Comprehensive review on importance, challenges and future prospects of nanotechnology and combination therapy for Alzheimer's disease

By

Name: Nowshin Ishrat
ID: 19146050

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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.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:

Nowshin Ishrat

19146050

Approval

The thesis/project titled "Comprehensive review on importance, challenges and future prospects of nanotechnology and combination therapy for Alzheimer's disease" submitted by Nowshin Ishrat, ID: 19146050 of Summer 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

Dr. Afrina Afrose
Assistant Professor
School of Pharmacy
BRAC University

Approved By:

Program Director:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study does not involve any kind of animal or human trial

Abstract

Alzheimer's disease (AD) is a progressive neurological condition marked by memory or cognitive impairment, behavioral changes, visuospatial difficulties, decreased propensity to carry out day to day living tasks, and language impairment. Alzheimer's disease originated through neuronal cell loss over time. It generally begins in the hippocampus's entorhinal cortex. Various risk factor is related to AD, but only a few therapeutic approaches available to treat this neurodegenerative illness to help manage symptoms, limit disease development, avoid complications. Certain therapies from combination drug configuration and nanotechnology based medicine can increase the levels of specific neurotransmitters to slow the advancement damaging brain cells that may help to delay AD development. Yet any article was not published about the comparison between combination therapy and nanotechnology on Alzheimer treatment. This paper will show new researches about combining drugs for combination therapy and experiments with nanoparticles for investigating new nanotechnology based medicines for Alzheimer's disease.

Keywords: Alzheimer's Disease, Combination therapy, Nanotechnology, Dementia, Cholinesterase inhibitors, Cognitive function

Dedication

Dedicated to my parents and husband to whom I owe my achievements.

Acknowledgement

Beyond everything, I would like to express my gratitude to the Almighty, without whose consent nothing is achievable.

I would like to express my heartfelt appreciation and sincere respect to my supervisor, Dr. Afrina Afrose, for leading me with her wholehearted support and motivation through this year-long endeavor. Her whole hearted encouragement and friendly personality helped me a great deal to take this project forward. She was still there for me, aside from offering scholarly advice, be it called some sort of research materials or career-related guidance or going through the official formalities. I'm very happy to thank her for trusting me throughout the progress of this work.

Last but not the least; I am obliged to thank my parents and husband whose love and guidance were the working forces behind every bit of success that I have accomplished so far in my life.

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List of Acronyms

AD	Alzheimer’s Disease
EOAD	Early Onset Alzheimer’s Disease
LOAD	Late Onset Alzheimer’s Disease
ChEIs	Cholinesterase inhibitors
MEM	Memantine
SPs	Senile plaques
PSEN-1	Presnilin-1
PSEN-2	Presnilin-2
APOeε4	Apolipoprotein E
NAPA	The National Alzheimer's Project Act
AChEIs	Acetylcholinesterase inhibitors
BDTF	Bangladesh Dementia Task Force
ASB	Alzheimer's Society of Bangladesh
ADI	Alzheimer's Disease International
YPSA	Young Power in Social Action
PKSF	Palli Karma Sahayak Foundation
NGOs	Non-governmental organizations

SCEP	Service Centre for Elderly People
NMDA	N-methyl-d-aspartate
PnBCA	Poly n-butylcyanoacrylate
LDL-r	Low-density lipoprotein receptors
PLGA	Poly (lactide-co-glycolide)
SLN	Solid-lipid nanoparticles
SOD	Superoxide dismutase
GSH-PEG	Glutathione PEGylated Liposomes
EGCG	Epigallocatechin-3-gallate
APP	Aβ precursor protein
RCTs	Randomized controlled trials
NMDAR	N-methyl-D-aspartate receptor
BuCHE	Butyrylcholinesterase
MPAC	Metal protein-attenuating compound
GSK-3	Glycogen synthase kinase 3
MCI	Moderate cognitive impairment

Chapter 1

Introduction

1.1 Background

Alzheimer's disease (AD) is a terrible neurological illness that fundamentally affects the elderly. The mechanisms behind AD pathogenesis have yet to be fully established, but there are various hypotheses addressing AD (Mashal et al., 2022). Intensive research has been organizing in recent years to dissect the molecular events that lead to AD. (Davinelli et al., 2012).

From this review article, we will be able to learn about some nanoparticles such as magnetic and gold nanoparticles are frequently employed in nanomedicine for diagnostic and therapeutic purposes and whether they proficiently intersect the blood-brain barrier to get as far as their target to the brain or not, which illustrate a dominant part in the generation and support of chronic sensitivity during AD (Zenaro et al., 2017). Other nanoparticles like liposomes, solid lipid nanoparticles, polymeric nanoparticles and their targeting sites also discussed in this work (Martín-Rapun et al., 2017).

On the other hand, combination therapy for Alzheimer's disease counting both cholinesterase inhibitors (ChEIs) and memantine (MEM), has recently been approved, they both have slight symptomatic but not curative effects (Shuaib et al., 2008). ChEIs include galantamine and rivastigmine (both were accepted as slight to alarming Alzheimer's disease) and donepezil (approved for light to critical Alzheimer's disease), which is used with MEM (approved to apply in moderate to extreme AD) (Patel & Grossberg, 2011). Whether this combination therapy is safe and tolerable or not, and what is the comparison between nanotechnology and combination therapy, will be discussed in this article.

1.2 Research gap

There is currently no medically acknowledged treatment for Alzheimer's disease. Expanding therapeutic plans for AD is a huge issue in the healthcare domain because the fundamental mechanics generating its terrible symptoms are still undiscovered (Dabur et al., 2020). Any article about the comparison between combination therapy and nanotechnology on Alzheimer treatment yet not published in any website or journal or any book. Though few articles about the combination therapy and nanoparticles for the treatment of Alzheimer's was published on websites, journals individually. This article will show new researches about combining drugs for combination therapy and experiments with nanoparticles for investigating new nanotechnology based medicines for AD.

1.3 Objectives

- The objective of this review is to discuss the significance and obstacles of combination therapy and nanotechnology-based treatment for Alzheimer's disease.
- Pointing out the challenges and future prospects involved to Alzheimer's treatment.

1.4 Significance

Alzheimer's disease awareness in our country is still in its early stages. As our knowledge about Alzheimer is very limited, we do not know about the symptoms and proper care of a person suffering from this disease. Because of our ignorance, people with Alzheimer's disease are living with social prejudice, misconceptions, social stigma, neglect and hardship even though they have the right to better treatment and quality care. This article will help to review and find a new way to compare nanoparticles and combination or blending therapy methods

for the nursing of AD. The effectiveness of nanotechnology methods to diagnosis and cure of AD shown in this research illustrates the importance of multidisciplinary research in the fast diagnosis and achievable cure for AD. The effectiveness of combination therapy is received via numerous experiments and drugs were successfully coupled with other medicines in studies for the treatment. This experiment not only revealed the clinical benefit of the combination treatment, offering hope to thousands of Alzheimer's patients and their family, but it also demonstrated the value of finding the proper individuals using biomarkers (Stephenson et al., 2014) (Nazem & Mansoori, 2011) (Li et al., 2015).

Chapter 2

Methodology

Using multiple research papers, academic published journals, and relevant websites such as AlzheimersDisease.net and Alzheimer.ca, a comprehensive review focused on combination therapy and nanotechnology therapy in the cure of AD was accomplished. The material for this comparative review was gathered from several studies published in various journals. Among the journals are Google Scholar, Science Direct, PubMed, Frontiers, Elsevier, Springer, and others. At first, fundamental research on Alzheimer's disease, combination treatment, and nanotechnology was conducted, and an initial collection of research publications was generated. Then, in order to perform the review in a methodical manner, an outline was created. Keywords were used to search for papers for the review. Almost all literature was published from 1990 to 2022.

