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**Project On**

**A review on recent therapeutic approaches in the Management of Alzheimer’s Disease.**

A review paper submitted to Daffodil International University's Department of Pharmacy to complete the B.Pharm program.

Submitted To:

Department of Pharmacy

Faculty of Allied Health Sciences

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**APPROVAL**

The project ' A review on recent therapeutic approaches in the Management of Alzheimer’s Disease,' which was submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, was accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy, and its style and contents were approved.

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**Declaration**

This is to certify that the work in this project is unique and has never been submitted to this university before.

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**Dedication**

This work is dedicated to the Almighty GOD, as well as my parents, supervisor, and friends.

**Acknowledgement**

First and foremost, as a human being, I want to express my gratitude to Almighty GOD for allowing me to successfully accomplish this job.

**Sadia** **Afruz** **Ether**, my supervisor, deserves my heartfelt gratitude. Lecturer (senior scale), Daffodil International University's Department of Pharmacy, for her outstanding leadership and for overseeing and inspiring the completion of the project.

I'd want to express my gratitude to **Dr**. **Muniruddin** **Ahmed** Sir, Head of the Department of Pharmacy at DIU, for allowing me to finish the task and for his support.

I'd want to express my gratitude for all of my dear friends' assistance and support. Finally, I am grateful to my parents and other family members for their support and encouragement throughout the process.

**Abstract:**

Alzheimer's disease (AD) is a worldwide epidemic that is spreading at an alarming rate. Alzheimer's disease (AD) is a neurodegenerative disease of the brain that is genetically complex, slowly progressing, and irreversible. Cognitive impairment must be severe enough to interfere with daily activities for a clinical diagnosis of dementia to be made. Descriptive memory problems are common in moderate dementia; depressed symptoms are common, although the patient may normally live alone.Since its inception in 2004, the Alzheimer's Disease Neuroimaging Initiative (ADNI) has aimed to speed therapy development by verifying imaging and blood/cerebrospinal fluid biomarkers in Alzheimer's disease clinical trials. ADNI is a multisite longitudinal research with a naturalistic (nontreatment) approach.Cholinergic insufficiency, oxidative stress, the amyloid cascade, inflammation, and excitotoxicity are among the treatments for Alzheimer's disease. For early and intermediate stages of Alzheimer's disease, second-generation cholinesterase inhibitors remain the primary treatment, but the glutamate antagonist memantine has also been approved for advanced stages of the illness. While research on other experimental medicines is ambiguous at best, antioxidants may slow disease development.

**Keywords:** Neuropathological,Neurofibrillary tangles, Biomarkers,Dementia,Amyloid

beta,Oxidative stress,Histopathology,Tau.

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**Chapter 1**

**Introduction**

**1.Introduction**: Alzheimer's disease (AD) is the most common neurodegenerative disease and one of the most frequent diseases worldwide. Clinically, it is characterized as a gradual loss of cognitive functions that eventually leads to dementia and mortality. In terms of genetics, Alzheimer's disease is usually divided into two types: 1) familial cases with Mendelian inheritance of predominantly early onset (60 years, early-onset familial AD [EOFAD]), and 2) so-called "sporadic" cases with less apparent or no familial aggregation and typically later onset age (R60 years,late-onset AD [LOAD]). It is important to note that this traditional dichotomy is unnecessarily simplistic, as there are cases of early-onset AD without evidence of Mendelian transmission, while LOAD is frequently reported with high familial clustering, sometimes approaching a Mendelian pattern [12].According to the 2009 World Alzheimer Report, 35.6 million individuals worldwide would suffer from dementia in 2010 [13].The current research reveals that the fundamental histopathologic lesions of AD are external amyloid plaques and intracellular Tau neurofibrillary tangles, based on the core pathophysiology and neuropathology of AD (NFTs)[14].

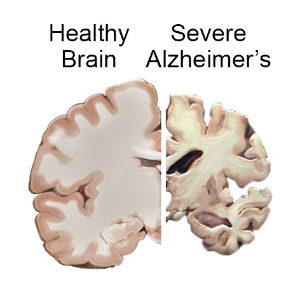


Figure 01: Alzheimer's disease fact

This data is crucial for Alzheimer's research, which includes epidemiology studies, economic impact studies, and, most importantly, treatment and preventative trials. With the exception of disorders caused by single gene abnormalities, histopathological analysis of tissue samples from afflicted locations provides the most precise diagnosis. This is conceivable for many conditions during life through biopsy, but biopsy has long been avoided in the case of Alzheimer's disease due to a high risk/benefit ratio [15].The number of persons with dementia living in their own homes for extended periods of time is steadily rising, typically with the help of a family member. They may be cared for in their former home or other places by paid caretakers. However, when considering Bangladesh's socioeconomic structure, this figure appears to be relatively little, given the cost of such services frequently exceeds a family's gross income. According to WHO data published in 2017, Alzheimer's or dementia fatalities in Bangladesh totaled 9, 917, or 1.26 percent of all deaths, the most recent data available, ranking Bangladesh 152 in the world [16].

