process of Amyloid precursor protein (APP) as shown in figure 1, and aggregation of hyperphosphorylated tau protein leads to neurodegeneration, reduced synaptic strength and function. Other significant elements in the pathology of Alzheimer's can be altered metabolism, inflammation, impaired vascular disease and other concomitant diseases. Currently approved drugs for Alzheimer's can only provide symptomatic relief, so there is crucial need for disease modifying medicines (Lopez et al., 2019).

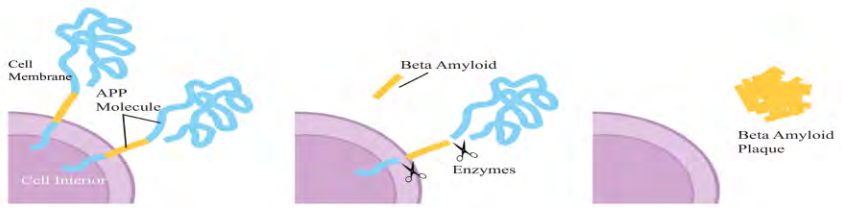


Figure 1: The formation of Beta Amyloid Plaque (Ricciarelli & Fedele, 2017).

1.2 Prevalence

The majority of the Alzheimer's patients are over the age of 65. Approximately 1 in 14 individuals over 65 and for 80 years and up 1 in 6 people faces the risk of developing Alzheimer's or other form of dementia. Figure 2, illustrates how with age the risk of Alzheimer's increases vastly. However, Alzheimer's can also attack people below 65 years old. 1 in 13 Alzheimer's patient are below the age 65 ("2024 Alzheimer's Disease Facts and Figures," 2024). According to a nationwide survey conducted in the US 6.9 million people over the age of 65 are suffering from AD (Alzheimer's Association, 2024). Regional prevalence rates were 3.48% in China (Ji et al., 2024) and the Western Pacific, 1.6% in Africa, 5.4% in Western Europe, 4.6% ("Prevalence of Dementia in Europe," 2019) in Latin America, and 6.4% in North America (Alzheimer's Association, 2024).

It is estimated that at least 55 million people worldwide suffer from Alzheimer's. If no significant medical advancement can be achieved for the treatment of this disease, this figure might triple and surpass 152 million by 2050, and more than half of these cases will be prevalent in low and middle-income countries. (*Alzheimer's: Facts, Figures & Stats | BrightFocus Foundation, 2022*). The

prevalence of AD varies depending on age, gender, socioeconomic condition, cultural background in both developed and developing countries (Tóth et al., 2018). Reports from the United States and much of Europe indicate that women make up two thirds of clinically confirmed cases of AD. Women's longer lifespans have been proposed as the main cause of this gender disparity because dementia risk escalates with age (Beam et al., 2018).

AD has a substantial social and economic impact in addition to having risk factors that are worrying for the health sector it has a significant negative social impact on the elderly in several overpopulated countries. The burden of AD impacts the patient, their families, and the economy; it is estimated that the annual global expenses are $1 trillion. (Skaria, 2022).

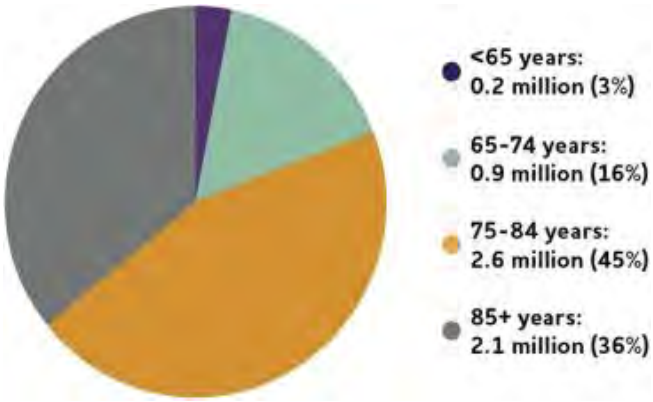


Figure 2: Percentage of different age-group affected by Alzheimer's disease (Alzheimer's Association, 2023)

1.3 Causes and Risk factors

AD is a complex and multifactorial disease which can have several risk factors acting behind it such as aging, genetic abnormalities, injury to the nervous system, vascular disorder, inflammation, and environmental factors. Although the pathological changes that occurs in Alzheimer's is still unknown, there are two most widely believed hypotheses. One of them suggests that damage to the cholinergic function can worsen the neurodegeneration in AD, whereas others believes that

alteration in the cleaving and formation of amyloid beta is the main facilitating factor. Currently, no recognized theory explains the pathogenesis of AD (Breijyeh & Karaman, 2020).

The risk factors associated with Alzheimer's disease can be categorize into three main factors as shown in figure 3. They are:

Biological factors: Aging is the primary risk factor for AD. Ageing is a multifaceted, irreversible process that affects many organs and cell systems. It is characterized by a decrease in brain mass and volume, loss of synaptic function, and modification in the cerebral ventricular system, which is accompanied by the deposition of amyloid beta proteins and the formation of neurofibrillary tangles (NFT). Furthermore, as people age, a number of illnesses could manifest, including depression, mitochondrial dysfunction, imbalance in the amount of cholesterol in the blood, decreased metabolism of glucose, and decline in cognition. It is difficult to separate the symptoms of early onstage of AD and the natural changes that occurs due to normal. Four cardiovascular disease-related factors—obesity, high blood pressure, high cholesterol, and diabetes—can also raise the chance of developing AD. (Riedel et al., 2016).

Genetic factors: Over time, genetic factors were identified to be crucial in the development of AD. Mutations in dominant genes such as apolipoprotein E (ApoE), presenilin-1 (PSEN-1), presenilin-2 (PSEN-2), and amyloid precursor protein (APP) have been linked to AD in 70% of cases. Mutations in the chromosome 21 amyloid precursor protein (APP) gene can result in increased production of (42 amino acid) form of β-amyloid which is longer and has higher aggregation levels than the shorter (40 amino acid) version (Van Cauwenberghe et al., 2016).

Environmental Factors: A steady decline in cognitive abilities and an increased risk of neurodegenerative illnesses have also been linked to chronic exposure to heavy metals and

pesticides, such as lead and aluminium even in small amount. Adverse weather conditions and environmental exposures may cause inflammation, irregular body temperature, and heat stress. It has been seen that environmental pollution, heavy metals, and oxidative stress have all considerably decreased Ach (Ayeni et al., 2022).

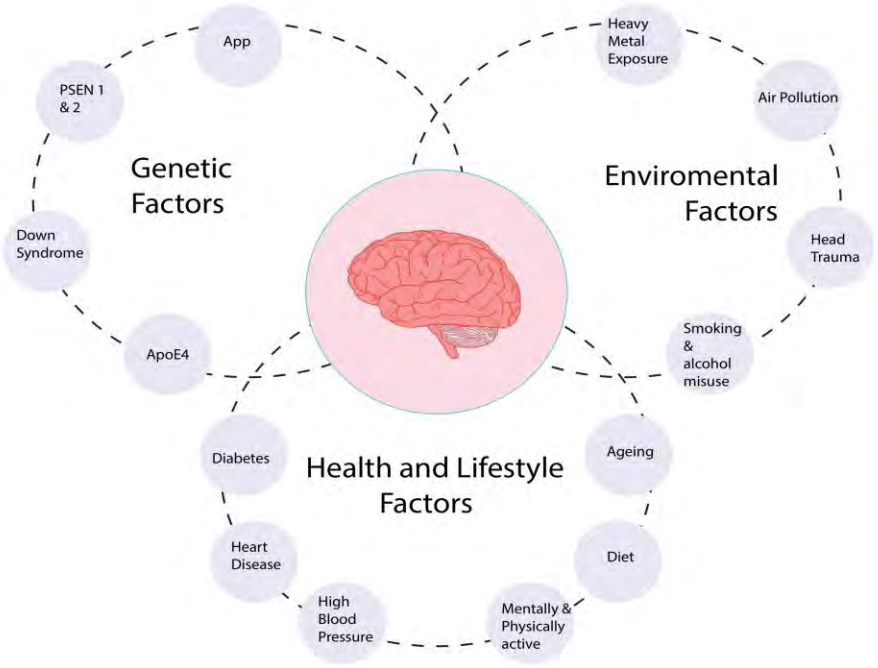


Figure 3: The risk factors for Alzheimer's disease (Breijyeh & Karaman, 2020).

1.4 Signs and Symptoms

Alzheimer's disease symptoms may vary from person to person. Usually, one of the first indications of the illness is memory loss. In the initial stage AD can be also detected by abnormalities in non-memory related cognitive functions such as-speech impairment, difficulty in understanding visual imagery, and spatial relationships, and problems with reasoning or judgement. The illness worsens with time, causing increasingly severe symptoms such increased disorientation and behavior (*What*

Are the Signs of Alzheimer's Disease?, 2022). Alzheimer's disease symptoms can often be categorized into three basic stages. Such as: mild, moderate, and severe.

Alzheimer's disease advances over time. This indicates that symptoms begin mildly and then get worse with time, becoming more and more disruptive to day-to-day activities. The progression of Alzheimer's disease can be divided into seven clinical stages. Likewise called "Reisberg stages." There are four divisions throughout the seven phases (AlzheimersDisease.net, 2019). They are-

1) In "Reisberg stage 1" no dementia is observed. The symptoms in this stage are-
    - There is no complains of memory loss
    - Also, there is no evidence of cognitive deficit.
2) Early stage of Alzheimer's disease shows mild cognitive decline and it consists of "Reisberg stages 2 and 3". The symptoms in these stages are-
    - Reports of memory problems like misplacing objects, or forgetting names.
    - Does not face problem in work or social situation
    - Impaired concentration
    - Mild anxiety in certain challenging situations.
3) Middle stage of Alzheimer's disease shows moderate to moderately severe cognitive decline it consists of "Reisberg stages 4, 5, and 6". The symptoms in these stages are-
    - Difficulty in managing finances and remembering personal history.
    - Withdrawal from situations that are challenging
    - Evidence of short-term memory loss.
    - Disorientation about time, place or date.
    - Evidence of bowel issues

- Sleep disturbances
- Hallucinations, anxiety, agitation, and obsessive behavior.