Inclusion criteria for the article were:

- Studies that contain information about Alzheimer’s disease (AD), diagnosis, treatment, safety.
- Which include current status about AD situation and current treatment.
- Give overview of the current treatment with combination therapy for AD.
- Give overview of the current treatment with nanotechnology treatment for AD.
- Clinical control of these two methods.
- Complete studies along with the conclusion.

Exclusion criteria for the article were:

- Studies that cannot give current status about Alzheimer’s disease (AD).
- Several limitations exist in the article.
- Incomplete research about combination therapy for AD.

- Incomplete research about nanotechnology based treatment for AD.
- Research that yielded no outcome about AD or combination therapy or Nanotechnology.
- Cases that yielded no conclusion about clinical trial of medicines and safety issues.

Number of articles identified: 127

Number of articles screened: 96

Number of articles eligible: 35

Number of articles included: 33

Number of articles excluded: 2

Identification

Articles were pointed out by searching on websites like Google Scholar, PubMed, Science direct:

↓

Number of irrelevant and equivalent articles: 31

Screening

Number of article that were screened: 96

↓

Exclusion of the articles on the basis of limitations, duplication, completion: 42

Eligibility

Eligible articles for this review: 35

↓

Removal of articles for having no significant results: 3

Inclusion

Number of article included on this review: 32

Chapter 3

Importance of combination therapy and nanotechnologies in the management of Alzheimer's disease

3.1. What is Alzheimer's disease?

Alzheimer's disease (AD) is a gradual neurodegenerative indisposition distinguished by memory or cognitive impairment, alterations in behavior, visuospatial deficits, diminished propensity to carry out day after day living activities, language deterioration which primarily address behavioral problems (Patel & Grossberg, 2011). AD is a remarkable concerning difficulties to the global health protection system, and it is the consequence of extensive sequence of factors that leads to neuronal debilitation and destruction in recollection and cognitive potentiality (Davinelli et al., 2012). The principal cause of dementia syndrome is AD. The frequency and extent of AD rise with age. As the older population grows on the world, AD is swiftly turning into the key omnipresent healthcare issues. In spite of that, there are currently no exact diagnostic tools or effective therapy drugs for AD (Nazem & Mansoori, 2011). AD is the mass prevalent genesis for dementia and particularly most pressing medical provocation of our time. Individuals suffering from AD experience countless symptoms that change over time. It is a neurological indisposition that is gradually escalating and noxious, accounts for up to 80% of total dementia spotting globally. Alzheimer is considered as a fatal disease (Association, 2018). The two substantial pathological features of AD are senile plaques (SPs) and neurofibrillary tangles (NFTs). There have been diverse investigational statements that back up the hypothesis that oxidative trauma is correlated to the expeditious development of AD. Besides that, recent findings indicate that inflammatory processes play a

crucial function in progression of the AD. (Davinelli et al., 2012). As providing equitable treatment and nursing for mortals with Alzheimer's is difficult, so report shows that, AD infect an appraised 6.2 million mortal senior 65 age and older now a days. As stated in the "Global Alzheimer Report, 2015: The Global Impact of Dementia" (World Alzheimer Report, 2015), more than 35 million individuals are now affected by dementia. AD affects people all throughout the world. Furthermore, the numeral quantity of sufferers is look for to extend 60 million by 2050. If no medical breakthroughs are made to prevent or cure or slow Alzheimer's disease, this figure could rise to 70.8 million by 2060. Departure from AD was devious by more than 145% between 2000 to 2021 (“2021 Alzheimer’s Disease Facts and Figures,” 2021) (Guo et al., 2020).

3.2. Effects of Alzheimer’s disease on the brain

In Alzheimer's disease, difficulties arise as a termination of nerve cell (neurons) damage or destruction in areas of the brain involved in cognitive function. Neurons of the brain that allow a person to walk and swallow, are eventually damaged or destroyed. (Association, 2018) A healthy and fine adult brain contains approximately 100 billion neurons, one and all of which has long, spreading extensions. Sensory neurons can form connections with each other with the help of these extensions. Information flows through such connections, known as synapses. They enables signals to proceed quickly through neuronal circuits in the brain, initiating the cellular foundation of memories, skills, sensations, thoughts, emotions, and movements (“2021 Alzheimer’s Disease Facts and Figures,” 2021) Amyloid-β peptide (AB) simulate a significant function in the neuropathology of AD. β-amyloid-$_{(1-42)}$ is a key portion of amyloid deposits in the cerebrovascular system. Two several brain switching is linked with Alzheimer's are the buildup of the amino acid segment beta-amyloid into clusters (β-amyloid plaques) surrounding neurons and

deposition of a deviant construction of the amino acid tau (tau tangles) innermost neurons. Beta-amyloid clusters (Oligomers) and plaques are thought to play a part to cell proliferation by interrupting with neuron to neuron connectivity at synapses. Whereas tau tangles prevent nutrients and other crucial molecules from being transported inside neurons. Whenever beta-amyloid levels grow, a breaking point is attained at which aberrant tau distributes all around the brain. (“2021 Alzheimer’s Disease Facts and Figures,” 2021) (Application & Data, 2011). When tau is phosphorylated to a high level, it becomes non - functional; as a result, microtubules collapse and eventually block neurofibrillary tangles (NFTs) neurotransmitters and neuronal signaling (Davinelli et al., 2012). A well controlled microenvironment is essential for appropriate neuron and neural signaling function. The critical significance of brain barriers in shielding and sustaining brain health microenvironment is well established. At three major interfaces between blood and brain tissue, three types of brain barriers emerge around cells. The arachnoid barrier, blood brain barrier, blood cerebrospinal fluid barrier are the three brain barriers. The BBB is the most essential of these three brain barriers in supporting brain function. Evidence shows that solitary the most prevalent pathophysiologic features of AD implicated in cardiorespiratory risk factors is the malfunction and degradation of the blood-brain barrier (BBB). Numerous study findings indicate that cerebrovascular lesions typically coincide with BBB breakdown and malfunction in the neurodegenerative state of Alzheimer's disease. BBB debilitation causes amyloid-β (Aβ) shifts from the brain to the peripheral motion to malfunction across the BBB (Cai et al., 2018). Nevertheless, Alzheimer's disease is a complex and nuanced neurodegenerative indisposition (Davinelli et al., 2012).