**Chapter 2**

**Goal of my study**

**&**

**Methodology**

**Goal of my study:**

1. To define the cause of Alzheimer's disease.

2. To determine the number of people affected by Alzheimer's disease.

3. To see the current Perspective for Alzheimer's disease

4. Create a new aria for higher education.

**Methodology:**

A literature review is carried out as part of the investigation. For this investigation, I read approximately 41 publications. I gathered articles for this study by using Google Scholar and other websites. Between 1985 and 2021, all data was gathered. I'd like to attempt to discuss Alzheimer's illness after gathering knowledge.

**Chapter 3**

**Alzheimer Diseases**

**3.Alzheimer Diseases**

**3.1. Diagnostic criteria:** The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria have been the gold standard for diagnosing Alzheimer's disease since their proposal in 1984.This standards incorporate clinical as well as neuropathological features to provide diagnoses of "potential AD,"'probable AD," & "definite Alzheimer disease," respectively.The Alzheimer's disease currently, the spectrum understood to be more inclusive than ever assumed, & pathological alterations in addition to amyloid plaques and NFTs are now recognized. In response, the criteria established by NINCDS–ADRDA are as being revisited [1]. The modified criteria include biologicSS that are intended to improve diagnostic specificity. Mild cognitive impairment (MCI) was coined in 1999 to describe a state that falls between between normal cognition and dementia. MCI has proven to be an effective designation in clinical settings for identifying persons who are at risk of acquiring Alzheimer's disease [1-2].

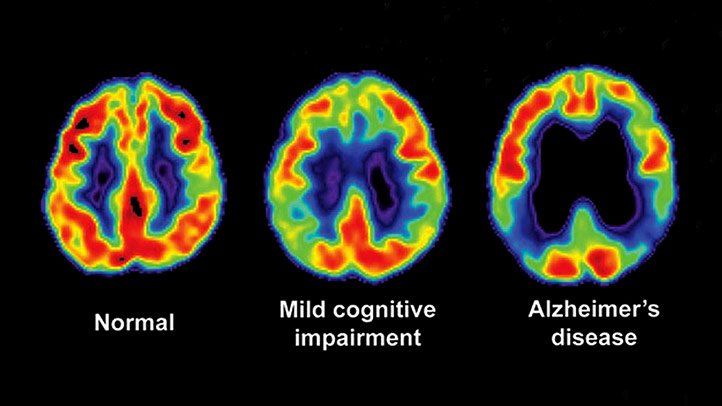


Figure 02: Early Alzheimer's diagnosis.

**3.2. Prevalence,incidence and cost burden related to AD:**   Dementia affected 24.2 million people globally in 2005, with 4.6 million new cases per year. Alzheimer's disease was blamed for almost 70% of these cases. North Americans & West Europeans are thought to have the highest dementia incidence and prevalence rates among 60-year-olds, followed by Latin Americans and China and its Western Pacific neighbors.Dementia rates rise exponentially with age in all of these populations, with the greatest number severe increases occurring in the 7th and 8th life’s decades. Occurrence and prevalance of Alzheimer's disease follow similar patterns. There is evidence that prevalence and rise in western countries have a group of people impact, individuals who were born later having a reduced risk than those born in the century are at a higher risk than those born later in the century [20].Dementia has a huge economic impact, costing more than s177 billion in Europe alone in 2008.The annual expense of dementia is projected to be about s20,000 per person. This estimate is higher than the estimated costs for cancer or cardiovascular disease patients. The epidemiologic and economic evolution of Alzheimer's disease is a severe reason for concern since it shows that the disease will soon have a massive impact on society and might be classified as a modern epidemic. As a result, global preventive, diagnostic, and therapeutic efforts are urgently needed to mitigate the disease's deadly effects [2].