4) "Reisberg stage 7" is the late stage of Alzheimer's disease where severe to very severe cognitive decline is observed. The symptoms in this stage are-

- Significant personality and behavior changes.
- Inability to hold a conversation.
- Difficulty moving, eating and swallowing.
- Impairment in bladder and bowel movement.
- Need assistance in carrying out day to day activities
- changes in personality, such as becoming aggressive, demanding, and wary of people and crowds.

1.5 Pathogenesis

The two characteristic pathologies necessary for the diagnosis of Alzheimer's disease (AD) are the β-amyloid peptide (Aβ) plaque accumulation in the extracellular space and the neurofibrillary tangles of the microtubule binding protein tau (Murphy and LeVine, 2010). Although the primary cause of the disease and its progression are still unknown there can be several multifactorial pathways that might play critical role in the progress of the disease such as- oxidative stress, neuroinflammation, glutamate excitotoxicity, reduction in acetylcholine levels, and low levels of neurotrophins, as illustrated in figure 4. (Lopez et al., 2019).

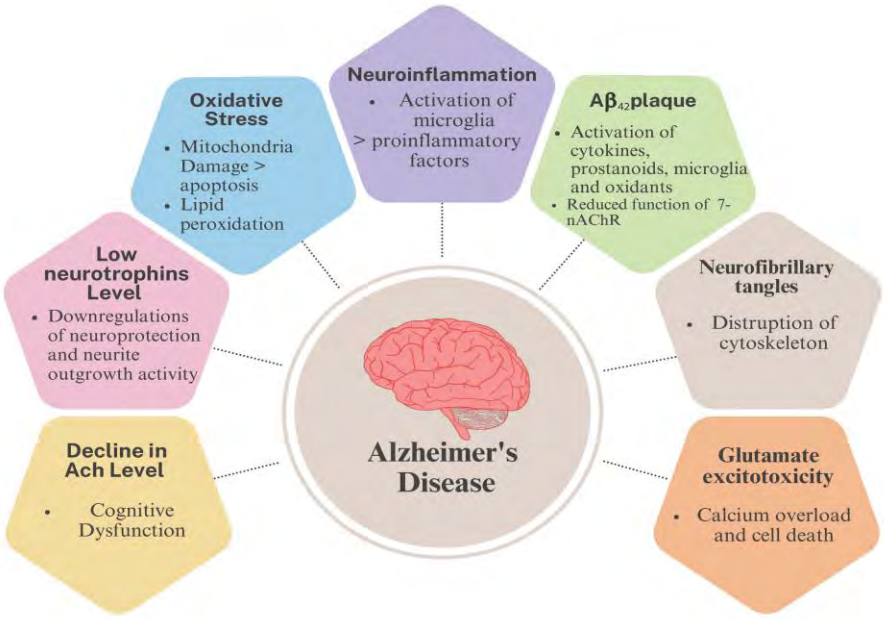


Figure 4: Pathogenesis of Alzheimer's Disease (Lopez et al., 2019).

1.5.1 Amyloid aggregation

Aβ protein is formed through the cleaving of APP by the action of β- and γ-secretase. Aβ1-42 is one of the most prevalent isoforms of Aβ. This amyloid beta monomer is most susceptible to form oligomers, which are extremely toxic and thought to be the primary neurotoxic in this condition. Therefore, these excess Aβ monomer then self assembles to form the insoluble Aβ aggregates that deposit extracellularly to form amyloid plaques surrounding neurons. Hence this mechanism, is known as the "amyloid cascade hypothesis," which suggests that AD pathogenesis is stimulated by the aggregation of amyloid proteins (Kametani and Hasegawa, 2018). Moreover, the central nervous system recognizes these plaques as foreign material. So, microglia are activated in the brain which triggers the releases of cytokines, initiating an inflammatory and immunological

response that ultimately results in cell death and cognitive dysfunction. (Musiek and Holtzman, 2015). As shown in figure 5, amyloid plaque can cause oxidative stress and mitochondrial dysfunction which ultimately leads to neuronal cell death and the progression of the AD.

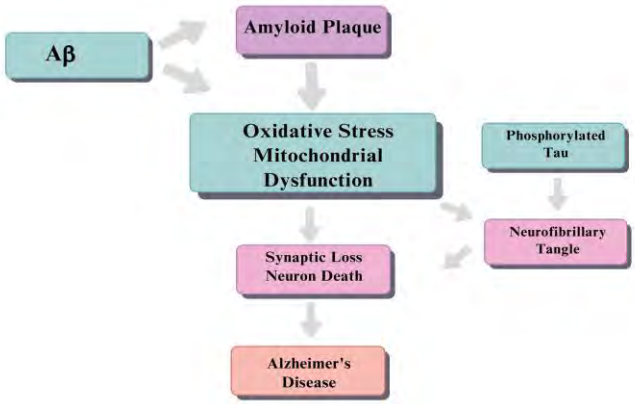


Figure 5: The role of Amyloid Plaque in the pathogenesis of AD (Kametani and Hasegawa, 2018).

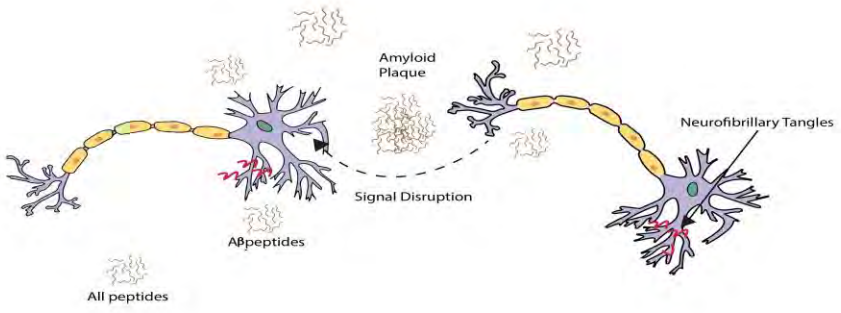


Figure 6: The disruption of neurotransmission by the formation of Amyloid Plaque (Iadanza et al., 2018).

Moreover, the Aβ aggregates was found to be more neurotoxic than insoluble. These Aβ plaques also significantly disrupts the signal transduction among the neuronal cells by accumulating the synapse between two nerve cells, as shown in figure 6. (Iadanza et al., 2018).

1.5.2 Oxidative stress

Oxidative stress is related to several medical problems, including cancer, neurological disorders, diabetes, and asthma. Oxidative stress mainly occurs due to overproduction of oxidants or insufficiency of antioxidants. As a result, reactive oxygen species (ROS) and other free radicals accumulate with the ability to harm lipids, proteins, and DNA, among other components of cells. Because the brain has a high concentration of unsaturated fatty acids, which are vulnerable to lipid peroxidation and free radical damage, it is especially vulnerable to oxidative stress (Garbarino et al., 2015). Although the level of antioxidant activity is less in the brain, it has an extraordinarily high oxygen concentrations, and aerobic oxidation in the mitochondria controls the metabolism of energy. (Zhao & Zhao, 2013). And during this process a huge amount of ROS are produced by the electron transport system. ROS have the ability to produce lipid peroxidation, which is linked to most neurodegenerative illnesses. Attacks by free radicals on the lipids of the bilayer of cellular membranes cause membrane-bound receptors and enzymes to become inactive, which can harm biological proteins and DNA. (Bai et al., 2022).

1.5.3 Metal ion imbalance

Metal elements like copper (Cu), iron (Fe), zinc (Zn), and manganese (Mn) are essential for brain development, growth and metabolism in the body within the physiological range but an imbalance of metal ions is linked to a number of dysfunctions in human body. Extensive research has revealed

that metal ions may be involved in a number of pathophysiological pathways associated with AD, including deposition of toxic protein, neurofibrillary tangles (NFTs), oxidative stress, neuroinflammation, and neuronal death (Su et al., 2007). Recent research has found a connection between aberrant Cu metabolism and the pathophysiology of AD. Moreover, genetic data found by various researches indicates that the gene governing the Cu pathway is a susceptibility gene for AD. (Liu et al., 2022). According to studies, abnormally metabolized Cu can upregulate the expression of proinflammatory factors like tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β). Hence, these findings suggest that inflammation induced by metal ions like copper (Cu) might have an integral role in the development of AD (Kitazawa et al., 2016).

1.5.4 Neurofibrillary Degeneration/ Tau aggregation

Neuronal microtubular proteins are called tau proteins. And in theses tau proteins the microtubule binding domains are present which are crucial for the stabilization and polymerization of microtubule assembly, which upholds the cytoskeleton's integrity. (What Happens to the Brain in Alzheimer’s Disease?, 2024). But the affinity of these tau proteins for microtubules is reduced when they are hyperphosphorylated. Whereas normal tau helps to assemble and stabilize the microtubule structure abnormally hyperphosphorylated tau, which causes microtubule disruption while normal tau promotes assembly itself into tangles of paired helical and/or straight filaments. Many different protein kinases phosphorylate tau. Among the kinases most linked to aberrant tau hyperphosphorylation are glycogen synthase kinase-3 (GSK-3) and cyclin-dependent protein kinase 5 (cdk5) (Mietelska-Porowska et al., 2014). And these two protein kinases are found abundantly in every stage of neurofibrillary pathology in AD. The hyperphosphorylated tau can no longer maintain the cell's structure because it forms neurofibrillary tangles (NFTs) and are

deposited in the cytoplasm. The transport system among the neurons is blocked by these NFTs, impairing synaptic transmission between the nerve cells (Islam Khan et al., 2018).