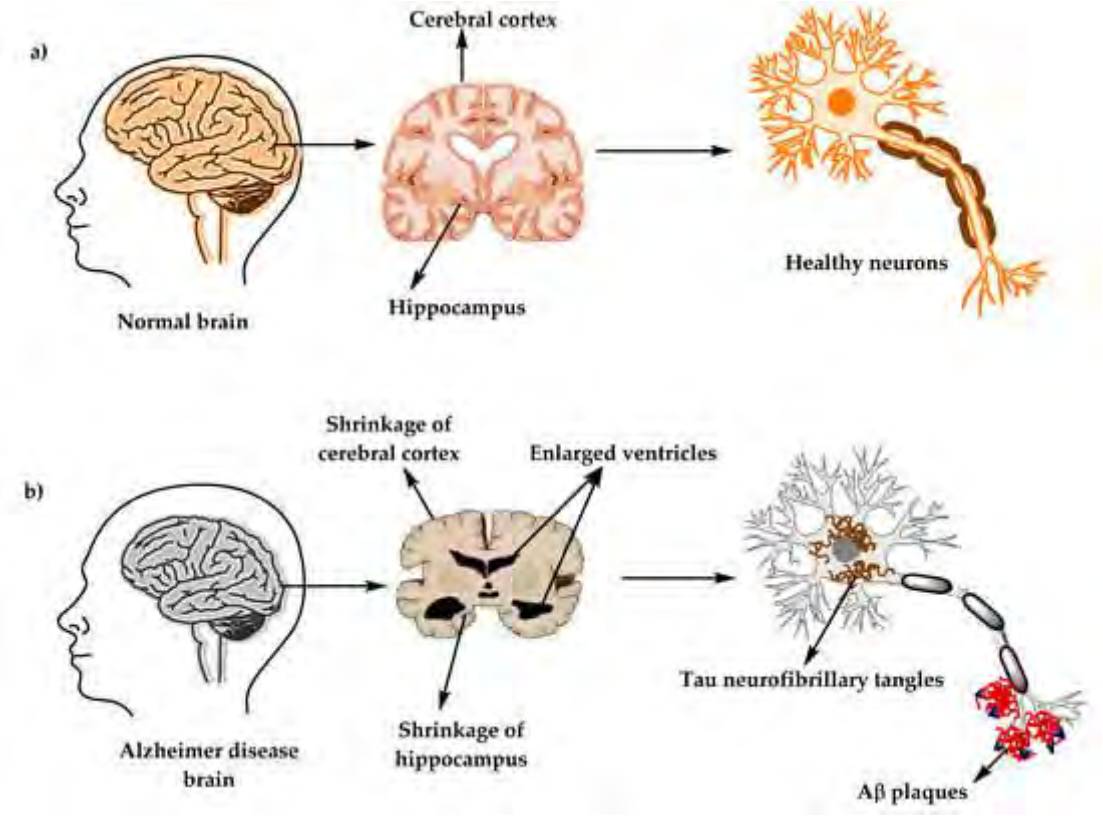

Figure 1: The physiological formation of the brain and neurons in (**a**) well strong brain (**b**) Alzheimer's disease (AD) brain (Anwal, 2021).

3.3. Types of Alzheimer's disease

Alzheimer's Disease is categorized into two order constructed on the age of onset and other pathological factors such as individual's age, behavior, history:

- **Early Onset Alzheimer's Disease (EOAD)/ Familial AD:** EOAD seems in patients between the young ages of 30- 60. Familial Alzheimer's disease affects approximately 5% of patients with a three-generation family story of the disease. The expense of treating EOAD sufferers is significant. It can address as genetic in origin. In most cases, patients features mutations in Presnilin-1 (PSEN-1), Presnilin-2 (PSEN-2), Amyloid Precursor Protein (APP). Deformation within those precursor amino acid yield the building of

amyloid -42, the most neuro infective or lethal form of amyloid scrap currently consists about 42 amino acids. Correspondingly, the inception of Alzheimer's disease is delayed (Dobricic et al., 2012). There are genes that enhance the chance of getting EOAD. The most significant are the apolipoprotein E (APOE)ε4 alleles. APOEε4 is a resistance gene that lowers the age of onset for normal AD, and it connects with the occurrence of memory loss and hippocampus atrophy in AD. The APOEε4 allele may be causative for EOAD individuals with typical amnestic symptoms. In comparison, EOAD patients with unusual nonamnestic presentations are more likely to be APOEε4 negative (Mendez, 2012).

- **Late Onset Alzheimer's Disease (LOAD)/ Sporadic AD:** This is the bulk frequent kind of AD. Symptoms become visible usually in mid-60s or later. Although no specific gene has been identified as directly causing late-onset Alzheimer's disease, but research showed that a form of Apolipoprotein E (APOE) gene carrying can increase individual's risks. Not everyone who carries the ε4 allele somewhere at APOE locus might generate late-onset Alzheimer's disease, though asset of the ε4 allele so at APOE locus on a person's chromosome 19 has been shown to be a risk factor for LOAD development. Minor memory loss is clearly apparent at first, but progresses to massive cognitive dysfunction. These include, severe memory loss, language problems, behavioral disorders, motor difficulties, paranoia, and other characteristics. The risk of recurrence to cognitive dysfunction varies between individuals, it can last for two decennary. Late-onset disease is becoming most frequent as people get seniority. It is forthwith believed to be the leading foundation of dementia among the elderly. Unlike the EOAD, documentation proposed that late-onset Alzheimer's disease is not genetically determined (Balin & Hudson, 2014). (-Précoma, Rodríguez-Cruz, Berumen L, & García-Alcocer, 2016)

3.4. Symptoms of Alzheimer’s disease

Alzheimer's disease is thought to emerge at least 20 years before symptoms appear. It begins with alterations to the brain that seem to be unnoticeable to the individual who is affected. People only notice noticeable symptoms after years of brain deficits (“2021 Alzheimer’s Disease Facts and Figures,” 2021) . AD is a steadily progressing neurological sickness that manifests long prior to clinical features appear (Association, 2018). The features and symptoms of Alzheimer's dementia fluctuate from person to person, and the distinctions between regular age-related cognitive functions changes and early symptoms of Alzheimer's disease might be slightly changed. Individuals suffering from Alzheimer's disease experience a diversity of symptoms that change over time. The severity of these symptoms reflects the level of neuronal loss in various sections of the brain. Individuals differ in how quickly their symptoms facilitate from mild to moderate to severe.

- Individuals going through the mild stage, can independently operate most activities such as, regular and habitual activities, driving, activities of own hobbies. Though sometimes they require assistance for some activities to remain protected. They may be able to do daily work, drive, and participate in favorite activities.
- People carrying out the moderate stage, which is the longest phase, could have trouble functioning for routine tasks, as it could be notice that, they become puzzled about their surroundings and begin wandering, and begin to experience behavioral and personality changes, along with nervousness and agitation.
- Assistance is must require for individuals who are going through the severe stage for their basic daily tasks like bathing, dressing, and use of the bathroom. Soon or later, their capability to communicate orally or in writing become limited.

Damaging of some parts of the brain is accountable for eating and drinking difficulty as these part is liable for controlling swallowing. As a result, people may swallow food into their trachea rather than their esophagus. Food granules can become lodged in the lungs and lead to illness. This sort of illness is known as aspiration pneumonia, which is a leading cause of mortality in many Alzheimer's patients. Some people experience challenges on their ability to plan, judge or decision-making or solving problems. Vision difficulties are an indication of Alzheimer's disease. They could struggle with reading, assessing distance, recognizing color (Association, 2018).

3.5. Current treatment and diagnosis

There is a scarcity of comprehensive knowledge more about the pathophysiology of AD, and there are only a few therapeutic approaches convenient to handle this neurodegenerative illness. In view of the heterogeneity of Alzheimer's disease, treatment medicines that operate on various levels of pathology are required (Davinelli et al., 2012). Global controller have targeted a 2025 deadline for discovering a constructive solution to cure or intercept Alzheimer's disease. The National Alzheimer's Project Act (NAPA) was approved and signed into legislation in the USA in 2010/early 2011. It necessitated the development of a national policy hope to address the fast spreading Alzheimer's disease epidemic, in addition to the coordination of AD initiatives throughout the federal government. The main scientific objective of the initiative is to "avoid or successfully cure Alzheimer's disease by 2025". Despite the examination of various possible therapies in clinical studies, mainly four ChEIs and memantine have demonstrated adequate well-being and effectiveness to warrant worldwide trading authorization. These five medications are symptomatic therapies that briefly improve memory and cognitive issues; their clinical impact is moderate; they do

not address the root genesis of AD and do not halt the evaluation of deterioration (Cummings et al., 2016).

