Bio-similar drug development and accessible drugs in the market for the treatment of Alzheimer's Disease: Current status

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 (Hons.)

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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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Ethics Statement

The study does not involve any kind of animal and human trial

Dedication

Dedicated to my teachers, family, and friends.

Acknowledgement

First of all, my highest gratitude is for Almighty Allah SWT for giving me the opportunity, strength and patience to complete my project work properly. I am thankful to Dr. Sabrina Sharmin miss (Assistant Professor, Department of Pharmacy, Brac University), my respected project supervisor for her kind guidance regarding my work. Moreover, my special thanks to Dr. Eva Rahman Kabir, (Dean and Professor, Department of Pharmacy, Brac University) for giving me the opportunity to conduct my project work successfully. Lastly, my sincere gratitude is towards my parents, family and friends for their motivation and support throughout the journey.

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List of Acronyms

APP	Amyloid Precursor Protein
ApoE	Apolipoprotein E
ABCTA1	ATP Binding Cassette Transporter A1
BIN1	Bridging Integrator 1
CLU	Clusterin Gene
ESR	Estrogen Receptor Gene
ECSIT	Evolutionarily Conserved Signaling Intermediate in Toll pathway
NAAQS	National Ambient Air Quality Standards
Presenilin-1	PSEN-1
Presenilin-2	PSEN-2
VILIP-1	Visinin-like protein-1

Abstract

A decade has passed since no new Alzheimer's disease (AD) therapies were approved, even though it is the leading motive of dementia in the modern era. The community of patients with AD leads to expansion. Anxiety, anger, and inappropriate behavior, as well as sleep difficulty and psychosis are frequent symptoms of Alzheimer's disease, which is characterized by cognitive decline but also by mood and behavioral symptoms. This study aims to assemble all probable bio-similar drugs of Alzheimer's disease that predict to help slow down the disease's development. In this study, we try to express the genetic factors, environmental factors and treatment associated bio-molecular drugs. Research articles, news stories, academic papers published in journals and government websites such as PubMed were used to conduct a comprehensive literature analysis on the development and availability of bio-similar drugs to treat AD. Alzheimer's disease affects an older population, making treatment more difficult. There is currently no medicine that can prevent or cure the condition. In order to improve public health, even a slight delay in the start of symptoms might have a significant influence. Studying prospective treatments for Alzheimer's disease as the illness's incidence rises is an ongoing process for researchers.

Keywords: Senile Plaques, Alzheimer’s disease, Apolipoprotein E, Bridging Integrator 1, Drug Development, etc.

Chapter 1

1.1 Introduction

Amyloid-beta peptide (A.A.) aggregation in the medial temporal lobe and neocortical designs is the reason for Alzheimer's disease (A.D.), which is the most well-known sort of dementia (De-Paula V.J. et al., 2012). It is characterized as a constant dynamic neurodegenerative disease defined by neural plaques. Also, neurofibrillary nodus due to amyloid-beta peptide's (Aβ) aggregation in the A.D. was named after the German scientist Alois Alzheimer (J.P. B., 1985). Alzheimer's disease was to begin recognized within his brain to start with persistent, who had suffered from memory damage and personality changes before passing away when Alois Alzheimer revealed the appearance of amyloid plaques and massive damage to neurons (Cipriani G. et al., 2011). It is expressed as a chronic disease in the human brain's cerebral cortex (Terry R.D. & Davies P. 1980). Conditions like Alzheimer's disease (A.D.), pulmonary intoxications and circulatory abnormalities that reduce brain oxygen supply, vitamin B12 deficiency, tumors, nutritional deficiencies, and other conditions can cause progressive cognitive loss (Rathmann K.L. & Conner C.S. 1984). Currently, there are around 50 million Alzheimer's disease sufferers globally, with the number hoped to double every five years and reach 152 million by 2050, according to projections (Yiannopoulou K.G. & Papageorgiou S.G. 2020). Individuals, their families, and the economy are all oppressed by the burden of Alzheimer's disease, which is projected to cost the worldwide economy US$1 trillion every year. There is no known cure for A.D., while there are several therapies available that can only help alleviate the symptoms (Livingston G. et al., 2020). This study describes the recent upliftment of elements that could confine or treat Alzheimer's disease by targeting pathogenic pathways such as Aβ and tau aggregation, misfolding, and inflammation.

1.2 Rationale of the study

This study aims to assemble all probable bio-similar drugs of Alzheimer's disease that predict to help slow down the disease's development.

1.3 Aim of the project

The following are the review's goals:

- Gathering data on Alzheimer's Disease (AD) therapy.
- Figure out the bio-similar drugs of Alzheimer's disease.
- Figure out the most effective and feasible lifestyle which causes the course of AD to slow down.

Chapter 2

Methodology

Research articles, news stories, academic papers published in journals, and government websites such as PubMed were used to conduct a comprehensive literature analysis on the development and availability of bio-similar drugs to treat AD. This research examined articles from prestigious publications, including Nature, Elsevier, and MDPI. This review was also conducted using a qualitative manner. Variable clinical data that might play a vital role in the future elements of this immunotherapy, such as combination treatment, were identified by analyzing data from multiple publications.

Chapter 3

An overview on Alzheimer Disease

When it comes to Alzheimer's disease (commonly referred to by its abbreviation, AD), it's common to see it in the elderly, although it does not come with the territory of old age. Deterioration in thinking, memory, and language, personality shifts, and brain abnormalities are all hallmarks of Alzheimer's disease, which progresses over time. Capacity of doing the most usual chores is lost progressively by the people who suffer from Alzheimer’s disease. It is the most frequent cause of dementia in old age, Alzheimer's disease. There are many different types of dementia, each affecting other parts of the brain and harming everyday life. Alzheimer's disease affects just a tiny percentage of those suffering from memory loss. For those suffering from the typical brain abnormalities that identify Alzheimer's disease, the condition is "Alzheimer's disease." Damage and loss of nerve cells and connections, twisted fibers, protein clumps, and inflammation are among the brain alterations. Ten to twenty years before any symptoms arise, AD develops deep inside the brain and slowly spreads to other brain regions.

According to the Alzheimer's Association, Alzheimer's disease progresses in seven phases. There is "no impairment" in Stage 1. When a person is in the second stage of Alzheimer's, they show signs of "very slight deterioration," such as memory lapses, but no one else or a doctor can notice them. Age-related changes, not AD, may be to blame for sure signs and symptoms. When other people begin to see a person's memory issues, they are in "moderate cognitive decline" stage 3. Some, but not all, patients with modest cognitive deterioration may be diagnosed with Alzheimer's disease. Moderate to severe damage occurs in phases 4-7. The rate at which Alzheimer's disease progresses and develops differs significantly from person to

person. A medical expert's judgment is recommended when making the diagnosis to rule out other disorders that need treatment that mirror or coexist with Alzheimer's disease.

3.1 History of Alzheimer's disease

Ancient Greek and Roman physicians were well aware of the formal relationship between dementia and old age today. Alzheimer's disease is not a new ailment. However, it was the German physician Alois Alzheimer and the prominent psychiatrist Emil Kraepelin. They were the first to characterize the typical brain lesions in persons with Alzheimer's disease in the early twentieth century. Alzheimer produced a landmark study in 1907. He described the tangled fibers and clumps in the brain of a lady in her fifties who was suffering from dementia, which are today known as "neurofibrillary tangles" and "amyloid plagues."

When Robert Katzman published a significant editorial in 1976, a renowned Alzheimer's disease researcher, it catapulted the illness to the forefront of neurologic study. Alzheimer's disease had previously been regarded as a mysterious neurologic ailment. As claimed in this study, "Alzheimer's disease" and "senile dementia" are the same, and they are the most significant cause of disability and mortality in the United States. Alzheimer's disease and senile dementia have not previously been recorded as causes of death in the United States' vital statistics records.

Alzheimer's disease is becoming a more serious public health issue as individuals live longer and many countries' populations grow older. As of 2016, the Alzheimer's Association estimates that over 5 million Americans have Alzheimer's disease. For the first time since the US government started producing Healthy People reports in 1979, Healthy People 2020 includes Alzheimer's disease goals and objectives.