1.5.5 Secretases

Three main enzymes play the main role in cleaving and processing APP: α-secretase, β-secretase, and γ-secretase. Abnormal processing of APP causes an accumulation of the neurotoxic forms of Aβ into plaques, which contributes to the characteristic neuronal dysfunction and death in the brains of AD patients (O'Brien and Wong, 2011).

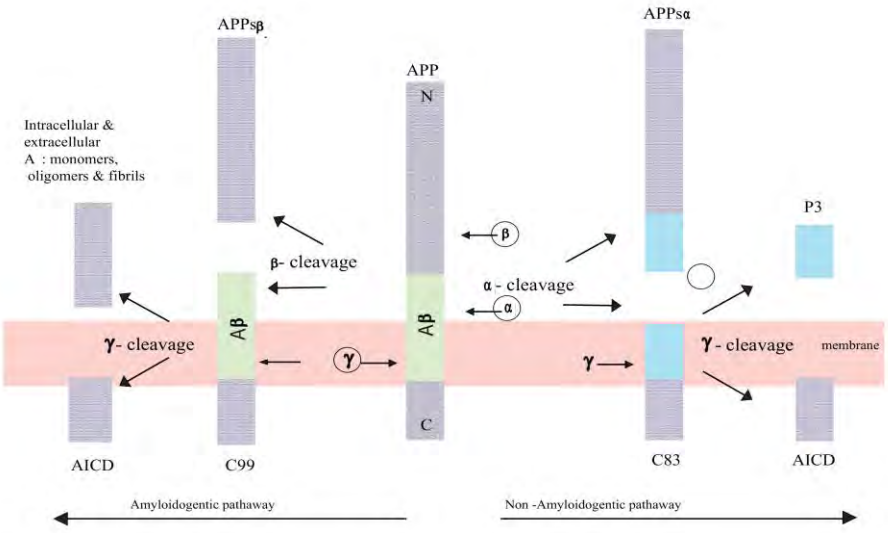


Figure 7: The function of secretase enzyme in the breakdown of the Amyloid Precursor Protein (APP) (Von Bergen et al., 2005) .

As shown in figure 7, through a non-amyloidogenic route, the α-secretase enzyme breaks down APP to create soluble peptide fragments that are not harmful. But, the β-site APP-cleaving enzyme

1 (BACE-1), or β-Secretase enzyme cleaves APP following an amyloidgenic pathway and forms amyloid beta monomers which eventually forms the amyloid plaque characteristic to AD. Lastly, the γ-secretase enzyme is in charge of producing Aβ and post-translationally altering APP (Von Bergen et al., 2005).

1.5.6 Excitotoxicity

Excitotoxicity refers to the overstimulation of N-methyl-D-aspartate (NMDA) receptor that occurs due to the prolonged exposure of the neurotransmitter glutamate on the NMDA receptor. The excitatory glutamatergic neurotransmission mediated by N-methyl-d-aspartate receptor (NMDAR) is significant for neuronal survival and synaptic development. Nevertheless, increased NMDAR activity results in excitotoxicity and facilitates apoptosis, which may be the origin of the neurodegeneration associated with Alzheimer's disease (AD) (Wang and Li, 2016). Researched based data indicates that increased Ca2+ entry, mainly via NMDARs, is the primary mechanism causing the toxicity. because if NMDARs are overstimulated it becomes more permeable to Ca2+. and this abnormal level of Ca2+ in the cell causes persistent loss of synaptic function, abnormal neuronal structure, progressive cognitive decline and eventually lead to cell death (Wang and Reddy, 2017).

1.5.7 Cholinergic enzymes

The discovery in the 1970s that the cholinergic function in AD patients' brains is impaired due to the activity of the choline acetyltransferase enzyme, marked a significant advance in the field of AD research (Francis et al., 1999). The cholinesterase enzyme breaks down acetylcholine into choline and acetic acid. This process is essential for both preventing overstimulation of the neurons

and for ensuring normal cell signaling. The choline nervous system consists of two main enzymes they are-Acetylcholinesterase enzyme (AChE) and butyrylcholinesterase enzyme (BuChE). significant decrease in the function of cholinergic neurons is linked to AD. Whereas as the disease progress it is observed to have a marked rise in AChE levels near amyloid plaques and NFT, and it is believed that AChE may interact directly with Aβ to facilitate the production of plaques (Colovic et al., 2013).

1.6 Rational of the review

This review aims to summarize the existing landscape of drugs, focusing on both established and emerging therapeutic strategies for Alzheimer's disease. While traditional approaches have primarily targeted amyloid-beta and tau proteins, recent research highlights the importance of neuroinflammation, synaptic integrity, and metabolic processes in AD progression. The drugs that are currently approved by regulatory bodies around the world for the treatment of AD are-Acetylcholinesterase inhibitor such as- donepezil, rivastigmine and galantamine, NMDA antagonist like memantine, and most recently approved disease modifying medicines the anti-amyloid antibodies such as- lecanemab and donanemab. Therefore, there is a pressing need to continue developing more disease-modifying medications. Additionally, the review will gather information on the most recent progress made in researching and developing of novel compounds that hold potential for future treatment strategies.

1.7 Objective

The objective of this review is to thoroughly summarize and evaluate and limitations of approved drugs for Alzheimer's disease, while also focusing and commenting the on novel potential drug

candidates for Alzheimer's disease that could lead to more effective therapeutic strategies for the prevention and treatment of this neurodegenerative disorder. Also, the therapeutic prospective of these drugs and the challenges involved in their clinical application, are also discussed.

Chapter 2

Methodology

Each piece of data used in this review study was acquired by a literature search. The information was compiled from a variety of reputable sources, such as well-known scientific websites, research papers, peer-reviewed publications, clinical trial papers, and peer-reviewed journals. The majority of the articles are part of prestigious and outstanding online databases such as PubMed, Google Scholar, Elsevier, SpringerLink, Science-Direct, Research Gate, and The Lancet. Moreover, open Athens account from university library was also very helpful for accessing relevant articles. Using appropriate keywords like "Alzheimer's disease," "drug targets," "FDA approved drugs," "novel therapeutic targets," etc., relevant papers were chosen for this review study. After carefully reading and analyzing each article from multiple sources, current and credible information was gathered to construct the review article titled "An Updated Review on the Approved and Potential Drugs for the treatment of Alzheimer's Disease". Finally, to preserve the original author's credit for their work, proper referencing has been done.

Chapter 3

Approved and Potential Drugs for the treatment of Alzheimer's Disease

3.1 Approved Drugs for the treatment of Alzheimer's Disease

Only three groups of drugs are currently approved by regulatory bodies for the treatment of Alzheimer's disease. These are the-

- Acetylcholinesterase Inhibitors. Such as- Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razadyne).
- NMDA receptor Antagoinst. Such as- Memantine (Namenda)
- Anti-Amyloid Antibodies. Such as- Lecanemab (Lequembi), Donanemab (Kisunla) (Medications for Alzheimer's Disease, 2024).

3.1.1 Acetylcholinesterase Inhibitors

Brain function depends on the balance of several neurotransmitter systems, including glutamate, acetylcholine (ACh), noradrenaline, dopamine, gamma-aminobutyric acid, and serotonin (Marucci et al., 2021). Among them acetylcholine is released by cholinergic neurons and carries out signal transduction that is connected to memory and learning. Although the pathogenesis of AD unclear and complex, the cholinergic hypothesis was established as the oldest idea about the pathogenesis of AD. In age-related neurodegenerative illnesses like AD cholinergic atrophy is largely observed and it facilitates cognitive abnormalities. Moreover, aberrant central cholinergic alterations can

also cause abnormal tau protein phosphorylation, nerve cell inflammation, cell apoptosis, and other pathogenic events (Chen et al., 2022). The cholinergic theory of geriatric memory failure was developed since the early 1970s due to observations of a rapid decrease of basal forebrain cholinergic neurons in the brains of AD patients (Bartus et al., 1982). Also, the neurochemical evidence supports this theory that the Ach biosynthesis enzyme choline acetyltransferase (ChAT) is reduced in cognition-related brain regions such the cerebral cortex and hippocampus in AD patient (Marucci et al., 2021). Therefore, after it was identified that AD affects cholinergic pathways in the cerebral cortex and basal forebrain, to the development of certain types of drugs were initiated that could enhance the cholinergic activity in the brain (Bowen et al., 1976). Central acetylcholinesterase (AChE) inhibitors which is also known as cholinesterase inhibitors are drugs that prevents the hydrolysis of acetylcholine (Ach) into choline by acetylcholinesterase enzyme.