AD progresses through 3 stages: preclinical, moderate cognitive impairment, and dementia. Whereas a 7-phase version perhaps further accurately described, the progression of AD perchance classified into three stages: preclinical, moderate cognitive impairment, and dementia. Impairment steps and levels include: 1. No impediment. 2. Minimal intellectual deficits 3. Mild cognitive impairment 4. Mild cognitive deterioration (advance stage dementia) 5. Moderately extreme cognitive deterioration (beginning of mid-stage dementia) 6. Critical cognitive impairment (delayed mid-stage dementia) 7. Major cognitive deterioration (delayed stage dementia) (Rasmussen & Langerman, 2019). The choice of medication should be based on the patients' particular circumstances. Sufferer with AD of any stage and with dementia, furthermore, Parkinson's disease dementia, usually take galantamine, donepezil, rivastigmine, which are cholinesterase suppressor. On the other hand, Memantine is known as a non-competent N-methyl-D-aspartate receptor antagonist and dopamine agonist sanctioned for the nursing of tolerable to extreme AD (Weller & Budson, 2018). Hardly the one FDA-authorized AD medications are the galantamine, AChEIs, rivastigmine, donepezil, in addition to the NMDA antagonist memantine. AChEIs function by blocking the enzyme molecule acetylcholinesterase from disintegrating acetylcholine. This implies there is more acetylcholine in the brain, which causes improved services across nerve cells. That may temporarily alleviate certain Alzheimer's disease symptoms. As a response, AChEIs increase essential cholinergic neurotransmission and, as a direct consequence, mitigate cognitive decline, at least in the time of initial year of medication. Further worsening occurs, even though quitting

these drugs for a short period produces rapid reduction (Yiannopoulou & Papageorgiou, 2020).

On the other hand, multivariable customized treatment for Alzheimer's disease is currently being explored, through using these following sections:

- Communication of joining, linking, connecting the doctor, the caregiver, and the patient: a natural and productive flow of data and feelings across them will permit for quick symptom recognition, correct diagnosis, and adequate counseling.
- Mental perspectives of patients can be on control by:

❖ Established unique routine for each patient.

❖ Cognitive behavioral treatment.

❖ Environment consistency and simplification.

❖ Maintaining a natural communication circumstances.

❖ Providing enjoyable activities such as light exercise, music therapy.

❖ Timely taking medicines and medical decisions and needs (Rasmussen & Langerman, 2019).

3.6. AD in Bangladesh circumstances

Bangladesh, a lower-middle-income country, isn't yet prepared to manage AD. AD awareness is still now in its early stages. As a result, impacted patients and their families are constantly confronted with new challenges. The funds available for AD research are minimal. Since, the majority of the country's population is young now, during the next 20-30 years, this state will allow a huge aged population. For this consequence, the

likelihood of AD incidence will increase. As a result, current time is a good pattern to contemplate the disease and management in a constructive approach and catch the required necessary measures. Health experts, Policymakers, and additional inquisitive organizations should collaborate to signify AD as a national precedence. As, Bangladesh ranks among the world's top tobacco-consuming countries, it is high time to reduce the smoking rate to avoid future circumstances of AD. According to a global research, about one-fifth of the grown up population in Bangladesh is plumped which indicates the high risk of AD occurance (Rahman et al., 2017).

3.7. Organizations that focuses on AD treatment

- SAJIDA Home Care provides patient's house installation health institution care coverage to 36 sufferer in various locations in Dhaka, with 62 nanny, who have Dementia Care Skills training also works there. Caregivers who successfully complete the training receive certificates from the Bangladesh Dementia Task Force (BDTF). BDTF is a civilized platform that includes raising consciousness about dementia analysis in Bangladesh.
- The Sir William Beveridge Foundation contains a single unit namely "Dementia Bangladesh," which concentrate on delivering dementia care pedagogy for top personnel through Alzheimer's Associations in Australia. Moreover professional experts in Bangladesh. In 2014, they organized their inaugural International Dementia Conference in Dhaka in Bangladesh, to make people aware with regard to the issues of an elderly society for a Developing Country.
- The Alzheimer's Society of Bangladesh (ASB) which was the first to organize the Dementia awareness in Bangladesh. From its opening, ASB has tirelessly worked

diligently to promote initiatives for dementia awareness, education, training, as well as support but also research. It is an organization of humanitarian, non-governmental and non-profit volunteer foundation originated in 2006 to serve as an opportunity for social workers, ex: doctors, caregivers to react, address and fulfill the demand of dementia sufferers with the intention of improving their aspect of life. ASB Alzheimer's Disease International (ADI) granted Alzheimer's Society of Bangladesh (ASB) full membership in 2009, confess its essential needs and outstanding services to the study of dementia.

- Life-style Upgradation Project for senior people is a unique and comprehensive Young Power in Social Action (YPSA) initiative that is funded by the PKSF (Palli Karma Sahayak Foundation) that is concerned with the well-being of the elderly. YPSA is committed to working on problems connected to the empowering of the elderly and improving their quality of life by developing strong ties with local government. Counseling is being offered. Bangladesh's Ministry of Social Welfare has engaged on a initiative called Oboshor, which is an old age care service and hospitality complex in Sreemangal. Apon Nibas Old Home Care, and others are worth mentioning.
- The Bangladesh Association for the Aged and Institute of Geriatric Medicine has been seen as solitary country's leading non-governmental corporation dedicated to the care management of the elderly. It is organized with the Institution of Social Services and Social Welfare and is devoted to the welfare of those over the age of 55. This Association offers neurological assistance among other services. Other non-governmental organizations (NGOs) that work with the elderly include Help Age International Bangladesh (works globally for the elderly), Dhaka Ahsania Mission, Resource Integration Centre, Old Rehabilitation Centre. With the tagline "A Care for

the Generation," the Service Centre for Elderly People (SCEP) in Rajshahi started working for the elderly in 1994. It is beneficial to one's health for emotional peace (Roy et al., 2020).

3.8. What is nanotechnology

The discovery of nanotechnology's potential has opened up new chapters in many parts of our life, particularly in the detection and treatment of human ailments. In present time, a large amount of research has been devoted to the discovery of so-called "neuroprotective medicines," or treatments that potentially halt disease advancement by targeting specific molecular processes in the AD pathogenesis process. Recent discoveries suggest that phytochemical substances with neuroprotective properties could be useful in the hunt for therapeutic prospects for Alzheimer's disease. Approaches that can restore damaged tissue, known as "regenerative agents," are more futuristic. These two techniques (neuroprotective and neuroregenerative) are referred to as "disease-modifying approaches" when combined. They differ from symptomatic therapies in that, in addition to alleviating symptoms, they attempt to halt disease progression and repair defective or dead tissue. Controllable manufacturing of desired structures and devices with desired structures is possible. Nanotechnology is enhancing molecular detection, medication development, delivery, and monitoring for a diversity of difficult human affliction, such as cancer and neurological disorders (Nazem & Mansoori, 2011) (Davinelli et al., 2012) (Brambilla et al., 2011).

3.9. What is combination therapy

Using two or more drugs in combination for increasing treatment efficacy. Here drugs using together with the purpose of improving drug effectiveness and to block the spreading of drug resistance. Given the accumulating evidence that numerous molecular, biochemical, and cellular mechanisms interact to generate the illness, the fact that somehow a single-target approach to a complex disease like Alzheimer's has yet to provide an effective therapeutic effect. Drugs are combined based on multiple researches to treat complex infections including cancer, HIV, Alzheimer's, tuberculosis. But combination therapies require many researches to determine how their mechanisms interact. One drug may attack one pathway while another targets another. It may happen that, different infected cells grow at various speeds. At that time, some antibiotic classes are more effective at killing fast-growing cells whereas others are more effective at killing slow-growing cells. Thousands of different combinations is possible to test. If such appropriate combinations can be discovered, then multidrug therapy may improve effectiveness of the treatment while also preventing the rise of drug resistance, both of which are major long-term goals. It's difficult to predict which drugs will work well together because drugs in combination always don't behave in the same way they do alone ((*What Is Combination Drug Therapy?*, 2022) (Stephenson et al., 2014).