**3.3. Genetic epidermiology of AD:** Alzheimer’s disease with an early onset (EOAD, onset 65 years) accounts 1% to 5% of the total number of cases, while delayed onset AD (LOAD, onset -65 years) accounts for more than 95% of all cases. While in a therapeutic setting similar to LOAD, EOAD is linked to a faster pace of advancement and a pattern of inheritance pattern. The pathophysiology of EOAD has been linked to 3 genes , all of which encodes APP related proteins degradation & Ab production. This 3 genes have a (>85%) high penetrance , are usually dominantly inherited autosomal , & cause Ab aggregation and early-onset illness with certainty. As a result, they're referred to as disease's "diagnostic biomarkers."The genes associated with LOAD, on the other hand, raise illness risk in a non-Mendelian manner [1]. People with an AD-affected first-degree relative have double the predicted the chance of a life time as people who do not have Alzheimer’s disease but have a first degree relative who has alzheimer’s. Furthermore, there is a higher LOAD common monozygotic cotwins are more common than dizygotic co-twins, implying a 60–80% genetical component to the condition. Only the APOEe4 allele on chromosome 19q13 is a genetical risk factor, was a clearly confirmed non-Hispanic European Whites have a "susceptibility" gene descent for more than a decade. APOE is a lipid-binding protein that plays an important role in the humans as 3 different isoforms, APOEe2, e3, & e4. Only one copy of the APOE-e4 allele is a kind of a increased risk by 2 to 3 times, whereas 2 copies is linked to a three times increased risk.Furthermore, each APOEe4 allele inherited reduces the age at which 6–7 years from the time of onset. APOEe4 is also an acronym for linked to poor cognitive function, particularly the sphere of memory, in moderate cognitive impairment (MCI) and dementia development. While the prevalence of APOEe4 is estimated to be 20–50% in the general population, neither the presence of e4 required nor adequate for disease development. The relationship between APOE and LOAD was mostly inconsistent across investigations among ethnic groups other than White non-Hispanic [9-13].

**Chapter 4**

**Clinical features of Alzeimer Disease**

**4. Clinical features of AD:** The most common cause of dementia is Alzheimer's disease (AD). It frequently follows a predictable clinical pattern, which reflects the underlying neuropathology's progression. Our contribution describes the gradual course of dementia from a subclinical to a severe state. After clinical diagnosis, the typical survival time for Alzheimer's patients is 5 to 8 years (Bracco et al. 1994; Kurz and Greschniok 1994; Walsh et al. 1990).The clinical stages described in this work overlap, and individuals advance from moderate to severe illness presentations [9].

**4.1. The pre-dementia stage:** A careful neuropsychological examination could indicate very minor cognitive impairment five years before a clinical diagnosis of dementia syndrome can be made using current diagnostic criteria. A modest impediment in obtaining new information is part of the subdiagnostic difficulty pattern. Other difficult cognitive processes, such as planning and accessing the semantic memory store, can be harmed, resulting in comparable cognitive issues. It's difficult to tell the difference between incipient Alzheimer's disease and a reversible disorder (such as dementia syndrome of depression) or benign, non-progressive memory impairment. Patients do not show signs of a major decline in regular living activities during Alzheimer's disease is currently in its pre-dementia stage. Individuals can use memory aids and other supporting measures to overcome or compensate for their cognitive deficiencies at this point [10].

**4.2. Mild dementia stage:** The most prominent clinical symptom in most individuals is a substantial impairment in learning and memory. However, aphasic or visuoconstructional impairments may predominate in some people. Short-term memory, old declarative memory from the patient's childhood, and implicit memory are all impaired to a lower extent than declarative current memory. Memory loss frequently affects multiple cognitive domains and is a major contributor to the patient's difficulty with ADL. The patient's diminished ability to plan, judge, and organize may manifest itself not only in complicated tasks, but also in more challenging home tasks (managing bank account; preparing meals, etc.). Even if a patient appears articulate, "fluent," and even verbose, communication may suffer from a reduced vocabulary, decreased word fluency, and less precise expressive language.Patients with moderate Alzheimer's disease may be able to live freely for the majority of the time. They will, however, require assistance with a variety of organizational issues due to significant cognitive impairments in numerous domains. If a patient wants to stay at home, plans for a support system should be undertaken now, before more intensive or permanent supervision is required. These emotional disturbances are usually moderate and changeable, although full-fledged depressive episodes can also happen. While his understanding is at least partially intact, the person may exhibit partially understandable emotional reactions to decreasing cognitive and ADL skills or reduced social connections [13].

**4.3. Moderate dementia stage:** Patients may appear to "live in the past" due to severe impairment of recent memory. At this point, logical reasoning, planning, and organizational skills substantially deteriorate. As word finding difficulties, paraphasia, and circumstanciality rise, language challenges become more apparent. Reading abilities degrade, and text comprehension becomes inadequate. With a growing number of errors and omissions, writing becomes increasingly insecure. Patients become distracted and lose awareness of their condition over time. At this point, one-third of Alzheimer's patients experience illusionary misidentifications and other delusional symptoms, which are prompted by both their cognitive deficiencies and the underlying disease process. Up to 20% of patients experience hallucinations, mainly of poor visual quality, which may be linked to a significant cholinergic deficiency. Patients frequently lose emotional control and have outbursts [15].