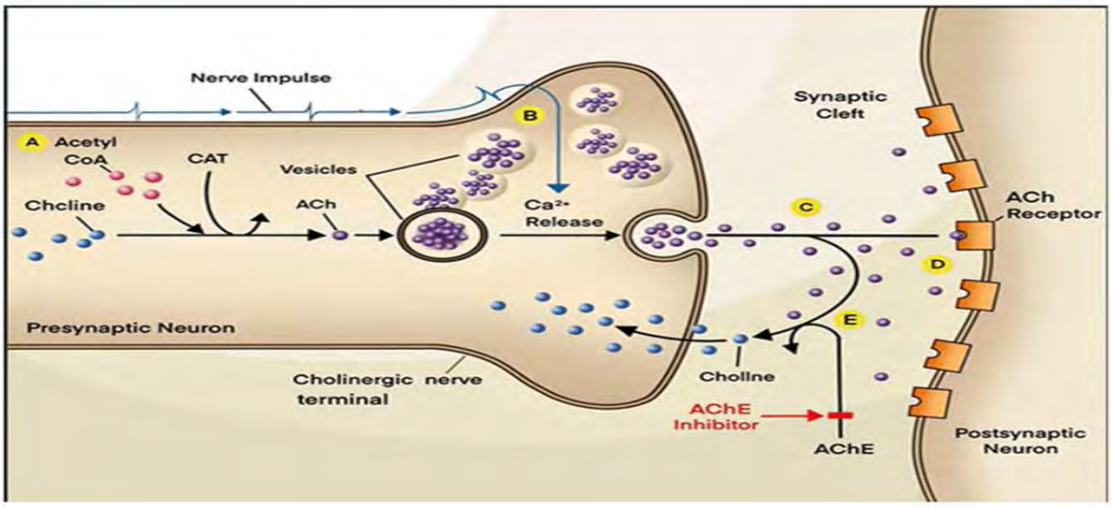
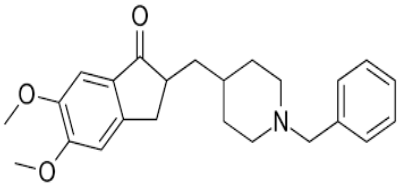
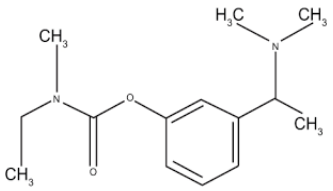


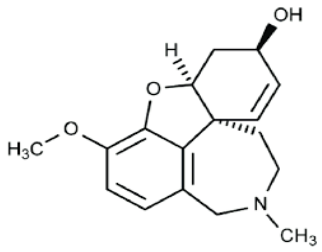
Figure 8: Schematic diagram indicating the sequential steps following which ACh is synthesized and metabolized and the action of AChE inhibitor (Chen et al., 2022).

As shown in figure 8, ACh produced from the presynaptic membrane is rapidly broken down into choline by AChE in the synaptic cleft and re-ingested by the presynaptic neuron to produce more

acetylcholine. But this further decreases the amount of already less Ach level in the CNS of AD. Therefore, the process of Ach being hydrolyzed is inhibited by Acetylcholinesterase inhibitors (AChEIs). And subsequently raise the concentration and duration of action of Ach in the CNS (Mbbs, 2021). The FDA approved acetylcholinesterase inhibiting drugs are Donepezil, Rivastigmine, and Galantamine (Hansen et al., 2020).

Table 1: *Approved acetylcholinesterase inhibitor drugs for Alzheimer's disease.*

Name of the drug	IC_{50} Value	Limitations
Donepezil  Approved by FDA in 1997 Company-Eisai	IC_{50} = 5.7 nM	Lacks data on the long-term effect of the drug. Research showed that rate of donepezil discontinuation is very low in patients with severe dementia. Also, withdrawal of the drug resulted in faster behavioral problems (32%), functional decline (26%), increased caregiver burden (22%), and lower quality-of-life by 17% (Adlimoghaddam et al., 2018).
Rivastigmine  Approved by FDA in 2000 Developed by- Mart Weinstock-Rosin	IC_{50} = 5.5 µM. IC_{50}= 4.15 µM (AChE) IC_{50}= 37 nM (BuChE)	Only manages the signs and symptoms of Alzheimer's, such as disorientation and memory loss; cannot reverse Alzheimer's. The transdermal patch delivery system causes allergic reaction. (Patel & Gupta, 2020).

Galantamine  Approved by FDA in 2004 Company- Johnson & Johnson Pharmaceutical.	IC_{50} = 0.31 µg/mL (AChE) IC_{50} = 9.9 µg/mL (BuChE)	A large number of side effects. It extends the effect of succinylcholine-type and other neuromuscular blocking medicines. Worsen bladder outflow obstruction in people with prostatic hyperplasia (Kalola et al., 2024).

Donepezil is a piperidine type noncompetitive reversible inhibitor of acetylcholinesterase. It inhibits the hydrolysis of acetylcholine after being released from the pre-synaptic neuron, which increases the amount of acetylcholine available for enhanced cholinergic transmission (Kumar et al., 2023). It is short acting and when taken orally and has a bioavailability close to 100%. According to table 1, the IC_{50} of donepezil is only 5.7nM that mean it will only 5.7 nM donepezil to inhibit acetylcholinesterase function by half (Marucci et al., 2021). Moreover, Donepezil increases neural plasticity, decrease pro-inflammatory cytokines and increase blood flow in the brain. It also lowers excitotoxic injury, amount of amyloid precursor protein (APP), and manages oxidative stress. (Jacobson and Sabbagh, 2008).

Rivastigmine is a noncompetitive pseudo-irreversible carbamate Acetylcholinesterase inhibitor. It inhibits both AChE and BuChE and promotes cholinergic neurotransmission unlike donepezil which only inhibits AChE. Furthermore, rivastigmine is attached to the active centre of AChE more firmly than a naturally occurring choline ester, in contrast to donepezil (Birks et al., 2015). It is an intermediate acting drug with oral bioavailability 36% for 3 mg dose (Jann 2000) and there

is little chance of drug-drug interaction (Grossberg 2000). Several studies have shown that the inhibition of both AChE and BuChE is important in the pathophysiology and pharmacological treatment of AD. So, the dual inhibition may offer additional benefits (Kandiah et al., 2017). But as shown in table 1, the IC_{50} of rivastigmine is more than both donepezil and galantamine. So, rivastigmine needs to be administered in higher dose/amount to be as potent as the other two AChEIs. Also, rivastigmine has also been linked with an increased risk of mortality compared to patients treated with donepezil long-term use (Patel & Gupta, 2020).

Galantamine belongs to the tertiary alkaloid class which works as a reversible, competitive inhibitor of acetylcholinesterase (AChE).

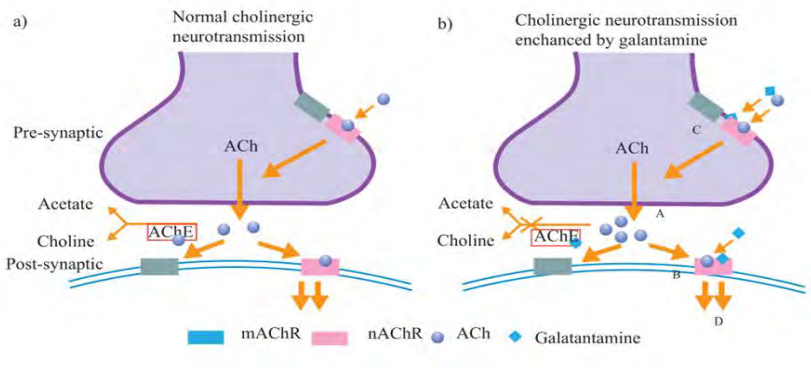


Figure 9: AChE inhibition, nAChR modulation and correction of the cholinergic deficit by galantamine (Lilienfeld, 2002).

As shown in figure 9, galantamine acts as an allosteric modulator when it binds with the nicotinic acetylcholinesterase receptors (nAChRs) in the presynaptic neuron and make it more receptive to acetylcholine. (Lilienfeld, 2002). Short acting, good pharmacokinetic properties, bioavailability of 90%, consistent linear elimination, potentially harmful drug interactions are minimal (Lilienfeld,

2002). According to the IC_{50} value mentioned in table 1, Galantamine is by far the most potent inhibitor of acetylcholinesterase (HV et al., 2020). But Galantamine has a large number of side effects such as- it can induce bronchospasm, so it cannot be used for patient suffering from severe asthma or chronic obstructive lung disease. It also causes drug-drug interaction with cholinergic drugs (Kalola et al., 2024).

Moreover, results from different research and clinical trial suggests that galantamine is slightly less efficacious than donepezil and rivastigmine. Also, donepezil has the lowest occurrence of adverse effects while rivastigmine has the highest (Hansen et al., 2008). Despite the potency of these approved AChEIs, only works to alleviate the cognitive symptoms of Alzheimer's disease, it does not modify/ reverse the disease, neither does it address other pathological process of AD except choline deficit.

3.1.2 NMDAR antagonist

The N-methyl-D-aspartate (NMDA) receptors has many vital functions in the nervous system like synaptic transmission and synaptic plasticity which is considered to have an effect on learning and memory and also critical for the activity and development of the nervous system. But NMDA receptors are also observed to be involved with neurotoxicity. Recent research has linked the over activation of NMDA receptor with synaptic impairment and progression of Alzheimer's disease (Liu et al., 2019). A substantial amount of research indicates that excitotoxicity and neurodegenerative diseases are patho-physiologically related to dysregulation of glutamate. As a result, glutamate NMDARs have become significant targets for AD treatment. Glutamate is the primary excitatory neurotransmitter in the brain is mediated by a number of glutamate receptors to cause excitatory postsynaptic transmission. There are three kinds of glutamate gated ion

channels and among them the ion channels connected to classical NMDARs are often the most permeable to Ca^{2+}. Glutamate released from presynaptic neurons binds to the receptors in the cell membrane of the postsynaptic neuron which causes positively charged Na+ ions to enters the postsynaptic neuron, resulting in a brief depolarization called excitatory postsynaptic potential. And the glutamate present in the synapse remove the Mg2+ blockage of the NMDAR and enabling Ca2+ to enter the cell (Olivares et al., 2012). Although high glutamate levels cause NMDAR to become overactivated, which increases the quantity of Ca2+ that enters the nerve cell. Multiple brain diseases are associated with NMDAR overactivation. Excitotoxicity is brought on by this high activity, which also increases p-Tau, neuroinflammation, OS synthesis, and neuronal death (Companys-Alemany et al., 2020).