3.10. Benefits of combination therapy and nanotechnology on AD treatment

Degeneration of neuronal cells or nerve tissue occurs several years, if not decades, before the patient exhibits any signs of AD. Additionally, the present treatments for AD simply alleviate its symptoms. As a result, whether the sickness is detected without

delay or not, standard medical methods are incapacitated of completely stopping or reversing disease progression. Nanotechnology has the capability to treat Alzheimer's disease through both neuroprotective and neuroregenerative techniques. Furthermore, nanotechnology has demonstrated auspicious uses in choose drug transportation for AD, and multiple nanocarrier approaches have been investigated in recent years to boost the bioavailability and effectiveness of several Alzheimer's disease treatment agents (Nazem & Mansoori, 2011) (Brambilla et al., 2011). On clinical studies of a sequence of anti-amyloid monotherapies, though some medications were successful in eliminating amyloid, but failed to prevent the course of cognitive impairment. Both of the lines of Research suggests that intermediate processes, like as tau pathology, may be mechanistically connected to or caused by Aβ deposition, but may have a more significant role in mild cognitive decline. As a result, while recent evidence suggests that anti-amyloid therapy, including aducanumab, may limit cognitive deficits to some extent when administered during an earlier stage of AD, such an agent may be more constructive when combined with one targeting a method that has a more significant affect on cognitive decline (Salloway et al., 2020).

Chapter 4

Challenges and future prospects associated to Alzheimer's treatment

4.1. Nanotechnology

Aβ oligomers and free radicals are the two leading sources of neurotoxicity in AD pathogenesis. Some nanotechnology-based techniques are efficient for shielding neurons from Aβ lethality by blocking amyloid oligomerization (anti-assembly strategy) and/or Aβ oligomeric species accumulation. Additional nanotechnology neuroprotective techniques have included that defend neurons from free radical oxidative stress, these are also known as antioxidant sponges, which are:

- **Nanogels:** To prevent Aβ toxicity due to oligomers and free radicals nanogels would effectively suppress the amyloidogenesis process via regulation of protein folding and aggregation method. Because Protein-containing amphipathic nanogel that regulates protein folding and aggregation.
- **Diamondoid Derivatives Diamondoids:** These anti-bacterial and anti-viral drugs are the most prospective molecular building blocks in nanotechnology. Diamondoid based (memantine) drug and Namenda together is a FDA-approved drug which delays the growth of Alzheimer's disease. Memantine is a neuroprotective drug against excitotoxicity, which is specified as an overexposure to the excitatory neurotransmitter glutamate or excitability of its membrane receptors, resulting in neuronal damage or death. Hyper excited N-methyl-d-aspartate (NMDA)-type glutamate receptors granted to excitotoxic neuronal cell death though NMDA receptor activation, on the other hand,

is required for optimal neuronal function. Memantine selectively obstructs imprudent NMDA receptor scheme while without interfering with expected pastime.

- **Nano-Ceria:** Cerium oxide has anti-oxidant properties. By regulating intracellular signaling pathways responsible for cellular death and neuroprotection, nano-ceria shields neurons from the cytotoxic activity of Aβ.
- **Fullerene:** The administration of carboxyfullerenes prevent $A\beta_{42}$-induced neuronal apoptosis. Water-soluble hydroxyl functionalized metabolites of fullerene, have been demonstrated to be neuroprotective against $A\beta_{42}$. The neuroprotective impact of fullerenols is most likely related to anti-oxidant responses as well as prevention of A_{42}-induced Ca2+ neurotoxicity. Hydroxyfullerene (fullerenols), carboxyfullerene and other functionalized fullerene derivatives are being investigated for the development of narrative treatments for AD.
- **Gold Nanoparticles:** Their depiction was focused on dissolving Aβ aggregates and preventing future Aβ aggregations at the molecular level by delivering local thermal energy. :
- **Physical interaction with Aβ peptide:** An exogenous material that can minimize peptide toxicity might indeed act via two opposing mechanisms: (1) By lowering monomer nucleation and thus blocking accumulation, resulting in a depletion in the synthesis of fibrils, oligomers, plaques (2) By separating amyloid plaques or fibrils.
- **Dendrimers:** Another use of nanotechnology is the prevention of Aβ's cytotoxic effects, and the use of altered dendrimers is a new recommendation for this strategy. As they might protect the cell layer against Aβ membrane arbitrate neuro lethality caused by Aβ electrostatic contact with the cell diaphragm. Furthermore, dendrimers may trap the A harmful species, so blocking their detrimental impacts on the cell membrane (Nazem & Mansoori, 2011).

- **Polymer NPs:** Sulfated, sulfonated, and fluorinated PS NPs have similarly been shown to decrease Aβ oligomerization and lethality against cultured neurons. Furthermore, it was demonstrated that hydrogenated NP equivalents had lower effectiveness, resulting in the creation of sheet nanostructures and aggregation. These findings underlined the critical necessity of the outward properties of the NPs used. Linse's group, for example, latterly revealed a binary impact of cationic amino-functionalized PS NPs on aggregation of Aβ fibril. The ability to modify peptide assemblage merely by adjusting the NP content was thoroughly reported, emphasizing the critical role of NP dosage in aggregation behavior.
- **Liposomes:** SPR tests revealed that liposomes designed with planar curcumin manifested the greatest affinity constant for Aβ fibrils reported thus far, but nonplanar curcumin equipped liposomes did not demonstrate any conclusive.
- **Inorganic NPs:** the ability to natively and casually heat and disintegrate the Aβ1-42 deposits by blended use of mild microwave fields and Au NPs with no bulk effect. Despite the fact that this method appeared promising, it resulted in the creation of soluble oligomers, monomers whose are currently thought to be the most hazardous species in Alzheimer's disease.
- **PEGylated micelles:** In the extracellular media, these micelles must earlier engage with the peptide, burying its hydrophobic domains mostly in the micelle's hydrophobic cavity by dint of a preferred α-helical configuration that resists self-assemblage. Finally, the PEGylated micelles will indeed protect the unveiled hydrophobic province of tiny $A\beta_{1-42}$ complexes with their hydrophobic acyl groups, preventing the development of more $A\beta_{1-42}$ aggregates.

One key use of nanomedicine is targeted medication delivery. It becomes even more problematic in the case of central nervous system (CNS) illnesses as a consequence of the extra barrier of the BBB opposed to the entrance of a number of chemicals into CNS tissue. The application of biocompatible nanoparticles is to promote therapeutic agent passage over the BBB has been intensively investigated over the last decade. In this section, we will look into nanocarrier systems that have been proposed for delivering therapeutic medicines for Alzheimer's disease into the brain (Nazem & Mansoori, 2011).

4.1.1. Transporting of bioactive molecules to the brain:

A robust blood brain barrier is a consequential impediment to the generation of the pair of small and big neurotherapeutic compounds (ex: Aβ fragments, antisense oligonucleotides, recombinant peptides, viral vectors). The BBB has a detrimental impact on therapeutic efficacy and tolerance because high dosages of medicines are required to achieve concentrations in excess of the minimum appropriate quantity in the brain. Nanoparticulate approaches provide a solution to these issues by acting as "Trojan systems" for moving dynamic atoms over the BBB, lowering damage and boosting curative effectiveness (Brambilla et al., 2011).