3.2 Neuropathology of Alzheimer’s Disease

The AD brains display two neuropathological changes: (1) positive lesions with tangles, dystrophic neurites, neuropil threads, amyloid plaques, and other deposits (Serrano-Pozo A. et al., 2011); and (2) negative lesions (due to deposition): dystrophic neurites, neuropil threads, neurofibrillary tangles, amyloid plaques, etc. Negative lesions induce atrophy of neuronal, neuropil, and synaptic fibers (caused by losses) (Spires-Jones T.L. & Hyman B.T. 2014). Additionally, neuro-inflammation, oxidative stress, and cholinergic neuron damage can all contribute to neurodegeneration (Singh S.K. et al., 2016).

3.2.1 Senile Plaques

The senile plaques are extracellular accumulates of beta-amyloid protein (A) that may be neuritic, diffuse, dense-cored, classic, or compact in form. Neuritic plaques are a kind of neuritic plaque (Cras P. et al., 1981). Accumulation of Amyloid is formed by proteolytic cleavage enzymes such as alpha- secretases and beta-secretases (APP) (D. Perl., 2010). Some of the amino acid fragments cleaved by these enzymes include Aβ40 and Aβ42 (Armstrong R.A., 2009). There are soluble oligomers and substantial insoluble amyloid fibrils that may form amyloid plaques (Chen G.F. et al., 2017), polymers that may go throughout the body. Because Aβ is involved in neurotoxicity and brain function, thick plaques in the amygdala, hippocampus and cerebral cortex may induce astrocyte and microglia activation, axonal, dendritic, and synaptic damage, as well as cognitive deficits (Tabaton M. & Piccini A. 2005).

3.2.2 Neurofibrillary Tangles (NFTs)

NFTs, which are aberrant filaments of the hyperphosphorylated tau protein that may be twisted around each other to create the paired helical filament, impact dendrites, axons, and the neural perikaryal cytoplasm (PHF). This results in the loss of microtubules and tubulin-associated proteins in the cytoskeleton (Brion J.P., 1998). Among the NFT morphological stages are the pre-tangle phase, when phosphorylated tau proteins accumulate in the somatodendritic

compartment without the formation of PHF, and mature NFTs, which are characterized by tau protein filament aggregation and displaced (Metaxas A. & Kempf S.J., 2016).

3.2.3 Synaptic Degeneration

It is common to observe memory loss in the early stages of Alzheimer's because of synaptic damage in the neocortex and limbic system. It's likely that synapse loss is caused by a variety of events that all contribute to synaptic loss, including axonal transport failures, damage to mitochondria or oxidative stress (Overk C.R. & Masliah E. 2014). The loss of dendritic spines, pre-synaptic terminals, and axonal dystrophy that these processes cause are all harmful to the brain's functions (Lleo A. et al., 2019). Biomarkers of synaptic loss and severity include synaptotagmin-1, a postsynaptic neuronal protein, VILIP-1, and neurogranin, a postsynaptic neuronal protein. Postsynaptic neuron protein Neurogranin has been connected to Alzheimer's disease (Tarawneh R. et al., G.2016).

3.3 The Phases of Alzheimer’s Disease

Pre-clinical or pre-symptomatic Alzheimer's disease may endure for many years or longer; the clinical stage can last for many years or longer. There is only mild memory damage and early evidence of Alzheimer's disease degeneration in the brain and hippocampus during this stage, with no functional impact on daily activities (Dubois B. et al., 2016). It's also the most advanced step of the process. In the moderate stage of Alzheimer's disease (AD), the infection spreads to areas of the brain that govern impulses and memory, resulting in memory loss, difficulty distinguishing between family and friends, and issues with public speaking (Apostolova L.G., 2016). There is a severe accumulation of neuritic plaques and neurofibrillary tangles in the cortex of patients with late-stage Alzheimer's disease, resulting in progressive functional and cognitive disability to the point where patients are unable to acknowledge their loved ones, are

restricted to a bed, have difficulty swallowing and urinating, and eventually die of the complication. This is the final stage of Alzheimer's disease (Wattmo C. et al., 2016).

3.4 Causes of AD

Alzheimer's disease (AD) has been linked to several risk factors, including aging, genetics, head traumas, vascular problems, infections, and environmental factors (heavy or trace metals and others). Pathological alterations linked with AD still have no known cause (such as amyloid plaques, NFTs, and synapse loss) (R.A. Armstrong., 2009). It is commonly acknowledged that a failure in cholinergic function and an impairment in amyloid-protein generation and processing are the two most probable causes of Alzheimer's disease. However, the etiology of AD is still mostly unknown at this point (Anand P. & Singh B. 2013).

3.5 Risk Factors of AD

3.5.1 Aging

Alzheimer's disease's pathological alterations are still a mystery to researchers (such as amyloid plaques, NFTs, and synapse loss) (Guerreiro R. & Bras J, 2015). Only two theories have been universally acknowledged as the most probable causes of Alzheimer's disease: a loss in cholinergic function and a modification in the generation and processing of amyloid -protein are primarily considered the most significant (Riedel B.C., 2016). The pathogenesis of Alzheimer's disease, on the other hand, has not been universally accepted at this point. One to six percent of Alzheimer's patients is diagnosed with early-onset Alzheimer's (EOAD). In most instances, Alzheimer's disease runs in families where more than one person in a generation is affected, and the average age of those affected is 30–60 or 65 years old (Hou Y. et al., 2019). Late-onset Alzheimer's disease (LOAD) is more common in those over 65 and is the second

kind of Alzheimer's disease. In families with a history of Alzheimer's disease, both the early and late forms of the disease may occur in individuals (Bekris L.M. et al, 2010).

3.5.2 Genetics

Alzheimer's disease progression may be influenced by various genetic factors that have been discovered over the years (Van Cauwenberghe C. et al., 2016). More than 70% of instances of Alzheimer's disease may be attributed to a family history of the condition. Presenilin-1 (PSEN-1), Amyloid precursor protein (APP), Presenilin-2 (PSEN-2), and apolipoprotein E (ApoE) mutations are among the most common causes of early-onset Alzheimer's disease (EOAD) (Khanahmadi M. et al, 2015).

APP: Amyloid precursor protein

Cleavage of this transmembrane protein by secretases such as alpha, beta, and gamma results in the release of Aβ as well as other proteins. Alpha, beta, and gamma secretases encode the APP gene, which is located on chromosome 21 and is responsible for the production of APP. An additional thirty APP mutations were discovered, twenty-five of which are associated with AD and result in an accumulation of Aβ in high concentrations (Li N.M. et al., 2019). Meanwhile, there is one protective mutation, A673T, that protects against Alzheimer's disease by lowering the release of Aβ, Aβ40, and Aβ42 (Tcw J. & Goate A.M., 2017). For example, animal models' KM670/671NL mutation has shown a rising level of amyloid plaques in the hippocampus and cortex with no NFTs. Still, the KM670/671NL mutation in human models has revealed an increasing amount of NFTs (Bi C. et al., 2019). The D678N, E682K, A673V, D678H, and K687N mutations have all been associated with cortical atrophy, while the E682K mutation has been associated with hippocampal atrophy (Dai M.H. et al., 2018). The existence of NFTs and A and activation of microglia and astrocytes were seen in neuropathological studies for the A673V mutation. According to neuropathological data, this is in contrast to the

other conversions, which have shown no change in intracellular A. Mutations such as L723P, V717I, K724N, V715M, T714I, V715A, V717L, and I716V influence the cleavage site of -secretase and induce an increase in the Aβ42/Aβ40 ratio, while mutations such as E693G, D694N, E693K, and A692G affect the cleavage site of beta-secretase In addition, the E693delta mutation is a deletion mutation that increases the production of synaptogenic Aβ in the brain (Zhao J. et al, 2020).