Excessive calcium influx in the cell influences AD pathology following four different pathways:

- Excessive calcium influx results in calcium homeostasis disturbance, which leads to neuronal cell necrosis, damage and impairment.
- Higher intracellular calcium concentrations facilitate Aβ to be deposited.
- An excess of intracellular calcium results in aberrant tau phosphorylation and damages tau's ability to link to microtubules, which leads to the creation of neurofibrillary tangles.
- A calcium homeostasis issue causes impaired brain synaptic plasticity, which is linked to cognitive decline in AD patients.

Furthermore, moderately elevated intracellular calcium concentrations stimulate cell division but if the concentration of calcium in the mitochondria is very excessive then it triggers the release of pro-apoptotic proteins that encourage cell death. (Ge et al., 2022).

Memantine

Memantine is a a low-affinity, uncompetitive NMDAR antagonist was approved by FDA in 2003 to treat moderate-severe Alzheimer's. Forest Laboratories Inc. made the first memantine tablet Namenda to be approved in the USA. Memantine's ability to prevent Aβ pathology and recover memory deficits was established by its ability to reduce NMDAR overactivation and inhibit extra-synaptic NMDARs before synaptic ones. Furthermore, memantine has been shown to have an impact on a number of additional AD-related processes, including tau hyperphosphorylation and apoptosis by blocking the excessive influx of calcium inside the neural cell and also mitochondria (Johnson & Kotermanski, 2006).

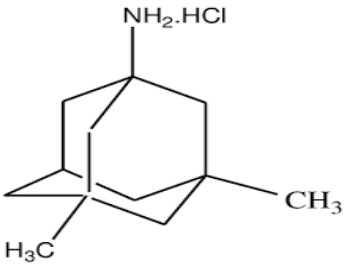


Figure 10: Structure of Memantine

As shown in figure 11, memantine works by inhibiting NMDA receptors which are voltage-gated cation channels, and this inhibits the overstimulation of the receptors and lowers the amount of calcium that enters the cells. Eventually preventing the array of pathological activity that occurs due to the high concentration of calcium inside the cell. The IC_{50} value of memantine as an NMDA antagonist is 112–173 ng/ml (Traynelis et al., 2010). When used orally, the medication has a linear pharmacokinetic profile and is easily absorbed through the digestive system. This drug is usually well tolerated and has shown good clinical efficacy in a number of randomized studies. Common

side effects are- fatigue, problems with bowel movement, agitation, urinary system inflammation and dizziness (Singh et al., 2024).

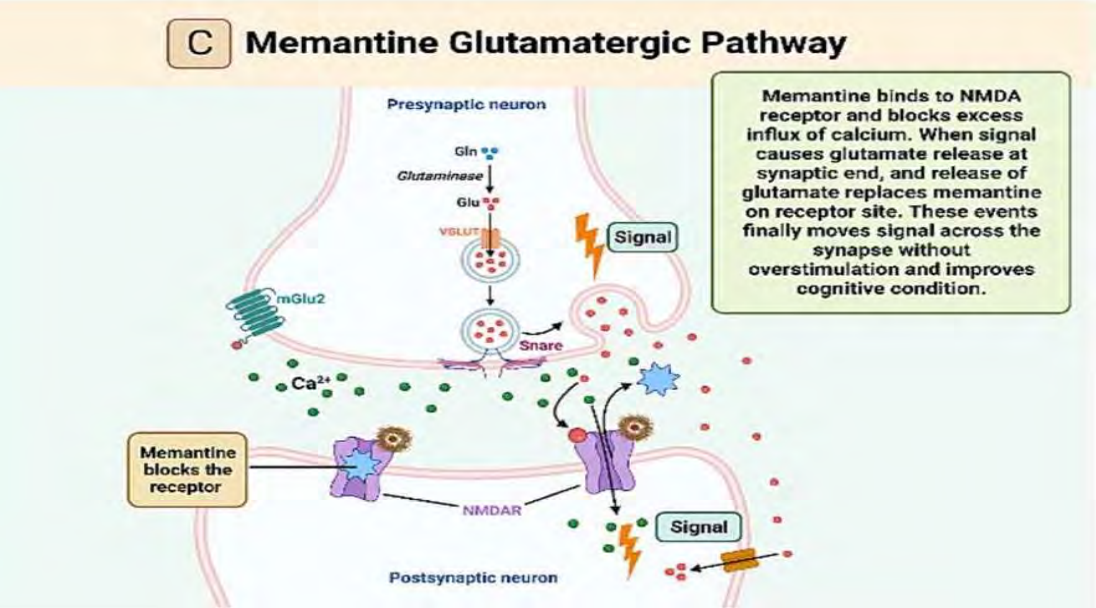


Figure 11: The mechanism of action of Memantine (Singh et al., 2024).

Memantine clearance is reduced by around 80% in alkaline urine conditions at pH 8, hence raising the pH of urine to an alkaline state may cause the drug to accumulate and perhaps intensify its negative effects. So, medications like sodium bicarbonate and carbonic anhydrase inhibitors that alkalinize urine should not be taken with memantine. Since there haven't been any documented drug-drug interactions between memantine and ChEIs, they can be used together without risk (Tampi & van Dyck, 2007).

Combination Therapy

The neuropathological aspects of AD are directly linked to how it is treated. Acetylcholine deficiency, glutamate excitotoxicity, extracellular accumulation of amyloid-β plaque, formation of

intraneuronal neurofibrillary tangles (NTFs), and neuroinflammation are the five neuropathological characteristics of AD. But one of the drawbacks of memantine is it can only reduce glutamate excitotoxity among the five neuropathological hallmarks of the disease. So, it can be understood that memantine's efficacy in treating AD can be improved or complemented by the addition of additional medications that can influence the neuropathological aspects of the disease. Such as combination therapy of memantine with donepezil which is an acetylcholinesterase inhibitor (Tang et al., 2023).

3.1.3 Anti-amyloid antibodies:

The approval of anti-amyloid monoclonal antibodies (mABs) and their inclusion into clinical treatment are redefining the field of Alzheimer's disease (AD) therapy (Cummings, 2023). Anti-amyloid antibodies are the first disease-modifying treatments for Alzheimer's disease (AD) that reduce clinical decline by affecting the condition's underlying cellular processes (Song et al., 2022). A lab-made antibody is called a monoclonal antibody, which adheres to and destroys targets inside the body. Anti-amyloid medications aids in reducing the brain's beta-amyloid concentration by targeting the amyloid beta protein and it is assumed that clearing plaques will prolong the normal function of brain cells. Donanemab (Kisunla) and lecanemab (Leqembi) are the two anti-amyloid antibody medications that are currently available. Aducanumab a third anti-amyloid, was approved by FDA in 2021; however, the manufacturer removed it from the market at the beginning of 2024 (Langmaid, 2023).

The mechanism of Aβ plaque reduction for all mABs is thought to involve microglia activation through fibrillar Aβ phagocytosis and eventually destroying the amyloid plague by endosomal/lysosomal system. As shown in figure 12, that lecanemab (Leqembi) clears amyloid

plaque with the help of activated microglia. Every approved monoclonal antibody targets a particular form of Aβ species. Donanemab targets pyroglutamate Aβ, while lecanemab targets protofibrils (Cummings et al., 2023).

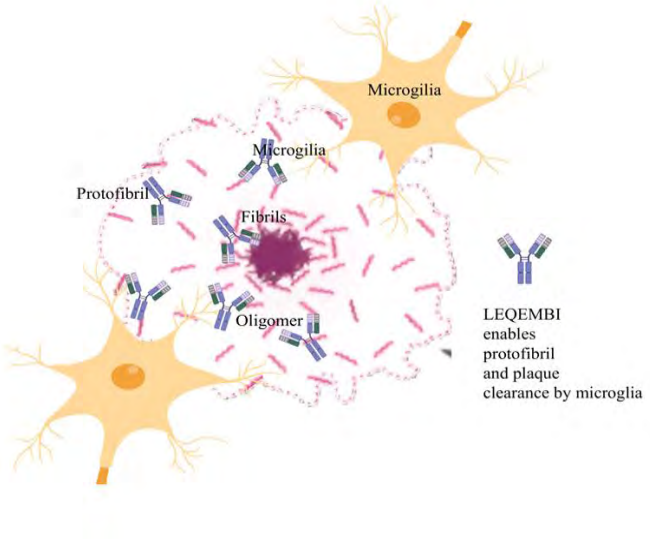


Figure 12: Mechanism of action of LEQMBI (lecanemab) by activating microgilia (Cummings et al., 2023).

Table 2: List of FDA approved Anti-amyloid antibodies for the treatment of AD

Name of the drug	**IC_{50} Value**	**Limitations**
Lecanemab Approved by FDA in July 2023 Made by the drug company Eisai	IC_{50} = 0.3 nM	Not enough data regarding the long-term efficacy and safety of the medication. Very high price, Infusion-related reactions Amyloid related imaging abnormalities (ARIA) (Chowdhury & Nurjahan Shipa Chowdhury, 2023).
Donanemab Approved by FDA in July 2024 Made by the company Eli Lilly	IC_{50} = 0.1-1 nM depending on the form of the targeted Aβ.	the long-term effect of donanemab is not well researched and documented (Sims et al., 2023). Effect of drug in people carrying ApoE4 is not studied (Rashad et al., 2022).