4.1.2. AChE inhibitors + acetylcholine (ACh):

A lack of cholinergic neurotransmission is thought to have a significant post in the memories and learning impairments seen in Alzheimer's patients. Enhancing cholinergic neurotransmission has shown to be the most victorious treatment technique for treating AD. Correspondingly, the FDA authorized rivastigmine, an accommodative and irreversibly inhibitors like AChE and butyrylcholinesterase, for the curative purpose of Alzheimer's disease in 2000. This medicine has been proven in studies to at least stabilize, if not promote cognitive and universal justification, etiquette in

Alzheimer's sufferers. Unfortunately, because of poor brain localization, therefore need repeated injections, but also its deleterious cholinergic impact on peripheral organs, its therapeutic usefulness remains restricted. The application of nanocarriers is to deliver rivastigmine towards the brain strength a viable way around these restrictions. Researchers encased rivastigmine in polysorbate 80-coated polymeric PnBCA NPs along with goal of enhancing brain transportation and reducing side effects reported when the free medication was used. During intravenous injection administration of rivastigmine into rats, the researchers discovered a 3.8-fold increase in rivastigmine absorption inside the brain region in comparison to free rivastigmine. The implimentation of NP displacement to the brain are associated with polysorbate 80 arbitrated affinities for apolipoproteins E and A-I, followed by NP incarnate via the BBB's low-density lipoprotein receptors (LDL-r). Using PnBCA nanocarriers, the identical group presented a comparable strategy of increasing the brain absorption of tacrine, additional AChE inhibitor. When contrast to the free medication, the operation of NPs boosted tacrine brain density level by a factor of four. Joshi et al. recently exhibited improved treatment outcomes with rivastigmine encapsulated in poly (lactide-co-glycolide) (PLGA) and PnBCA NPs in amnesic mice37. Hormone and anti-hormone bioavailability can be considerably increased using nanoparticles.

4.1.3. Curcuminoids:

Curcuminoids derived from Curcuma longa (turmeric), one of the popular instinctive yellow photoconstituents in the farming and food production, already been extensively concealed for bioactive compounds such as, antioxidant, anti-inflammatory, anticarcinogenic, antiviral, hepatoprotective, neuroprotective and several others. Report shows by several researchers that curcumin can greatly attenuate Aβ aggregate-related neurotoxicity. Consequently, this molecule is unstable since it quickly

hydrolyzes in the both acidic and alkaline circumstances. It can additionally be oxidized or photodegraded, resulting in low bioavailability and, as a result, low brain absorption. Poly n-butylcyanoacrylate (PnBCA) nanocapsules have indeed been employed to transport these therapeutic compounds across the BBB. In order to exploit LDL receptors for such BBB crossing, these nanocapsules were bound with the protein ligand apolipoprotein E3 (APoE-3) (Nazem & Mansoori, 2011) (Brambilla et al., 2011).

4.1.4. Non-functionalized NPs:

Two simultaneous experiments on the absorption of curcumin with polymeric PnBCA NPs found that the encapsulation process significantly boosted curcumin half-life and intensity in the brain, comparatively with natural curcumin. Furthermore, the restorative effectiveness of this strategy in Alzheimer's disease has yet to be determined.

4.1.5. Targeted NPs:

This method used curcumin stuffed PnBCA NPs patterned with ApoE3 ligands to target LDL-r-arbitrated transcytosis throughout the BBB and via SH-SY5Y neuroblastoma cells. On SH-SY5Y cells, ApoE3-functionalized nanocarriers inhibited $A\beta_{1-42}$-mediated toxicity and were compared to free curcumin. The results demonstrated a significant reduction in $A\beta_{1-42}$-related toxicity (40% relative to free drug at 100 nM A) on cells healed with functionalized nanospheres, as well as a drop in responsive oxygen species generation.

4.1.6. Immunotherapeutics:

Chitosan-based immunotherapeutic nanocarriers chemically modified by using $pF(ab')_2$, an Ab splinter muted with putrescine that is distinct to Aβ, were upto to traverse the BBB and attack brain amyloid plaques. These NPs might potentially be bundled with imaging techniques for medications that lessen the toxicity associated

amyloid plaques to treat AD. Though Immunotherapy at opposed to $A\beta_{1-42}$ peptide showed severe complications for AD cure.

4.1.7. Estrogens and androgens (Hormone Nanocarriers):

Treatment with estrogen can reduce the threat of AD. Estradiol has been shown in studies to boost the proliferation and endurance of cholinergic neurons while also drastically reducing cerebral amyloid formation. Considering this, estradiol was encased in PLGA NPs as an alternate strategy. They effectively enhanced the bioavailability of the medicine after orally ingestion by modifying the copolymer molecular mass and structure (ex: the proportion of lactide and glycolide molecules in the co-polymer). Mifepristone, known as an efficacious antiprogesterone substance, has been found to minimize the advancement of cognitive wreckage in AD patients most notably through a system associated to P- glycoprotein transporter-mediated Aβ efflux. Investigation showed the upgradation in drug bioavailability following oral administration of mifepristone encapsulated inside PLGA NPs. It has been demonstrated that nanoparticles can considerably improve the bioavailability of hormone and anti-hormone compounds.

4.1.8. Chelating ligands:

Evidence and examinations support the concept that oxidative stress, caused by multiple techniques, is the key threats that initiate and worsen AD. If the surrounding concentration of transition metals increases, oxidation processes accelerated by metals including copper (Cu2+), iron (Fe2+), zinc (Zn2+), aluminum (Al3+). Furthermore, recent research has demonstrated that biometals facilitate the displacement of Aβ in the CNS. Another research found that accumulated A from dissection AD brains may be resolvable by coincubation in the company of such as ion chelators. Thus, metal-

chelating agents including desferrioxamine, ethylenediaminetetraacetic acid salts, clioquinol have been employed to considerably upgrade clinical symptoms in Alzheimer's disease sufferers.

4.1.9. α-, β-, and γ-secretase inhibitors Aβ:

α-, β-, and γ-secretases are all potentially therapeutic targets. Nonetheless, due to the numerous biological roles associated with α- and γ-, β- secretase may be the bulky applicable and appealing target. Including a logical α-secretase exponent into lipidic NPs might upgrade vocal bioavailability.

4.1.10. Antioxidants species:

Another technique for treating Alzheimer's disease is to supply antioxidant species to the brain, which have the potential to reduce the irritability of reactive oxygen species. Solid lipid nanoparticles (SLN) have previously been pre own to escalate anti-oxidant agent delivery. SLN is one of the safe nanoparticles recommended for medication delivery to the brain. Researchers used SLN as a nanocarrier carrying ferulic acid [3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid], a phenolic molecule with high anti-oxidant action.

4.1.11. Glutathione:

One of the most significant intracellular antioxidants is γ-glutamylcysteinylglycine (glutathione, GSH), a water-soluble intrinsic antioxidant consisting of cysteine, glutamic, glycine. By neutralizing singlet oxygen (O_2), hydroxyl radicals (HO), and superoxide radicals (O_2), it perhaps shield cells from oxidative nervousness. Synthesizing PEG-GSH complex that self-assembled into NPs beneficial to increase GSH levels in the brain.

4.1.12. Green Tea Polyphenol:

Epigallocatechin-3-gallate (EGCG), the green tea polyphenol can reduce Aβ production in regard to anti-oxidant properties. A is thought to be formed via the successive cleavage of Aβ precursor protein (APP) by β-secretase and subsequently γ-secretase. Instead of β-secretase, APP might be broken by the other proteolytic enzyme called γ-secretase. In this situation, sequential cleavage of the residue by γ-secretase yields P3 rather than Aβ. It has been shown that EGCG can stimulate α-secretase and so divert the APP cleavage mechanism away from the synthesis of Aβ. However, because of its limited absorption, EGCG alone may not be of therapeutic use when taken orally. R ecent study showed that EGCG with a lipid nanocarrier to create EGCG:lipid complexes (nanolipidic particles) with a diameter of 30-80 nm. Because of its compact size, this novel formulation increased EGCG bioavailability and suggested a possible increase in EGCG brain absorption.