Presenilin-1 & Presenilin-2

Additionally, the PSEN1 and PSEN2 genes, noticed on chromosomes 14 and 1, cause the autosomal dominant type of EOAD (Lanoiselee H.M. et al., 2017). When compared to one another, PSEN-2 and PSEN-1 are homologous, with 67 percent similarity in their N-termini and hydrophilic regions. There are more than 200 mutations in the PSEN1 gene; however, fewer than 40 mutations in the PSEN2 gene are an uncommon version of the condition (Cai Y. et al., 2015).

It is essential for synthesizing A from APP since it is a component of the -secretase complex. PSEN1 deletion trials in mice resulted in synaptic dysfunction and memory impairment, showing that the protein plays a vital role in preserving memory and neuronal structure (B. De Strooper, 2007). Two kinds of PSEN1 mutations exist simple mutations that only change one amino acid and severe mutations that change two amino acids. PSEN1 gene mutations increase the Aβ42/Aβ40 ratio via decreasing Aβ40 levels. Compared to wild-type mice, those with the C410Y or L435F mutations in PSEN1 knock-in mice had a more excellent Aβ42/Aβ40 ratio, according to the study's results (Kelleher R.J., 2017).

When it comes to Aβ, PSEN-2 mutations are very uncommon and have only a minimal influence. PSEN-2 mutations may cause familial Alzheimer's disease is the appearance of normal PSEN-1 alleles, even if the Aβ42/40 ratio is average. The Aβ-42 and Aβ-40 ratios are

elevated in specific PSEN-2 mutations, such as T122P, M239V, N141I, and M239I, but in other cases, uncommon polymorphisms have no influence on the Aβ-42, Aβ-40, and Aβ42/40 ratio levels and are thus not deemed harmful alterations by the scientific community (Walker E.S. et al., 2005).

ApoE: Apolipoprotein E

The ApoE protein is also evolved by certain microglia in the brain and liver. Cholesterol, an essential component of myelin for proper brain function, is captured by the ApoE protein through receptor-mediated endocytosis. SNPs, which cause changes in the ApoE gene's coding sequence on chromosome 19, have resulted in three distinct ApoE isoforms, all of which are closely related: ApoE2, ApoE3, and ApoE4. In contrast, ApoEε2 and ApoEε3 alleles are linked with reduced risk and a protective effect, respectively (Kim J. et al., 2009). The ApoEε4 allele represents a significant risk factor for both early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD). ApoEε4 plays a critical role in the deposition of A in the form of a senile plaque and the development of cerebral amyloid angiopathy (CAA), which is considered a hallmark of Alzheimer's disease (Liu C.C. et al., 2013). ApoEε4 has also been demonstrated to be connected with a vascular injury in the brain, which is known to be an availing factor in the progression of Alzheimer's disease (Giau V.V. et al., 2015).

ABCA1: ATP Binding Cassette Transporter A1

As a part of the ABC transporter group, ABCA1 is responsible for regulating cholesterol efflux from the circulation and into the brain, like ApoAI and APoE. One of the ABC transporters, ApoAI and ApoE, ABCA1, regulates cholesterol efflux both in the circulation and the brain (Koldamova R. et al., 2014). In addition, ABCA1 helps maintain the stability of ApoE lipidation and acts as a fixer for the production of high-density lipoprotein, which is consistent with its function in the development of atherosclerosis and cardiovascular disease. It has been

shown that ABCA1 deficiency promotes amyloid plaque development and inhibits ApoE lipidation in studies using a mouse model of Alzheimer's disease (AD). When the ABCA1 gene mutation occurs, Tangier disease occurs in people. Deficiencies in high-density lipoprotein and ApoAI are signs of Tangier illness, as are cholesterol deposits in tissues and the onset of AD (Nordestgaard L.T. et al., 2015).

Clusterin Gene & Bridging Integrator 1

Unlike familial or early-onset Alzheimer's disease, LOAD is perceived by clusterin (CLU) and BIN1 mutations. Genome-Wide Association Studies in 2009 uncovered the CLU gene on chromosome 8 (GWAS), a possible biomarker for Alzheimer's disease, the CLU gene is elevated in the cortex and hippocampus of affected brains and AD cerebrospinal fluid (CSF) and plasma. Because of its interaction with Aβ and ability to increase clearance, the CLU has the potential to be neuroprotective. Still, it might also be neurotoxic if it inhibits Aβ release and leads to neurodegeneration. The CLU's influence on the neurological system is determined by its A-to-B ratio values. (Foster E.M. et al., 2019).

It is a Bin-Amphiphysin-Rvs (BAR) adaptor protein connected in membrane curvature and other endocytotic functions. Others are found in synaptic vesicles, where they regulate synaptic vesicle endocytosis (Holler C.J. et al., 2014). BIN1 is a BIN superfamily member. BIN1 has recently been discovered as the second most significant risk factor for LOAD, behind ApoE. It affects A production, tau pathology, and NFT pathology (Andrew R.J. et al, 2019).

ECSIT: Evolutionarily Conserved Signaling Intermediate in Toll pathway

A significant accumulation of Aβ in Alzheimer's disease brains leads to a substantial increase in protein oxidation, demonstrating the importance of mitochondria in Aβ cytotoxicity and AD pathogenesis. There is a link between an increased risk of Alzheimer's disease and the ECSIT gene, located on chromosome 19. ECSIT encodes an adaptive protein that functions as a

cytoplasmic signaling protein and a cytoplasmic protein in the cell (Soler-Lopez M. B. N. et al., 2011). The mitochondrial respiratory complex cannot function correctly without it. Nuclear factor (NF)-B, interferon regulatory factors (IRFs), and activating protein-1 are all triggered by the adaptor protein. Additional toll-like receptor (TLR), homeostatic bone morphogenetic pathway (BMP), and transforming growth factor-beta pathways are linked to it (Mi Wi S. et al., 2015).

After interacting with mitochondrial proteins, including Lon protease homolog (LONP1) and glutaryl-CoA dehydrogenase (GCDH), ECSIT interacts with AD seed nitric oxide synthase, which is involved in nitric oxide synthesis (NO). Furthermore, specific connections between ECSIT and the Alzheimer's disease genes PSEN-1, ApoE, and PSEN-2 have been discovered in the research. ECSIT's involvement in oxidative stress, inflammation, and mitochondrial dysfunction in Alzheimer's disease is supported by these connections (Soler-Lopez M. Z. A. et al., 2011).

ESR: Estrogen Receptor Gene

Adolescents are more likely than males to get AD. Several studies have revealed that female Alzheimer's patients had worse mental deterioration than males (Zhao L. et al., 2015). Women are more likely than men to get Alzheimer's disease due to genetic diversity in some genes, such as the ApoE4 allele, which increases the risk of dementia (Sundermann E.E. et al., 2010). Ovarian hormones are lost after menopause, increasing the incidence of Alzheimer's in women. Estrogen affects neurotransmission, neuronal growth, survival, protection against oxidative stress, a decrease of A peptide levels, and mitigation of tau hyperphosphorylation, among other actions in the brain. The estrogenic activity is due to ERs (intracellular, transmembrane, and membrane-bound ERs).

Notably, these receptors have two main subtypes: ER and Er, which are encoded by separate genes on chromosomes 6 and 14. The ER receptor is present in the hypothalamus and amygdala and the hippocampus and cortex (Yaffe K. et al., 2009). SNPs in the estrogen receptor (ER) genes may affect exogenous estrogen and cognitive aging in older women. PvuII (rs9340799) and Xbal (rs223493) are two SNPs in the ER gene associated with Alzheimer's disease and cognitive impairment. Several estrogen receptor SNPs have also been linked to an increased risk of Alzheimer's disease in women (Goumidi L. et al., 2011).

Other Genes

The vitamin D receptor (VDR) gene variation has been associated to neurodegenerative disorders and neuronal damage (Khorram Khorshid H.R. et al., 2013). Epigenetic factors such DNA methylation, histone modifications, and chromatin modifications have also been linked to Alzheimer's disease (Liu X. et al, 2018).