The first drug mentioned in table 2, lecanemab mainly targets soluble Aβ protofibrils but it also targets insoluble fibrils but mainly targets soluble (Chowdhury & Nurjahan Shipa Chowdhury, 2023). Lecanemab has the highest affinity for selectively binding with soluble Aβ aggregates including oligomers and protofibrils (Zhao et al., 2023). Extracellular amyloid-β (Aβ) plaques are characteristic to the pathogenesis of Alzheimer's disease (AD), and also Aβ plaques varies how they will affect the disease progression according to different properties such as composition, solubility and quantity (Lecanemab, 2023)

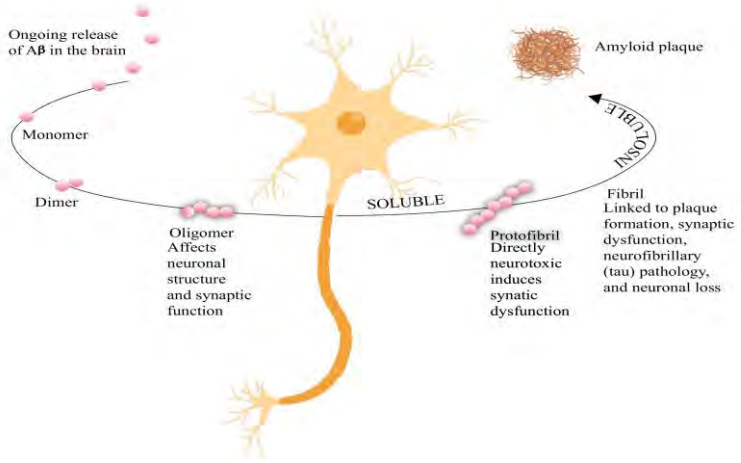


Figure 13: Different composition of the Amyloid Plaque (Mechanism of Action | LEQEMBI® (Lecanemab-Irmb), 2023).

Here, the Aβ protofibrils which are soluble aggregates are far more neurotoxic than monomers or insoluble fibrils. And Lecanemab particularly targets protofibrils, so it helps to lower the neurotoxic effect of amyloid beta plague in the brain drastically (Murphy & LeVine, 2010). To evaluate the efficacy of lecanemab a trial was conducted with 1795 patients having early-stage symptomatic Alzheimer's. And after the trial it was observed that, 18 months of treatment, lecanemab delayed clinical decline by 27% as compared to those who received a placebo (Lecanemab, the New Alzheimer's Treatment: 3 Things to Know, 2023). But lecanemab has some

drawbacks too like inadequate data on long-term effects, several sides effects like lymphopenia, rash, and Atrial Fibrillation (Leqembi (Lecanemab) Dosing, Indications, Interactions, Adverse Effects, and More, 2024).

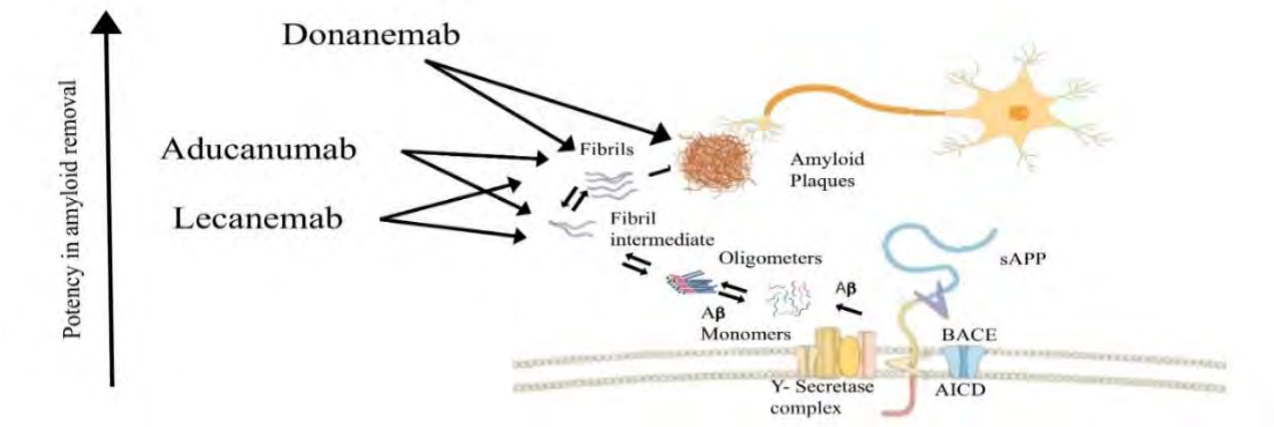


Figure 14: Mechanism of action of all the Anti-amyloid antibodies (Chowdhury & Nurjahan Shipa Chowdhury, 2023).

Donanemab particularly targets pyroglutamated type of Aβ (N3pG-Aβ) that aggregates in amyloid plaques. Due to its high toxicity and hydrophobicity, the shortened form of Aβ promotes quicker aggregation, stabilization of the β-sheet, and resistance to degradation. Donanemab's specificity makes it possible to bind these stable plaques efficiently, resolving the problem of soluble Aβ forms that may make it difficult to recognize deposited forms (Zhao et al., 2023). After carrying out a trial for 18 months to determine the efficacy of Donanemab it was observed that the drug reduces the risk of the disease moving on to the next clinical stage by up to 39% and also decrease

the speed of cognitive and functional decline by up to 35%. In addition, it is observed at the end of a 18 months study that Donanemab (Kisunla) has decreased the amyloid plaque by 84% of the amount that was seen in the beginning of the study (saha, 2024). But donanemab also have some side effects such as-intracerebral hemorrhage, ARIA identified by magnetic resonance imaging (MRI), infusion-related inflammation, hypersensitivity, imbalance in mortality (Buracchio, 2024). In figure 14 shows the different structure and stage of amyloid protein on which the anti-amyloid antibodies works and it also shown that donanemab have a higher potency than lecanemab this can due to the smaller IC_{50} value of donanemab (0.1-1nM) than lecanemab (0.3nM) as shown in table 2.

3.2. Potential Drugs for the treatment of Alzheimer's disease

There are many emerging drug candidates for the treatment of AD recognized in the Common Alzheimer's Disease Research Ontology (CADRO) including BACE1 inhibitors, tau protein-targeted inhibitors, apolipoprotein E 4 (APOE4) gene, lipids and lipoprotein receptors, neurotransmitter receptors, mitochondrial function, anti-inflammatory strategies, oxidative stress and many more (Cummings et al., 2023).

3.2.1 BACE 1 Inhibitors

β-site APP cleaving enzyme 1 (BACE1) and γ-secretase catalyze the proteolytic cleavage of amyloid precursor protein (APP) to create Aβ (Das & Yan, 2019). The fragmentation of APP by BACE1 functions as the step which regulates the rate at which Aβ is produced (Hampel et al., 2020). In several BACE 1 knockout mice model it is seen that mice lacking in BACE1 exhibit a reduced ability to produce Aβ (Cole & Vassar, 2008). Therefore, pharmacologically BACE1 has

been targeted, and a number of inhibitory drugs are now in clinical research and trials to effectively lower Aβ amounts in humans (Hampel et al., 2020). In addition to that several clinical trial for evaluating the inhibitory effect of BACE is carried out in rat and mouse. Because 96% amino acid sequence in the BACE1 orthologs in rat and mouse is identical with the human BACE protein (Hampel et al., 2020).

The generation of Aβ starts by following the amyloidogenic pathway where APP is cleaved at the Asp+1 residue of the Aβ sequence by BACE1 to form the N-terminus of the peptide. This fragmentation releases a APP ectodomain, APPsβ and a membrane-bound carboxyl terminal fragment (CTF), C99. γ-secretase then cleaves C99 to produce the APP intracellular domain (AICD) and the C-terminus of the Aβ peptide (Cole & Vassar, 2007). Following secretion, Aβ peptides oligomerize into several soluble species before changing into protofibrils and cross-β-sheet fibrils, which eventually form amyloid plaques. The harmful effects of Aβ aggregates are mediated by tau protein interactions (Zhang et al., 2023).

BACE1 is a type I membrane protein that initiates the peptide bonds hydrolysis in proteins using 2 aspartic acid residues in its active site. Furthermore, the two-lobed structure of the protein's extracellular catalytic domain is known as BACE1's bi-lobal structure and the enzymatic activity of aspartyl proteases is dependent on this structure. Additionally, the crucial aspartic acid residues that comprise the active site of the enzyme are included in the DTG (Asp-Thr-Gly) and DSG (Asp-Ser-Gly) motifs, which are particular sequences within the enzyme. These motifs are essential to BACE1's proteolytic action (Willem et al., 2009).

The crystal structure of BACE1 have proteolytic pockets that can contain 11 protein residue, so this make the BACE1 structure larger and less lipophilic (Turner et al., 2001). So, due the structure

of BACE1 it becomes more difficult to develop small molecules that can enter the brain (Yan, 2016). For BACE1 inhibitors to be effective it should be able to cross the blood-brain barrier, so that it can exert its inhibitory effect in the brain mostly in neuronal cells, and is easily identified in presynaptic hippocampal mossy fiber terminals (Kandalepas et al., 2013). So, the development of brain-penetrant, selective, orally bioavailable BACE1 inhibitors has face many challenges and drawbacks over the past 20 years. Small-molecular BACE1 inhibitors were innovatively designed following the advancements in the application of "fragment-based drug discovery" for BACE1 inhibitors, and they are currently undergoing trials in humans and animals. (Rollenhagen et al., 2007).