4.1.13. Gene Nanocarriers:

A transporter should carry the genetic material to protect it from biological barriers such as cell membrane charges and enzymatic destruction. So far, viral vectors have been used in the majority of gene therapy research for Alzheimer's disease. However, the use of alternative non-viral vectors has attained popularity in modern years due to some health hazards. The use of nanoparticles for nonviral gene carriers, has substantially enhanced the efficacy of this approach by reducing enzymatic degradation of genetic components (Shuaib et al., 2008)(Martín-Rapun et al., 2017)(Dabur et al., 2020)(Brambilla et al., 2011)(Nazem & Mansoori, 2011)(Shuaib et al., 2008).

4.2. Combination therapies

It was discovered that the combination of dopenzil and memantine had greater benefits on cognitive and neuropsychiatric indications, the global evaluation, and everyday task, but was slighter agreeable to sufferer than either memantine exclusively or placebo. Furthermore, on the normal course of AD, memantine with donepezil is consider as better cost-efficacious than donepezil alone since memantine may diminish the advancement of AD (Guo et al., 2020). Memantine and dopenzil together has been appeared to upgrade cognition in individuals with slight to average vascular dementia, the effectiveness of memantine or dopenzil alone didn't show better effectiveness (Farlow et al., 2004). But other combination therapies also can be used such as:

4.2.1. Donepezil and Vitamin E:

In a 24-week research, donepezil enhanced AD scores in individuals with AD contrasted to the placebo group. Vitamin E reduces symptomatic development in Alzheimer's disease patients, likely due to interactions with free radicals including disruption of mechanisms that result in cell damage. Donepezil and vitamin E, both presumably function through independent modes of action, are unlikely to interact in the nursing of AD. They allowed to function synergistically and, when combined, provide treatment to specific individual sufferer with Alzheimer's disease.

4.2.2. Memantine + ChEIs:

Until far, the most extensively researched combination medication therapy for AD treatment has been the concurrent usage memantine and ChEIs. Additionally, this medication has shown clinical success in the cure of AD. The consequence of this CT on AD have additionally been studied in open-label trials, long-term controlled studies, randomized controlled trials (RCTs). RCTs in AD typically examine pharmacological

performance, and these studies include the determination and confirmation of four primary criteria, including accomplishing in daily pastime and living, neuropsychiatric symptoms, cognition, and complete clinical outcomes globally. These parameters are seen to be evidence of clinical efficacy. These criteria are seen to be evidence of clinical efficacy. These studies' findings indicate that CTs with memantine and ChEIs reduce the amount of utility and cognitive deterioration. Importantly, as opposed to no care or ChEI monotherapy, similar CTs can lessen the occurrence and frequency of neurobehavioral trait (Tanvir Kabir et al., 2020).

4.2.3. Tacrine and estrogen:

Investigation showed that combined tacrine and estrogen hormone replacement care in AD sufferer may improve tacrine responses in women with AD.

4.2.4. Rivastigmine + memantine:

No significant variations in efficacy. There were no discernible variations in the treatment groups' safety and tolerability.

4.2.5. Galantamine + Memantine:

Memantine (N-methyl-D-aspartate receptor (NMDAR) antagonist). Biochemical data suggests that glutamatergic cell projecting is disrupted in AD. Consequently, their correlative failure, particularly with that of the cholinergic arrangement, is critical in the pathogenesis of AD. As a result, certain CTs simultaneously attacked glutamatergic and cholinergic pathways are termed the current norm of therapy for persons with AD. NMDAR is recognized to be involved in teaching and memory. Likewise, glutamate and glycine are indeed the agonists that must bind to the NMDAR at the same time in order to activate it. Clinical studies have demonstrated that NMDAR overactivation (by excess glutamate) can result in an unregulated influx of Ca2+ into the cell, ultimately generating to excitotoxicity. Galantamine, on the other contrary, has neuroprotective

properties in opposition to glutamate lethality as a means of the stimulation of nicotinic ACh receptors in incorporation to its inhibitory effects on AChE. Additionally, they indicated in their study that pairing subactive doses of memantine and galantamine might result in complete neuroprotection. Furthermore, their research gives a unique design technique for developing an MTDL with maximum efficiency.

4.2.6. Memantine + Nitroglycerin:

The second version of memantine analogs was created to increase memantine's effectiveness and supply it with a significant disease-modifying impact. To create these memantine analogs, an essential pharmacophore (nitrooxy moiety, -ONO2) from nitroglycerin was coupled with memantine. Nitromemantine and memantine were tested in vivo on extrasynaptic NMDARs in an AD mouse model with triple transgenic. In addition, only the nitromemantine-treated group performed significantly progressing on the spot novelty memory task. Furthermore, these investigations demonstrated that nitromemantine was capable of reversing the defeat of brain interrelation that restore the volume of synapses to normal in mice AD models after a few months of therapy. These data imply that nitromemantine may have disease-modifying capabilities. Similarly, nitromemantine had no adverse effects on blood pressure. These encouraging findings in animal sample have led the inclusion of nitromemantine in human studies. These approaches are restoring optimism in the nursing and care of primal and delayed phase AD.

4.2.7. Rivastigmine and Rasagiline:

The instance of ladostigil, a neuroprotective medicine incorporates the properties of existing pharmaceuticals also including rasagiline (anti-monoamine oxidase (MAO)-B), rivastigmine, that are pattern of effective molecular hybridization relying on a drug mixing method (ex: anti-AChE). Furthermore, this hybrid drug inhibited reversible

agents BuChE, AChE and irreversible MAO-B and preserved mice against deficits in motor function and memory. Ladostigil displayed antioxidant capabilities both directly by scavenging free radicals and seconderily by together with the production of cellular antioxidant enzymes. In vivo investigations revealed such ladostigil reduced the levels of holo-amyloid precursor protein (APP). likewise, ladostigil boosted the amounts of protein density of protein kinase C (PKC)a, p-PKC, PKCe in the hippocampus of mice.

4.2.8. Donepezil and Clioquinol:

Smaller hybrid molecules with superior pharmacokinetic characteristics may be advantageous. As a result, a connectivity technique was employed to create a novel sequence of hybrid compounds that link donepezil's pharmacophore with clioquinol's metal chelator. Amyloid plaques have elevated zinc and copper content, whatever is a typical feature of inflammation. Importantly, the compulsory sites for these two metal ions on Aβ oligomers might facilitate amyloid toxicity. As a result, metal chelating treatment may be an effective way to moderate the course of AD. A numerous tacrine-8-hydroxyquinoline hybrids, on the other hand, have demonstrated combination antioxidant, cholinergic activities, Cu(II)-composits. Based on these analysis and observations, a unique series of hybrid compounds were rationally constructed by intigrating the 8-hydroxyquinoline component with benzylpiperidines to achieve suppress of Aβ aggregation, removing free radicals possession, chelation of Zn(II) and Cu(II), and obstruction of ChEI. The aromatic 8-hydroxyquinoline replaces the indanone core of donepezil, preserving its affinity for the slightly different angle of AChE but increasing its molecular weight. It was discovered that the majority of the novel hybrids successfully repressed Aβ self-aggregation and preferentially targeted human butyrylcholinesterase (BuChE).

4.2.9. AChE inhibitor+ α-lipoic acid:

Alpha-lipoic acid may quickly enter the brain, it may serve to protect brain and nerve cells.