3.6 Environmental Factors associated with AD

3.6.1 Air Pollution

Air pollution occurs when pollutants (chemical, physical, or biological) are introduced into the atmosphere. It's connected to respiratory, cardiovascular, and Alzheimer's issues. These pollutants are detrimental to human health by the NAAQS in the United States (Moulton P.V. & Yang W., 2018). In research on animals and cell models, excessive amounts of air pollution harm the olfactory mucosa and bulb and the frontal brain. Exposure to pollutants causes oxidative stress, neuroinflammation, and neurodegeneration in the frontal brain. The air pollution may cause an increase in Aβ42 development, accumulation, and cognitive function (Moulton P.V. & Yang W., 2012).

Diet

The non-enzymatic glycolysis of free amino groups in proteins, lipids, and nucleic acids results in the degradation of heat-sensitive micronutrients (such as Vit-C and folates) and the loss of large amounts of water as well as the formation of toxic secondary products (such as advanced glycation end products, or AGEs). By modifying receptors' structural and functional properties and body proteins, AGEs may generate oxidative stress and inflammation (Hu N. et al., 2013). This is referred to as the toxic effect of AGEs. Many studies have demonstrated that AGEs serum levels are linked to cognitive decline and AD progression. A wide range of cells in the body, including microglia and astrocytes, express the AGE receptor (RAGE). In Alzheimer's patients, it is overexpressed and serves as both an A transporter and a cell surface receptor (Abate G. et al., 2017). Malnutrition is another factor that might lead to Alzheimer's. Anemia, vitamin B12 and D deficiency, and other dietary deficiencies have been linked to an increased risk of cognitive deterioration in people with Alzheimer's disease. Additionally, people with Alzheimer's disease may have difficulty eating and swallowing, which may raise the risk of malnutrition (Koyama A. et al., 2016).

3.6.2 Metals

Metals are found in both natural and biological systems, and they can be detruncated into biometals (e.g., Cu, Zn, and Fe) and toxicological metals (e.g., Pb, Hg, and Ag) (e.g., aluminum and lead) (Adlard P.A. & Bush A.I. 2006). Aluminum is critical to the performance of many industries, including food processing, cosmetics, medical preparations, and pharmaceuticals. The body's plasma transferrin and citrate molecules may aid aluminum's entrance into brain cells by attaching metals such as aluminum to these molecules. As a result of several research, it has been shown that Alzheimer's disease-related proteins such as tau protein are misfolded, aggregation-prone, and phosphorylated by Al in the brain's limbic and hippocampal regions (Colomina M.T. & Peris-Sampedro F 2017). Lead competes with bio-metals such as calcium for binding sites in the brain. It may penetrate the blood-brain barrier (BBB) quickly, causing

changes in neuronal differentiation and synaptogenesis and severe neurodegeneration. According to the research, acute lead exposure was shown to be connected with Alzheimer's disease and to produce an increase in the production of the enzyme β-secretase as well as an increase in Aβ buildup. It is a carcinogenic water-soluble metal that may pass the blood-brain barrier and induce neurological disorders like Alzheimer's disease (A.D.). According to these findings, cadmium ions have been implicated in the formation of Aβ plaques and the self-aggregation of tau in the Alzheimer's disease brain. Data gathered on metals lends credence to the hypothesis that they are among the risk factors associated with the development of Alzheimer's disease (Huat T.J. et al., 2019).

3.6.3 Infections

Persistent infections of the CNS may result in the formation of Aβ plaques and NFT, and as a result, they have remarked risk factors for AD. The DNA of the HSV-1 was detected in individuals who had the ApoE-ε4 allele, which explains the elevated risk of acquiring Alzheimer's disease (Sochocka M. et al., 2017). HSV-1 can reproduce in the CNS, resulting in the initiation of the inflammatory response and a rise in Aβ consumption, culminating in neuronal damage and the development of Alzheimer's disease over time. On the opposite, the findings of an investigation have demonstrated the importance of persistent bacterial infections in the development of Alzheimer's disease (Fulop T. et al., 2018). For example, syphilitic dementia is affected by spirochete bacteria (Treponema pallidum), which collect in the cerebral cortex, generating lesions that look similar to neurofibrillary nodus, which resulted in a result in catastrophic neurodegenerative illnesses. Furthermore, the Chlamydia pneumonia bacteria may cause late-onset Alzheimer's disease by activating astrocytes and cytotoxic microglia, disrupting Ca regulation and apoptosis, affecting in a decline in cognitive activity and an increase in the chance of developing Alzheimer's disease (Muzambi R. et al., 2019).

3.7 Medical Factors associated with AD

Several risk factors have been selected as being associated with the progression of Alzheimer's disease (M.J. Stampfer, 2006). In addition to these medical disorders, older adults with A.D. are more likely to have other medical disorders such as obesity, CVD, diabetes, and others. All of these disorders are associated with an increased risk of AD (Santos C.Y. et al., 2017).

3.7.1 Cardiovascular Disease (CVDs)

Many CVDs are discovered as significant risk factors for AD, including stroke, which is associated with a growing risk of dementia due to neural tissue loss, which enhances the degenerative effect and influences amyloid and tau pathology, among other things. Additionally, atrial fibrillation may result in embolisms, which can affect a stroke and the impairment of memory and cognitive abilities. The heart's inability to circulate blood throughout the body and the brain's hypoperfusion lead to hypoxia and neurological damage when someone has heart failure. According to the coronary heart disease hypothesis, atherosclerosis, peripheral artery disease, hypoperfusion, and emboli are all thought to raise the risk of Alzheimer's disease (AD). When you have high blood pressure, the thickening of the artery walls and narrowing of the lumen restricts cerebral blood flow. In chronic situations, it may induce cerebral edema, which are risk factors for Alzheimer's Disease and cardiovascular disease. CVD is a controllable risk factor, and by concentrating on its association with Alzheimer's disease, a road to preventing and delaying the condition may be discovered (De Bruijn R.F. & Ikram M.A., 2014).

3.7.2 Obesity and Diabetes

A person's body mass index (BMI) may be used to determine whether or not they are obese. Obesity is defined as having too much body fat owing to eating more calories than they burn

(BMI). Increased body fat is connected with a reduced blood flow to the brain, which causes cerebral ischemia, memory loss, and vascular dementia, among other symptoms (Alford S. t al., 2018). Obesity, a poor diet, or these factors might produce impaired glucose tolerance (IGT). Chronic hyperglycemia is linked to increased amyloid-beta accumulation, oxidative stress, mitochondrial dysfunction, and neuro-inflammation. Obesity causes macrophage and lymphocyte activation, which leads to local and systemic inflammation due to increased pro-inflammatory cytokine production from adipose tissue (Pegueroles J. et al., 2018). Obesity is associated with an increase in adipose tissue fat mass. Hyperinsulinemia and hyperglycemia are caused by the inflammation that occurs as a result of this condition. Diabetes type 2, cardiovascular disease (CVD), and cancer are all associated with obesity. These conditions have also been linked to Alzheimer's disease (AD). The inflammation in the brain leads to an increase in microglia, which results in decreased synaptic plasticity and poor neurogenesis, among other things (Anjum I. et al., 2018). Microglia can influence insulin receptor substrate 1 (IRS-1) and inhibit intracellular insulin signaling, both of which play critical roles in maintaining brain health and functioning. Insulin action may be altered, leading to Aβ buildup and a reduction in the tau protein breakdown linked with AD (Lee H.J. et al, 2018).

3.7.3 Regulation of Alzheimer's treatment

Alzheimer's affects roughly 24 million people worldwide, and the number of people living with dementia is anticipated to increase by 2050. Even though Alzheimer's disease is a public health issue, there are presently just two pharmacological types licensed for treatment: cholinesterase inhibitors (natural, synthetic, and hybrid analogs) and N-methyl-d-aspartate reuptake inhibitor antagonists (NMDA) (Cummings JL. Et al., 2014). AD is characterized by the death of Ach-producing cells, which leads to reduced cholinergic transmission throughout the brain. AChEIs, which are categorized as reversible, irreversible, and pseudo-reversible in action, function by blocking the release of acetylcholine (ACh) by cholinesterase enzymes (AChE and

butyrylcholinesterase (BChE)), leading to an increase in ACh levels in the synaptic cleft (Mizuno S, 2012). Over-activation of NMDAR, on the other hand, results in increased quantities of influx Ca2+, which causes cell death and synaptic dysfunction in the brain. Using an NMDAR antagonist, you may inhibit NMDAR glutamate receptor overactivation (and so Ca2+ influx) and restore normal function to your nerves and muscles (Schmitt B. et al., 2004). The fact that these two kinds of drugs have a therapeutic effect does not mean that they successfully cure or prevent Alzheimer's disease (Tomaszewski S. et al., 2016). Regrettably, just a few Alzheimer's diseases clinical studies have been conducted in the recent decade, and the results have been a resounding failure. Several processes have been postulated to understand Alzheimer's disease pathogenesis better to change its course and create effective therapies. These mechanisms include aberrant tau protein metabolism, β-amyloid, the inflammatory response, and cholinergic and free radical damage. In this paper, we summarize the medications and hypotheses now accessible for the development of novel therapeutics for Alzheimer's disease.