Table 3: List of compounds that can be developed into BACE1 inhibitor drugs for the treatment of AD

Name of the Compound	Clinical trial Status	Adverse effects	IC50 Value
Verubecestat	It was terminated in February 2018, before Phase III trial because the molecules can significantly reduce Aβ40 and Aβ42, in the cerebrospinal fluid but it was not effective in reduce the amyloid beta plaque load.	Hair depigmentation Worsen the cognitive symptoms in people with prodromal AD	IC_{50} = 13 nM
Lanabecestat	It was terminated before phase 3 trial because it did not meet the initial endpoint and lack efficacy.	Hypopigmentation of hair and skin.	IC_{50} = 450 nM (Sakamoto et al., 2017)
Atabecestat	Early phase 2 and 3 trial is going on and long-term phase 2 trial is terminated due to hepatic toxicity.	Shows unfavorable benefit to risk ratio in patient with severe liver injury.	IC_{50} = 1060 nM (Rampa et al., 2016)
Elenbecestat *This compound do not show any indication of liver toxicity.	Phase III trial is ongoing in patient having mild AD. It was observed following the 18-month-long phase 2 trial that the decline in cognitive function was less and also there was significant reduction in Aβ levels, in patients with mild to moderate AD.	Insomnia, Contact dermatitis, upper respiratory tract infection, nightmare,	IC_{50} = 46 nM (Pratsch et al., 2023)

CNP520 *Liver toxicity, depigmentation of hair, cardiovascular impairments were not observed in toxicology report	Phase 2 and 3 clinical trials are ongoing. A recently published study showed in case of rats and dogs there is a significant reduction of free and CSF Aβ levels, along with reduction of Aβ plaque in transgenic mice.	Upper respiratory tract infection, depression, anxiety, agitation, weight loss.	IC_{50} = 11 nM (Neumann et al., 2018).

So, according to the table 3, many of the compounds are discontinued from clinical trial because of lack of efficacy and excessive toxic effects. Also, the lack of selectivity towards the target molecule is also a limitation. Such as- Lanabecestat cause hypopigmentation of skin and hair because it also inhibits BACE 2 enzyme (control the pigmentation of epidermis and hair) along with BACE1 enzyme (Yan, 2016).it is seen that only Elenbecestat and CNP520 is showing promising results in the clinical trial and safety profile of the drugs are also satisfactory so far. So, these two drugs have the likelihood of becoming a future therapeutic strategy for Alzheimer's disease.

3.2.2 TNF-α inhibitors

Data derived from studies indicates that cytokine-mediated neuroinflammation might play a primary factor in the development and stimulating the pathogenic mechanism of Alzheimer's disease (Akiyama et al., 2000). Tumor necrosis factor α (TNF-α) is the most researched cytokine implicated in neuroinflammation because several animal and clinical studies have established a connection between excessive brain TNF-α levels and AD because level of TNF-α in the CNS of an AD patient is much higher than the level present in a healthy adult's CNS (Chang et al., 2017). A large number of evidence suggests that abnormalities in TNF-α signaling due to genetic and

pharmacological factors increases both tau and Aβ problems in vivo. Moreover, anti-inflammatory therapeutic strategies have reduced brain damage and improve cognitive functions in mice models. Also, animal and human clinical studies shows that cognitive decline is slowed by TNF-α inhibitors (Decourt et al., 2016). Some of the drugs that are being investigated and clinically trialed as potential TNF-α inhibitors (TNFIs) for Alzheimer's disease are- etanercept, monoclonal antibodies like infliximab and adalimumab (Torres-Acosta et al., 2020).

Table 4: An overview of studies on using TNFIs to inhibit brain TNF-α in AD patients.

TNF Inhibitors	IC_{50} value	Therapeutic effects
Etanercept	IC_{50} = 22.7 µg/mL (Lon et al., 2011)	Improvement in cognitive functions (Tobinick et al., 2006).
Adalimumab	IC_{50} = 0.1-0.2 nM (Thorlund et al., 2014)	Cognitive improvement, reduces neuroinflammation (Park et al., 2019).
Infliximab	IC_{50} = 0.1-0.3 nM (De Vries et al., 2012)	Decrease in the level of Aβ and tau in brain and improvement in cognitive function (Shi et al., 2011).

As mentioned in table 4, etanercept improves cognitive function by inhibiting TNF-α because this drug mimics the extracellular ligand binding region of the TNF-α receptors and binds with TNF to inactivate it. On the other hand, the monoclonal antibodies like Adalimumab and Infliximab directly attaches with TNF-α and prevent it from binding to the TNF receptors to exert their inflammatory effects (Torres-Acosta et al., 2020). Moreover, in a study done on mice injected with Aβ1-40 protein it was seen that adalimumab decreases the neuronal loss more than infliximab. Adalimumab also decreases BACE1 protein expression and amyloid beta plaque in the mice.

Therefore, it was suggested that adalimumab can be more effective for older patients with AD (Park et al., 2019).

From the early 1990s, it is suggested that that is a link between AD and the treatment of rheumatoid arthiritis (RA) because it has been observed that RA patient receiving long term treatment with non-steroidal anti-inflammatory agents have a remarkably lower chance of developing AD (Gianfranco Ferraccioli et al., 2012). Among patients with RA the prevalence of AD is decreased by 72%, 66%, and 48%, through treatment with adalimumab, etanercept, and infliximab respectively. Likewise, inpatient with psoriasis, etanercept and adalimumab reduced the possibility of Alzheimer's disease by 53% and 59%, respectively (Iqra Mumal, MSc, 2020).

But there are some drawbacks of using these drugs for the treatment of AD. One of the obstacles in the further development of TNF-alpha inhibitors for AD is the limited blood-brain barrier (BBB) penetration due to the larger molecular weight of the monoclonal antibodies used for TNF-α inhibition and invasive delivery methods which might not be safe for long-term AD dosage (Boado et al., 2010). Also, etanercept shows various side effects such as- lupus, lymphoma, and congestive heart failure (Torres-Acosta et al., 2020). Furthermore, TNFIs requires larger randomized controlled trials (RCT) to confirm the encouraging results observed in small open-label trials (Chang et al., 2017). Although the molecular size of etanercept is too large to pass the BBB and directly affect the cerebral tissue, it can still lower the peripheral TNF and reduce systemic inflammation and this can indirectly lower the TNF-α levels in the brain (José Manuel Carrascosa & E Del-Alcazar, 2018).

3.2.3 Tau Protein-Targeted Therapies

In a normal adult brain, the primary Microtubule Associated Protein (MAP), tau helps to assemble the tubulin to form microtubule structure and stabilize it. Whereas an AD patient has 3 to 4 times more tau protein in their brain then the normal level. It eventually causes the tau to polymerize into paired helical filaments (PHF) mixed with straight filaments (SF), which forms neurofibrillary tangles (Iqbal et al., 2010). And these pathogenic effects of tau's aberrant hyperphosphorylation ultimately result in neurodegeneration (Muralidar et al., 2020).

Research has shown that different tau protein kinase is heavily linked with tau phosphorylation. That is why tau protein kinase inhibitor like glycogen synthase kinase-3 inhibitor (GSK-3) is being largely investigated to develop it as a therapeutic strategy for AD. Moreover, tau aggregation inhibiting agents, microtubule structure stabilizing agent and immunotherapy is being researched to develop anti-tau drugs (Pluta and Ułamek-Kozioł, 2020).

Table 5: List of potential compounds that can be developed as anti-tau drugs for AD

Name of the Compound	IC_{50} Value	Observed beneficial effects
Phase 1		
BIIB076 passive immunotherapy	IC50 = 0.15 μM, Tau protein (Wischik et al., 2013)	Reduction in both free and Cerebral Spinal Fluid (CSF) tau levels (Nadia El Kadmiri,2024).
ACI-35 active immunotherapy	No reported IC50 value (BioSpace, 2024)	Does not show any non-target inflammatory response and reduces soluble tau (Hung & Fu, 2017).

Phase 2		
Tideglusib	IC50 = 0.73 nM, GSK-3 (Karimi et al., 2022)	Decreases tau phosphorylation, Inhibits GSK-3 irreversibly, but shows no clinical benefits (Lovestone et al., 2015).
Nilotinib	IC_{50} = less than 30 nM, c-Abl tyrosine kinase	Proven to be well-tolerated and safe in patients with mild to moderate AD (Turner et al., 2020).
Epothilone D	Clinical trial was discontinued for adverse effect	There were no clinically effective changes in tau protein pathology of the mice used in the study (Zhang et al., 2012). (Khodakiya et al., 2024).
AADvac1 active immunotherapy	IC_{50} = 3.29 μM, Tau protein (Novak et al., 2016).	Remarkable behavioural improvement, inhibition of tau aggregation and reduction in the formation of NFT (Nadia El Kadmiri, 2024).
Gosuranemab passive immunotherapy	IC_{50} = 60 pM, Tau protein (Sopko et al., 2020).	Although found to be well-tolerated and safe in phase 1 trial, no reduction in the biomarker of AD was observed (Peng et al., 2023).
Semorinemab passive immunotherapy	IC_{50} = 60 pM, Tau protein (Sopko et al., 2020)	Results from phase 2 clinical trial shows improvement in the symptoms of AD patients (Teng et al., 2022).
Phase 3 ongoing		
Methylthioninium chloride	IC_{50} = 0.15 μM, Tau protein (Wischik et al., 2013)	No clinical benefit was observed in phase 2 study (Tucker et al., 2017). Phase 3 trial is ongoing with older patient having mild to moderate AD (Hashweh et al., 2020).