4.2.10. Combination of VK-28 + Propargylamine:

M30 was created by synthesizing the propargyl component of rasagiline, an anti-PD medication, including the outline of VK-28. M30 contains the critical pharmacophores of the FDA-certified anti-PD rasagiline. The propargylamine portion in rasagiline's construction is critical to its disease-modifying prospective since it mediates the compound's interaction with numerous neuroprotective/neurorescue system. PBT2 is a second-generation metal protein-attenuating compound (MPAC) that is in phase II clinical studies at the present for the treatment of Alzheimer's disease. M30 has a metal protein attenuating or ionophore component that is comparable to PBT2. MPACs often have an approximate reversible affinity for metals and the ability to penetrate specific intracellular areas. M30 inhibits MAO-A and MAO-B activity selectively in the brain while inhibiting such enzymes poorly in the small intestine and liver in vivo. M30, like other MPACs such as clioquinol and PBT2, has a high propensity for metals (Zn, Fe, Cu). M30, on the other hand, had exceptionally powerful efficacy against iron- excited mitochondrial functional membrane lipid peroxidation, equivalent towards the prototype iron chelator deferoxamine (DFO). Incurable administration of M30 to elderly mice had a significant favorable effect on neuropsychiatric functioning and age-related cognitive loss. Furthermore, M30 drastically shrinkage Aβ and iron buildup in the brains of handled mice. It was also discovered in this work that prolonged injection of M30 decreases Aβ brain pathology and emotional disturbances in a transgenic mice sample of AD.

4.2.11. Combination of Antidiabetic Drugs:

Insulin resistance is a critical factor in the pathophysiology of diabetes and AD. Diabetes is associated to cognitive breakage and Alzheimer's disease. On new trial, people with AD and type 2 diabetes were given either oral diabetes meds or a blending of insulin and additional diabetes treatments. When set side by side to usual therapy without insulin, contributing therapy with insulin significantly reduced functional and mental deterioration in individual with type 2 diabetes and mild-to-moderate AD.

4.2.12. Anti-inflammatory Drug Combination:

Inflammation is strongly associated to a number of clinical disorders. Increased inflammatory signals are typical in the pathophysiology of AD. Regrettably, all phase III investigations on CTs in the company of anti-inflammatory drugs failed to demonstrate clinical effectiveness. Ibuprofen, celecoxib, rofecoxib, and naproxen had no beneficial benefits in the combination of AD therapy as compared to the placebo.

4.2.13. Combination of Antioxidant Factor:

Oxidant/antioxidant imbalances are significantly associated to various disorders, including Alzheimer's. Solitary pathological markers of Alzheimer's disease is oxidative damage. Vitamin E, B vitamins groups, omega-3 fatty acids were unsuccessful in abundant combination studies to treat Alzheimer's disease.

4.2.14. Combination of Anti-Tau Agent:

Several therapeutic techniques primarily target tau pathology. These approaches include the use of medicines that block tau phosphorylation, such as forbidder of glycogen synthase kinase 3 (GSK-3), along with antibodies or substances may diminish tau aggregation. CTs with anti-tau drugs, have investigated the efficacy of adaptable valproate dosages in persons with intermediate Alzheimer's disease without prior psychosis or agitation. Chronic divalproex sodium medication did not reduce functional

and cognitive deficits or postpone the advent of psychosis or agitation in individuals with mild Alzheimer's disease. Furthermore, patients reported observable toxic consequences. Furthermore, those given valproate had larger ventricular enlargement, greater loss of whole-brain and hippocampus volume, and a quicker heart rate.

4.2.15. PBT2 + ChEIs:

Frequent metal vulnerability has been linked to Alzheimer's disease. PBT2 (a copper or zinc ionophore) is a metal-chelating compound employed to reduce the hazardous effect of protein-metal compounds such as Aβ oligomers with zinc and copper. PBT2 has already completed early phase II clinical studies. In individual with advanced Alzheimer's disease, the mixture of PBT2 with ChEIs (galantamine, donepezil, rivastigmine) improved executive skills in the amount of drug dose dependent manner and dramatically reduced CSF fluid Aβ42 levels when compared to ChEIs alone.

4.2.16. Noradrenaline Reuptake Inhibitors + ChEIs/NMDAR Antagonists:

Numerous investigations have found severe noradrenergic impairment in Alzheimer's disease. Atomoxetine is a noradrenaline reuptake inhibitor. CT with atomoxetine was ordinarily considered as well indulged by patients in mild to moderately extreme AD, but did not boost the clinical efficacy of the monotherapy in slight to extremely dreadful AD.

4.2.17. Combination of Neurotrophic Agents:

Adverse regulation of insulin-like growth factor-I (IGF-I), brain obtained neurotrophic aspect, growth factor receptors, and IGF-I receptors has also been seen in individual with moderate cognitive impairment (MCI) and AD. In instance, reductions in neurotrophic waving can promote deterioration of basal prosencephalon cholinergic neurons, resulting in a slightly earlier event in the etiology of AD. Neurotrophic alterations, on the other hand, have been related to cognitive impairment, apoptosis,

impaired neuronal plasticity, synapse loss, and Aβ- and tau-corresponding pathologies. Consequently, mimetic peptides and medicines that could also boost brain neurotrophic signaling mechanisms are seen as promising treatments for Alzheimer's disease. There has been no clinical efficacy with xaliproden or MK-677 (a growth hormone). Conversely, a combination nursing with cerebrolysin (peptidergic medication) and donepezil demonstrated more superiority over donepezil alone in terms of improvements in overall patient's clinical outcome (Tanvir Kabir et al., 2020) (Bednar, 2019) (Stephenson et al., 2014) (Heuser, 2004) (Salloway et al., 2020) (Farlow, 2004) (Patel & Grossberg, 2011) (Yiannopoulou & Papageorgiou, 2020) (Athar et al., 2021) (Weller & Budson, 2018).

Chapter 5

5.1. Limitations

- Lacking of article with composition of combination drug and nanotechnology installed medicine was the main barrier for creating this article.
- Renowned authors and researchers wrote about combination therapy for AD and Nanotechnology based treatments for AD separately.
- Some articles were not sufficiently referenced with authentic sources.
- As only a few drugs are available for AD cure, it is hard to compare between them.

5.2. Conclusion

It is linked to both hereditary and habitat variables, but the mass significant threat is age, therefore it is more common in older people. This review article outlined possible pathophysiological pathways with possible significance to disease development in Alzheimer's disease, for which medicines are currently licensed and available for human use. Several other mechanisms, such as those affecting amyloid production or hyperphosphorylation, may be scrutinized to be persumed in the pathogenesis of AD but for which no treatments are now available. While the symbol and quantity of individual compounds for a background grows linearly, the amount of encouraging agent combination grows exponentially. Collectively, the issues in AD treatment have steered latest treatment strategies is connection with the examination and ranking of novel drugs as adjunctions to guidelines of care, the regenerating of clinically authorized therapeutic agents demonstrated for other medicinal conditions, and the mixture of targeted therapies that target multiple routes.

5.3. Future Recommendations

Comparison between combination and nanotechnology based treatment article should be published by renowned researchers and authors by researching more, by following some steps like:

- Further research on rational agent combinations and nanotechnology based medicine should be conducted. Recent findings suggests that they may have a crucial function in the treatment of neurodegenerative illnesses.

- Despite the fact that there are numerous unresolved issues and hurdles associated with the combination therapy and nanotechnology based medicine, the findings show that they are still a promising curative alternative for AD.
- This is a complicated illness with few FDA-approved single-target treatment medicines. Combining numerous pharmacophores into an exclusive molecule is indeed tough. Nevertheless, CT may also reduce the dosages of particular medications administered, resulting in a reduction in treatment costs and adverse effects.
- The architecture of interactive and revolutionary clinical trials could be fascinating for the probable advancement of curative blending across the advancement of the disease,
- Groupings of anti-amyloid and anti-tau therapies with neurotrophic drugs have additive or synergistic effects. Continuing randomized clinical trials (RCTs) are required to determine if CT prevents disease development in the primal point of Alzheimer's disease.
- Further findings with medications in the prodromal or early phases of Alzheimer's disease may need extensive follow-up periods to demonstrate efficacy because the patterns of disease development and clinical objective to reduce in patients are extremely varied and fairly unresponsive.

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