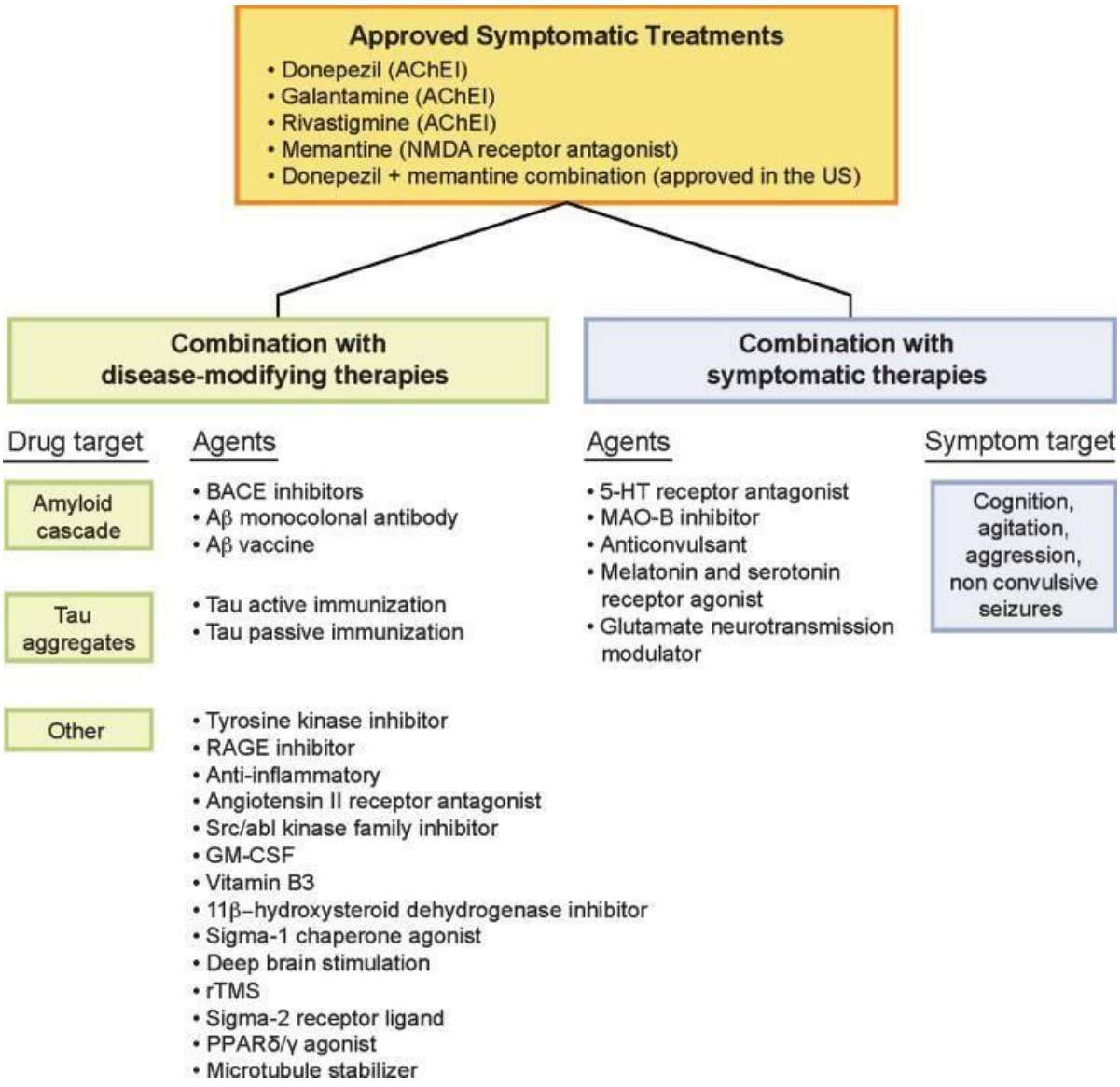

Figure 1: Symptomatic Treatment of AD

3.8 Symptomatic Treatment of AD

3.8.1 Cholinesterase Inhibitors

The cholinergic hypothesis states that Alzheimer's syndrome is characterized by declining brain acetylcholine production. One of the most efficient strategies to increase brain cognition and neural cell performance is boosting cholinergic levels by suppressing acetylcholinesterase (AChE). AChEIs block acetylcholine breakdown at synapses, resulting in acetylcholine accumulation and stimulating cholinergic receptors in the brain. (K., 2019). Even though

Tacrine (tetrahydroaminoacridine) was the first FDA-approved cholinesterase inhibitor drug for the treatment of Alzheimer's disease, which works by increasing ACh in muscarinic neurons, it was taken off the market almost immediately after it was approved due to a high incidence of side effects (M.L, 1994), including hepatotoxicity, and a lack of benefits, which were observed in several clinical trials. Many AChEIs were eventually created, including donepezil, rivastigmine, and galantamine, which are now widely used to treat Alzheimer's symptoms. Increasing choline reuptake and acetylcholine synthesis at presynaptic terminals is another possible Alzheimer's therapeutic strategy (Qizilbash N., 2000). Targeting the choline transporter (CHT1), which is responsible for delivering choline to the body to produce ACh, is one way to accomplish this goal. The development of medicines capable of boosting CHT1 levels at the plasma membrane may pave the way for future Alzheimer's disease therapies.

3.8.2 Combination Therapies for AD

Clinical investigations are currently looking at DMTs as an alternative to traditional treatments like cholinesterase inhibitors or memantine. Because these results allow for the inclusion of DMTs in a background standard of care medication, the studies will help determine if there are differences between combination therapy with the experimental drug and background treatment without it.

Agent	Dose	Type	AD Stage	Phase	Baseline Therapy
Aducanumab	NR	Amyloid passive immunization	Early	III	SOC†
Gantenerumab	NR	Amyloid passive immunization	Early	II/III	NR‡
Solanezumab	NR	Amyloid passive immunization	Early	III	
Masitinib	3.0 or 4.5 mg/kg/d	Selective tyrosine kinase inhibitor	Mild to moderate	III	Rivastigmine and/or memantine
ALZT-OP1 (cromolyn and ibuprofen)	NR	Anti-amyloid/anti-inflammatory	Early	III	AChEI's† and/or memantine†
Flebogama DIF 5% and Albutein 20%	NR	Intravenous human immunoglobulin, human albumin	Mild, moderate	III	AChEI's and/or memantine
BAN2401	2.5, 5.0, or 10.0 mg/kg once biweekly; or 5.0 or 10 mg/kg once a month	Amyloid passive immunization	Early	II	AChEI's† and/or memantine†
AADvac-1	Axon peptide 108 40 µg; 6 doses in 4-week intervals, then 5 doses in 3-month intervals	Tau active immunization	Early	II	AChEI; memantine (permitted but not required
Liraglutide	1.8 mg/d	GLP-1 receptor agonist	Mild	II	AChEI†
Saracatinib	100 to 125 mg/d	Src/abl kinase family inhibitor	Early		AChEI's† and/or memantine† and/or antidepressants†

Table 1: Drugs in clinical trial phages

3.8.3 Phase I combination treatments

Fourth, four DMTs are evaluated as a supplementary therapy to standard-of-care medications in phase I studies (Table 1). Researchers are testing ABvac40, LY3002813, and ACI-35 on Alzheimer's patients in the early to middle stages of the illness. Either individual on standard-of-care medicine or not is being studied with TPI-287, a tau-targeting therapy. A larger-than-expected reduction in MMSE score in the placebo group may have contributed to the possible advantage. The National Institutes of Health financed the research. (Biosciences, 2018).