Research has shown that GSK-3 can be an encouraging disease-modifying therapeutic strategy for AD, because it can reduce the production of amyloid protein and hyperphosphorylated tau both in vivo and in vitro. (Wegmann et al., 2021) As mentioned in table 5, Tideglusib is a GSK-3 inhibitor but it has shown no significant clinical efficacy and also have several side effects like

gastrointestinal symptoms (Karimi et al., 2022). Nilotinib is also a kinase protein inhibitor (table 5), which can pass through the blood brain barrier (BBB), so it can contribute in decreasing amyloid and tau aggregation in the brain (Pluta & Ułamek-Kozioł, 2020). It has also been established that lithium inhibits GSK3, which helps alleviate AD symptoms. But prolonged use of therapeutically available lithium causes significant adverse effects. So, it is required to develop a safer and more potent lithium that can be used for the treatment of AD (Luca & Luca, 2022).

Epothilone D works as a microtubule structure stabilizer by crossing through the BBB and increasing the density of microtubules (table 5). In transgenic tauopathy mouse model, it is found that epothilone improves their cognitive ability (Brunden et al., 2010). But there was no data/result was published regarding the clinical trial of Epothilone for the treatment of AD (Peng et al., 2023).

Methylthioninium chloride can reduce tau aggregation in brain. Though this compound has not shown satisfactory result in phase 2 of the clinical trial, but the phase 3 clinical trial is still ongoing (table 5) and it would be a remarkable breakthrough for the treatment strategy of AD. Because it is evident from research that methylthioninium can readily pass the BBB and stops the accumulation of tau protein in cells, animal models, and vitro (Peng et al., 2023).

Moreover, it is seen in table 5 that active and passive immunotherapy is being critical investigated to develop anti-tau drugs and although the clinical trial of tau protein targeted immunotherapies is in their early stage they are showing promising results.

3.2.4 ApoE4 Modulation

Among several genetic risk factor, Apolipoprotein E (ApoE) gene is the most significant gene to develop the risk of AD. ApoE gene encodes three subtypes of ApoE they are ApoE2, ApoE3, and ApoE4, respectively. It is found that E2 and E4 increases plasma triglyceride concentration which

contributes in the process of lipid metabolism (Zhang et al., 2023). Despite being the most prevalent ApoE3 is not linked to AD rather ApoE4 possess the highest risk for Alzheimer's. Phospholipids and cholesterol are transported throughout the body by ApoE protein. As suggested by recent studies, abnormalities in the method in which brain store and process lipids might be significant in the progression of Alzheimer's disease (Bryant, 2021). Moreover, impaired learning and memory function, neuronal damage and neuroinflammation can be caused due to ApoE4 induced Aβ and tau protein pathologies in the neuron (Flowers & Rebeck, 2020). Within ApoE, has two structural domain C-terminal and N-terminal where a low-density lipoprotein receptors (LDLR) binding site is located. The three common ApoE isoforms have difference in only two protein residues. Apoe3 have cystine in 112 position, whereas ApoE4 have Arg in 112 position. And this variation can change the interaction between the two domains in ApoE (Loch et al., 2023).

Table 6: List of ApoE4 modulating drug candidates for potential therapeutic strategy for AD.

Potential drug candidates	**Mechanism**	**IC_{50} Value**	**Beneficial effects observed**
ApoE 133-149	ApoE mimetic peptide	IC_{50} =10 μM	Reduces the release of TNF at 10 μM and through NMDAR inhibition prevents murine neuronal (Christensen et al., 2011).
CN-105	ApoE mimetic peptide	No direct value of IC_{50} is available (Saleh et al., 2022).	In a transgenic mouse model reduces beta amyloid protein, restores spatial memory after treatment with 4mg/kg s.c for 40 days (Krishnamurthy et al., 2020). It is well-tolerated in healthy volunteers and shows very few side effects such as -headache and slow heartbeat (Li et al., 2022).

PH002 (phthalazinone derivatives)	ApoE4 structure correcting small molecule	IC_{50} = less than 10 μM (Taheri et al., 2022)	Facilitates the growing of neurite in the hippocampus of injected mouse. Decreasing the production of fragment derived from ApoE4 decreases the accumulation of amyloid beta and increases GABA neuron density (Wang et al., 2018).
HAE-4 antibody	Anti-ApoE4 monoclonal antibodies	IC_{50} is not documented in public clinical trial data (Bhandari, 2021)	Regulates the damage down by inflammatory pathways by downregulates gene expressing proinflammatory cytokine and microglia (Poblano et al., 2024).
ApoE4 antibody (7C11)	Anti-ApoE4 monoclonal antibodies	IC_{50} = 6.7 nM	Lessens ApoE4 mediated neuronal cytotoxicity in neuroblastoma cells at the concentration of 6.7nM (Mariño et al., 2023).
Imipramine (antidepressant)	Potential drug targeting ApoE4	No reported IC_{50} value (Johnson et al., 2022)	Improves cognitive function and inhibits ApoE4 mediated potential Aβ aggregation (Johnson et al., 2022).
Gemfibrozil	Potential drug targeting ApoE4	Under investigation (Saleh et al., 2022)	Considerable effectiveness in enhancing memory and spatial learning in animal models, lower the rat plasma's levels of ApoE4(Luo et al., 2019).

Generally, ApoE is enzymatically cleaved into small fragment and ApoE4 is more susceptible to such fragmentation. But some of these fragments are neurotoxic whereas others are neuroprotective and inhibit the accumulation of amyloid beta. This encourages the development of ApoE4 mimetic peptides. These peptides are designed to resemble ApoE4's structure and functions without having any of its potentially harmful side effects. From table 6 it is observed

that ApoE 133-149 and CN-105 are two mimetic peptides which shows positive result in different preclinical trial (Vecchio et al., 2022).

Another approach of ApoE4 modulation is the use of small molecule compound which can modify the structure of ApoE4 to make it more similar to the less problematic isoforms like ApoE3 or Apoe3 (Williams et al., 2020). The goal is to find small molecules with the right pharmacological characteristics that can easily cross the BBB and enter into the brain, where they can interact with ApoE4 and modify its structure for beneficial effect. But more clinical trials data are required for improving safety and efficacy concerning these potential drug candidates (Poblano et al., 2024).

Table 6, shows two anti-ApoE4 antibodies that show encouraging result such as improving vascular integrity and reducing amyloid plaque accumulation. But there are still huge limitations that are need to overcome in order to optimize antibody selectivity, efficacy, and safety in clinical settings, as well as to find predictive indicators of therapy response (Poblano et al., 2024).

Repurposing drugs is becoming a critical approach to find drug molecule which already exist that can be used to change the biological effects or activity of ApoE4. Such as (table 6) antidepressant imipramine and Peroxisome Proliferator-Activated Receptors (PPRA) ligand Gemfibrozil have shown effectiveness in improving cognitive function and reducing amyloid plaque aggregation (Krass et al., 2022). Nevertheless, the inconsistent clinical trial for PPAR ligands and antidepressants is raising questions about their effectiveness in treating Alzheimer's disease (Poblano et al., 2024).

Chapter 4
Conclusion and Future Prospect

As of right now, there is no known cure for AD, almost all of the FDA approved medicines, aim to reduce symptoms and there are very few disease modifying drugs which are not very effective and do not have enough data on their safety, efficacy and long-term effect. Despite to having several beneficial effects the drugs, these drugs don't address the underlying reasons of AD (Sneh Prabha et al., 2024). Moreover, the clinical trial carried out for the development of new therapeutic drug molecules for AD remain susceptible to issues that compromises research validity (Becker et al., 2008). Recent research and clinical studies are opting to design and formulate potential drugs for AD such as-monoclonal antibodies, TNF inhibitors, BACE1 inhibitors, tau modulators, small molecules, gene therapy by understanding the molecular mechanism behind AD including accumulation of amyloid-beta and tau protein, and neuroinflammation. But as the pathological pathway following which AD progresses is not completely comprehensible despite of promising results from these investigational medications, obstacles exist in guaranteeing their effectiveness, security, and availability (Yu et al., 2021). But these investigational drugs have shown some remarkable results in the clinical trials such as-improving cognitive function, decreasing amyloid plaque and reducing inflammation. Some of the limitations of the drugs are the non-selectivity toward the target such as BACE1 inhibitors (Yan, 2016), inconsistent results from the ApoE modulating drug molecules (Poblano et al., 2024) and limited clinical trial data for different anti-inflammatory drugs (Chang et al., 2017).

Moreover, there is a second generation of medications undergoing phase 3 clinical studies, which can provide a successful Aβ-targeted therapy (Morris et al., 2012). Also, beside amyloid beta

targeted drugs, now non-Aβ therapeutics are also being developed. These include drugs focuses on reducing tau aggregration, neuroinflammation, oxidative stress, lessen ApoE4 levels, and enhance neuronal mechanism. Nasally inhaled insulin and small molecule α7 nicotinic acetylcholine receptor activators are also undergoing clinical trial. Both of which in smaller studies have been shown to improve cognition in AD, opening up the possibility for future treatment options. (Haydar & Dunlop, 2010).

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AI detection scores under 20%, which we do not surface in new reports, have a higher likelihood of false positives. To reduce the likelihood of misinterpretation, no score or highlights are attributed and are indicated with an asterisk in the report (*%).

The AI writing percentage should not be the sole basis to determine whether misconduct has occurred. The reviewer/instructor should use the percentage as a means to start a formative conversation with their student and/or use it to examine the submitted assignment in accordance with their school's policies.

What does 'qualifying text' mean?

Our model only processes qualifying text in the form of long-form writing. Long-form writing means individual sentences contained in paragraphs that make up a longer piece of written work, such as an essay, a dissertation, or an article, etc. Qualifying text that has been determined to be likely AI-generated will be highlighted in cyan in the submission, and likely AI-generated and then likely AI-paraphrased will be highlighted purple.

Non-qualifying text, such as bullet points, annotated bibliographies, etc., will not be processed and can create disparity between the submission highlights and the percentage shown.