3.8.4 Phase II add-on and combination treatments

There are 21 DMTs and symptomatic treatments in phase II clinical trials, 7 of which are symptomatic. Most of these studies are supplementary to traditional medicine. The medications employed in these add-on studies include amyloid vaccines, tau vaccines, glucagon-like peptide-1 receptor agonists, and serotonin-receptor agonists. The researchers combined a device (e.g., deep brain stimulation, repetitive transcranial magnetic stimulation) with standard-of-care treatment and lifestyle changes (e.g., yoga) with dietary supplements (e.g., vitamin D) in several studies (i.e., curcumin) (Youdim MB & Weinstock M., 2001).

Eli Lilly is testing passive amyloid immunization (LY3002813) alone and combined with a BACE 1 inhibitor in a phase II trial (LY3202626). Both drugs have been studied as monotherapies, with some studies still underway. Three treatment groups will be used to test for synergy between the two medications: intravenous amyloid vaccine (LY3002813) plus oral placebo, intravenous amyloid vaccination plus BACE 1 inhibitor (LY3202646), and intravenous placebo plus oral placebo. The idea behind this method is that addressing both processes at once will have a more significant effect on the amyloid cascade than targeting either approach alone. Patients enrolled in this study may also get regular therapy. The trial should be completed by 2020.

Patients with mild to severe Alzheimer's disease are also being studied with rasagiline, a selective MAO inhibitor (Youdim MB & Weinstock M. 2005). According to recent research, rasagiline exhibits neuroprotective and antiapoptotic properties mediated by the proteins Bcl-2, protein kinase C, and the proteasome-ubiquitin complex. A significant finding is that the S-isomer of rasagiline (TVP1002) has a 1000-fold lower potency than the equivalent MAO inhibitor and demonstrates similar neuroprotective efficacy. According to preclinical studies, the propargylamine moiety of rasagiline preserves mitochondrial viability by promoting the activity of Bcl-2 and protein kinase C, as well as by downregulating proapoptotic factors. Furthermore, from the standpoint of Alzheimer's disease (AD) treatment, drugs containing

propargylamine, such as rasagiline, modify proteolytic cleavage of the APP, lowering Aβ formation by activating the nonamyloidogenic alpha-secretase pathway, as previously reported. The activation of mitogen-activated protein kinase and protein kinase C is a component of this impact (Youdim MB W. M., 2001). Late 2018 will bring about the publication of the findings of this phase II proof-of-concept (POC) experiment. Rasagiline is an example of a combination medication delivered by a single multifunctional compound.

3.8.5 Phase III combination treatments involving disease-modifying therapies

Currently in phase III studies are ALZT-OPT1 and Gamunex (immune globulin intravenous (human), 10%; Grifols Therapeutics, Clayton, NC, USA). The ALZT-OPT1 research is looking for individuals with early Alzheimer's disease who are either taking or not taking standard-of-care medications at the time of enrolment (Merck, 2018). Cromolyn is an anti-amyloid drug approved by the US Food and Drug Administration for use in asthma (FDA). It should cross the BBB. In vitro, cromolyn reduced A fibrilization and oligomerization, but not Aβ40 and Aβ42 monomer concentrations in mouse brain. ALZT-OPT1 is one of the most comprehensive studies available, addressing two disease pathways (amyloid and inflammation) (intranasal inhaler for cromolyn and oral tablet for ibuprofen). ALZT-OPT1 is also an add-on study since it allows patients to keep their standard-of-care medications while in the trial. The study is expected to be completed in November 2019.

Gamunex is currently conducting a phase III combination trial in which human albumin is delivered in combination with intravenous immunoglobulin through plasma exchange. The amyloid in this combo experiment is targeted in two ways (Kennedy ME. et al., 2016). A has the ability to traverse the blood-brain barrier and bind to albumin, essentially sequestering the substance in the peripheral nervous system. With plasma exchange and albumin replacement,

the theory behind the procedure is that removing and replacing the albumin that is attached to pathogenic components would allow for more A to be transferred out of the central nervous system. Albumin also contains anti-oxidant properties that may be beneficial in the treatment of some diseases. It has been suggested that combining plasma exchange with intravenous immunoglobulin infusion (which also binds to amyloid) may further improve amyloid clearance from the brain (Egan MF, et al., 2018). It has not yet been possible to disclose the outcomes of this trial, which included patients who received stable dosages of standard-of-care medicines and was planned to be finished in December 2017.

In addition to its role in the pathogenesis of Alzheimer's disease, the receptor for advanced glycation end-products (RAGE), which is expressed by different types of brain cells and binds and transports A from the blood to the brain, is thought to play a variety of roles in the disease's progression (Schenk D, et al., 2012). There are a variety of therapeutic effects that agents that inhibit A-RAGE interaction may have. These include lowering neuro-inflammation, improving cognitive decline, and decreasing A levels in brain. Given that RAGE inhibitors operate to diminish both inflammation and the quantity of A in the brain, they are referred to as multifunctional molecules, meaning that they are a mixture of not only one medicine, but also of more than one mode of action. (Sevigny. J, et al., 2016) However, a phase III clinical study for the RAGE inhibitor azeliragon (also known as PF-04494700 and TTP488) failed to satisfy either of the co-primary effectiveness endpoints (improvement in cognitive or functional outcomes) and was thus discontinued.

Chapter 4

Mechanism of Action (MOA)

4.1 MOA of traditional drugs

Huperzine A has been identified to inhibit the acetylcholinesterase enzyme. Pharmaceutical medications used to treat Alzheimer's disease, such as galantamine and donepezil, work in the same way.

Alzheimer's disease is characterized by acetylcholine-producing neurons degeneration that is irreversible, cognitive impairment, and the formation of neurofibrillary tangles and amyloid plaques (H. Ferreira-Vieira et al., 2016). Memory, as well as other crucial brain activities including attention, learning, stress response, wakefulness and sleep, and sensory information, are all influenced by the cholinergic system (Lilienfeld, 2006). Acetylcholine (ACh) has been linked to memory acquisition, encoding, consolidation, reconsolidation, extinction, and retrieval in studies. As a result, the slow loss of cholinergic neurons in Alzheimer's disease (AD) patients may lead to memory loss (H. Ferreira-Vieira et al., 2016).

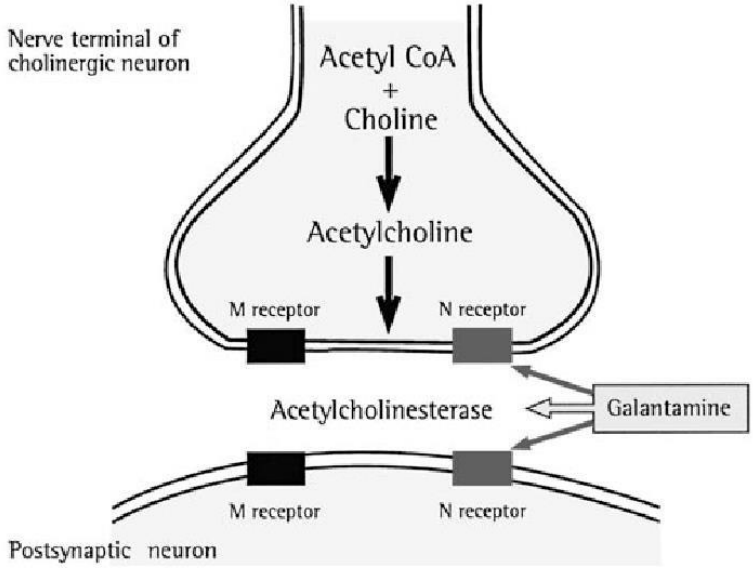

Figure 2: MOA of Galantamine

In the central nerve system, nicotinic acetylcholine receptors (nAChR) are predominantly expressed at the presynaptic neuronal membrane to govern the release of a variety of neurotransmitters such ACh, glutamate, GABA, dopamine, serotonin, and norepinephrine (Farlow, 2003). While nAChR agonists increase cognitive function, nAChR antagonists decrease cognitive processes. According to several research, persons with Alzheimer's disease have lower levels of nAChR expression and activity, which might explain why they have less central cholinergic neurotransmission (Akk, 2005). Galantamine binds to nAChRs at the allosteric site, causing a conformational change in the receptor, increased ACh release, and enhanced glutaminergic and serotoninergic neuron activity. Modulation of nAChRs improves receptor sensitivity while facilitating both excitatory and inhibitory cholinergic transmissions in brain tissues. Other neurotransmitters' release is influenced. Galantamine's ability to control the release of other neurotransmitters may potentially play a role in the elevation of nAChRs and the alleviation of behavioral symptoms in Alzheimer's disease (H. Ferreira-Vieira et al., 2016).

The widely recognized cholinergic hypothesis (Terry & Buccafusco, 2003) suggests that reduced cholinergic transmission in the central nervous system is responsible for some of the cognitive and behavioral impairment associated with Alzheimer's disease. Donepezil inhibits the acetylcholinesterase enzyme, which typically breaks down acetylcholine, in a selective and reversible manner. The main pharmacological effects of this medicine are thought to be due to the inhibition of this enzyme, which improves cholinergic transmission and alleviates the symptoms of Alzheimer's dementia. Other mechanisms of action of donepezil, in addition to those mentioned above, include the opposition of glutamate-induced excitatory transmission via downregulation of NMDA receptors and the regulation of amyloid proteins, both of which have shown significant effects on the Alzheimer's disease process (Shen et al., 2010). Donepezil's other putative targets include the suppression of several inflammatory signaling pathways, which could have neuroprotective effects (Srinivasan & Lahiri, 2015).

4.2 MOA of recent biosimilar drugs

Solanezumab's exact mechanism of action in AD is uncertain, but the treatment hypothesis is that it increases synaptic function by sequestering Aβ, altering equilibria between various species of Aβ, and eliminating tiny soluble species of Aβ that are directly harmful. A single injection of m266, the mouse equivalent of solanezumab, restored memory impairments in APP-transgenic mice models while leaving amyloid plaques intact in preclinical study, indicating the possibility of targeting the soluble pool of Aβ (NCBI - Error Blocked Diagnostic, 2019).

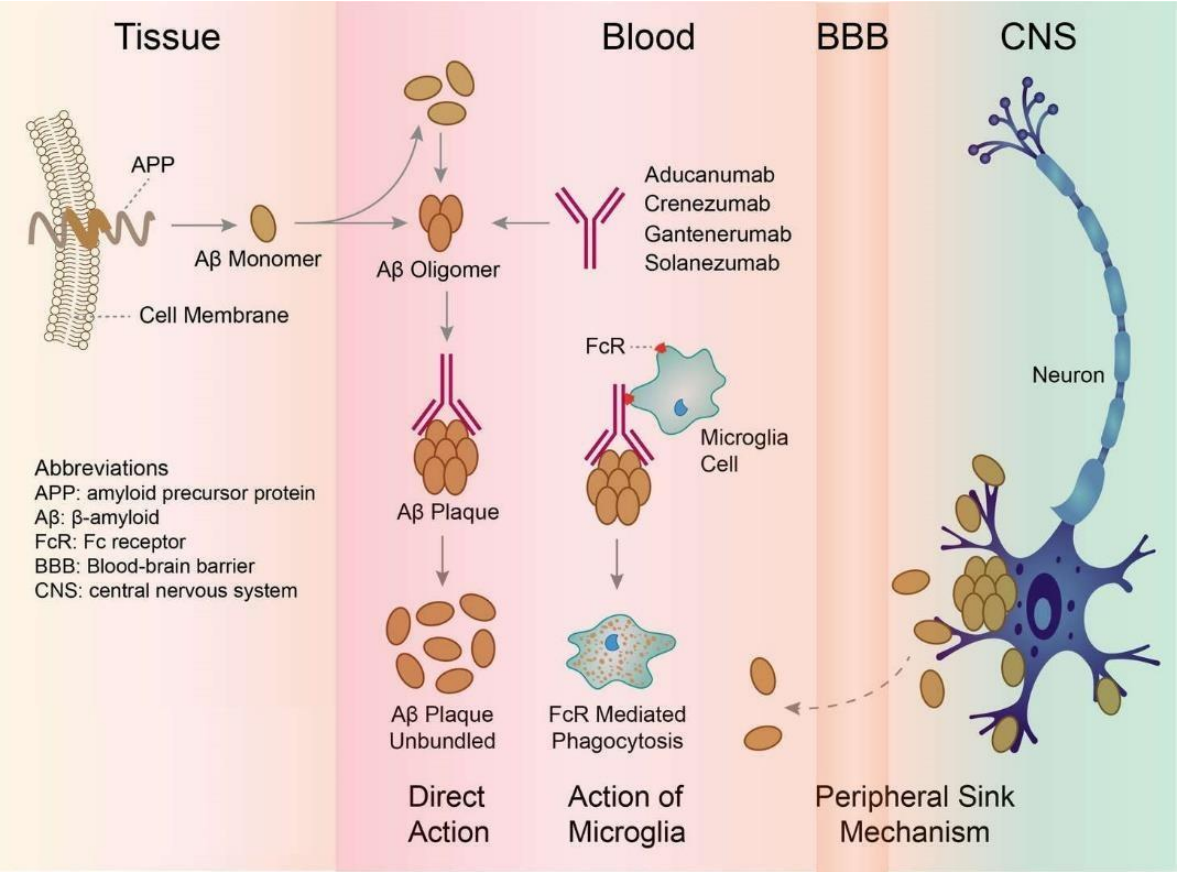

Figure 3: MOA of Solanezumab

Alzheimer's disease is a neurological illness that affects the brain. Plaques developing extracellularly in the brain are a part of the pathogenesis of Alzheimer's disease (Arndt et al., 2018). The majority of these plaques are made up of amyloid-β, a peptide generated by the breakdown of the amyloid precursor protein. According to the "amyloid cascade theory," the development of Alzheimer's disease is driven by the buildup of amyloid-β oligopeptides in the brain (Ferrero et al., 2016).

Aducanumab is a monoclonal IgG1 antibody that binds to the amino acids 3-7 of amyloid- β. Phe4, His6, Glu3, and Arg5 are the amyloid residues responsible for the bulk of the interaction between amyloid- β and aducanumab's Fab region (Arndt et al., 2018). Human trials reveal non-significant changes in amyloid-β40 and amyloid-β42 over a dosage range of 0.3-30 mg/kg

and an increase in amyloid-β40 and amyloid-β42 at 60 mg/kg, according to data from mice and people (Ferrero et al., 2016).

Based on the Mini-Mental State Examination, Clinical Dementia Rating, and levels of p-tau in the cerebrospinal fluid, aducanumab medication is related with a slower rate of Alzheimer's disease development (Cummings et al., 2021).

Chapter 5

Future Prospects of AD

Many of the current disease-modifying therapeutic targets are based on the amyloid cascade theory. Antioxidants, metal-chelating agents, immunotherapy, amyloid binders, anti-inflammatory agents, Secretase modulators, and neuroprotective compounds are just a few medications currently being developed as part of active, ongoing research. In previous AD therapy studies, estrogens, corticosteroids, naproxen, ibuprofen, indomethacin, rofecoxib, tarenflurbil, rosiglitazone, xaliproden, and dimebon were all ineffective. The discovery of immunotherapy has resulted in a decrease in the amyloid plaque burden in the brain, which is a positive trend. Six percent of those who received the active immunization (AN-1792) developed severe encephalitis. In APOE 4–harmful but not 4–positive AD patients, the monoclonal antibody bapineuzumab improved cognitive function following passive immunization. More information on the results of phase III trials of bapineuzumab will be available soon. Similar encouraging results have been reported from the open-label use of an intravenous infusion of immunoglobulins (IVIg), which is thought to be a form of passive immunotherapy (immunoglobulin replacement therapy). According to a previous study, approximately 75% of treated Alzheimer's disease patients experienced improved or stabilization in cognitive function (MMSE score) (Piau A, 2011). A phase III clinical trial involving IVIg in treating Alzheimer's disease is currently underway. Other clinical trials are currently underway, involving a diverse range of potentially helpful pharmacotherapy, including active immunization, passive immunization, gamma-secretase inhibitors, antiaggregation, and antifibrillation agents, advanced glycation end-product inhibitors, tau aggregation inhibitors, and neuroprotective or neurorestorative drugs, among other things. It is now recognized that late-onset Alzheimer's disease is a multifactorial illness with multiple

pathogenetic mechanisms. Most likely, a combination of several therapies targeting various sites will be more effective than a single treatment (Chu, 2012).

Drug	Class	Dose (mg/day)	Frequency (times/day)	Absorption affected by food	Metabolism
Rivastigmine	Cholinesterase inhibitor	3-12	2	Yes	Non-hepatic
Galantamine	Cholinesterase inhibitor	8-32	2	Yes	CYP2D6 CYP3A4
Donepezil	Cholinesterase inhibitor	5-10	1	No	CYP2D6 CYP3A4
Memantine	NMDA-receptor antagonist	5-20	2	No	Non-hepatic

Table 2: Promising drugs with dose parameter

5.1 Drug Development

On the other hand, there is no recognized structure for developing combination medicines. Some studies suggest that multiple treatments targeting the same route or complementary elements of the illness might benefit from synergy. Complementary and synergistic effects of combined therapy should be evaluated in animal models first. Not advancing a drug further in the pipeline would be based on failure in an animal model. Toxicological effects of combinations might be discovered by testing them in animals. Clinical studies in humans will also be required to report drug-drug interactions, safety, and tolerability. Phase II learning trials will obtain a target engagement and dose information on each element and the combination. More time will be available in Phase II to investigate dose-response relationships; lower doses of individual agents may be used in combination regimens when synergies are present. A positive outcome could help to reduce the possibility of toxic reactions when using multiple drugs in one setting. If the phase II studies are successful, confirmatory phase III studies will be carried out to further validate the findings. When combinations are planned from the

beginning, the advantage is that the candidate agents are all at the same stage of investigation when the time comes for combinations to be used. Using a combination of novel agents and better-understood repurposed agents is another method of building a pipeline of combination therapies. Several different targets, including Aβ, tau, inflammation, and neuroprotection, may be addressed by combination therapy regimens (Cummings, 2019).

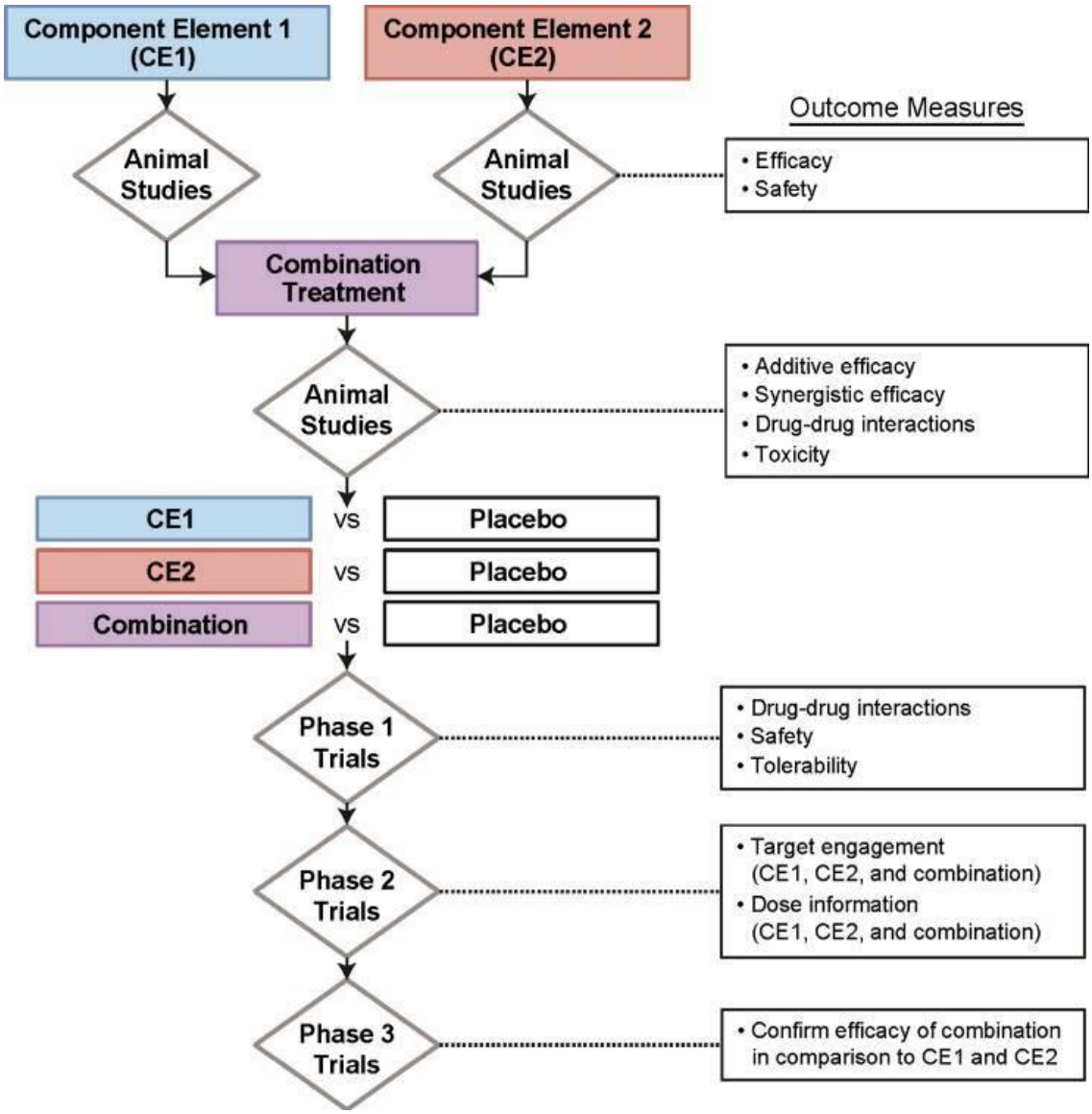

Figure 4: Drug Development Approach

Chapter 6

Conclusion

AD is a difficult disease to treat because of its complexity. Only cholinesterase inhibitors and memantine, or the combination of these agents, are currently approved treatments for Alzheimer's disease. Some new drugs, despite their promise at the outset of their trials, fail to meet efficacy endpoints in larger phase III studies despite promising results. Treatments for Alzheimer's disease (AD) have had a poor success rate in clinical trials and in part because of the disease's complicated pathology, and our lack of knowledge about the interrelationships among the numerous pathways that bear to AD and subsequent neurodegeneration. However, even though the treatment of AD with cholinesterase suppressors and memantine has had limited success, it's still likely that multiple pathways need to be targeted if treatment is to be successful. Therefore, further studies into logical combinations of agents should be carried out.

Multiple clinical trials are currently underway to investigate whether DMTs or symptomatic agents can be used as add-ons to background standard-of-care therapy. An opportunity for treating the disease with an abbreviation of two agents that target different pathways presents itself. Still, there are recently only a few of these in clinical trials, making them rare. Therapeutic compounds conducted in abbreviation may allow for a lower amount of the individual agents, thereby lowering costs and side effects. The lengthy and complicated path of disease development may be captured by innovative and strategic clinical trial models, which may include a different set of entities for preclinical AD, a different set for early-stage AD, and still another set for Alzheimer's dementia. To put it another way, the difficulties of treating Alzheimer's disease have led to the current treatment landscape to investigate new drugs as a supplement or supplement to standard-of-care and repurposing existing drugs indicated for other therapeutic conditions, and to look at successful treatments for other serious chronic diseases, such as cancer and HIV.

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