**4.4. Severe dementia stage:** Restlessness and hostility may be a symptom of discomfort or the result of a severely disrupted circadian cycle. A high percentage of patients are apathetic and exhausted. Patients require assistance during eating, and even the most basic motor processes (chewing and swallowing) may be affected by significant apraxia. Life expectancy drops by a third after a clinical diagnosis of Alzheimer's disease. Long-term symptom persistence, the severity of sickness, old age, male sex, and physical disease are all substantial risk factors for death in Alzheimer's disease. The most common causes of death in Alzheimer's disease are pneumonia, myocardial infarction, and septicemia [14-17].

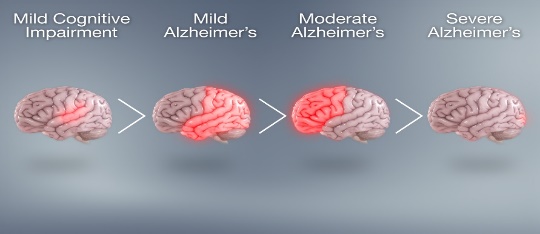


Figure 03: Stage of Alzheimer Disease

**Chapter 5**

**Non-genetic risk and protective factors**

**5.Non-genetic risk and protective factors**

**5.1. Cerebrovascular disease:** Cerebrovascular abnormalities such as hemorrhagic infarcts, small and large ischemic cortical infarcts, vasculopathies, and white matter changes all raise the risk of dementia, although the exact mechanisms behind these changes are unknown. Infarcts or white matter hyperintensities can harm memory-related brain regions like the thalamus and thalamo-cortical projections. They may, however, promote Ab deposition, which can contribute to cognitive impairment or trigger inflammatory responses that impair cognitive function. Finally, hypoperfusion may result in overexpression of cyclindependent kinase 5 (CDK5), a serine–threonine kinase important for synaptic plasticity and synapse formation. Apoptosis and death of neurons are linked to abnormal CDK5 activity. This kinase may potentially be implicated in aberrant tau phosphorylation, which contributes to Alzheimer's disease [18-19].

**5.2. Blood pressure:** Data from longitudinal & cross sectional research linking late-life levels of blood pressure to cognitive decline and dementia are mixed. To some part, these disparities in study design may could be related in research design must be unique, in particular differences in the duration into blood pressure standard & cognitive ability measurement, as well as the age at which these parameters were measured. However, results from observational studies looking at the link between high blood pressure in midlife (40–60 years old) and late-life cognitive impairment have been relatively consistent across cohorts, suggesting that high blood pressure in midlife does increase the risk of later-life cognitive impairment, dementia, and Alzheimer's disease. Hypertension may raise the risk of Alzheimer's disease by affecting the vascular integrity of the brain [21].

**5.3. Type 2 diabetes:** T2D has been reported to substantially double the risk of Alzheimer's disease (AD) in observational studies. T2D and LOAD may be linked by cerebrovascular and noncerebrovascular processes. T2D is connected to with other hypertension & other vascular risk factors and dyslipidemia, making it a risk factor for stroke. The fact that T2D is linked to infarcts but not AD pathology in people with clinical LOAD suggests that the existence of infarcts – which lowers the amyloid threshold required to trigger cognitive impairment – could be the fundamental mechanism linking T2D and LOAD. Hyperinsulinemia and enhanced glycosylation products are examples of noncerebrovascular pathways that may link T2D and LOAD. T2D is accompanied with hyperinsulinemia. Insulin has the ability to pass the blood brain barrier.Due to saturation above physiological levels, peripheral hyperinsulinemia may inhibit insulin uptake in the blood–brain barrier. Diabetic animal and human tissues have more sophisticated glycosylation products and their receptors are upregulated in a T2D environment. In LOAD, there is an increase in the expression of this receptor [23].

**5.4. Body weight:** Body weight (both low and high) have been related as well as a higher risk of cognitive impairment and Alzheimer's disease in prospective studies, implying a U-shaped association that is depending on the age at which body weight is examined and appears to be driven by central obesity [19].

**5.5. Plasma lipid levels:** Whilst, the majority of observational & cross-sectional research linking dyslipidemia may lead to cognitive later in life or Alzheimer's disease are contradictory, research looking at the relationship measurement of lipids in middle age and the incidental risk of Alzheimer's disease lot of a negative effect. Genetic linkage and association studies have convincingly identified numerous transport or metabolism of cholesterol genes as Alzheimer’s disease risk genes, together with apolipoprotein E , apolipoprotein J , ATP-binding cassette subfamily A member 7 , & sortilin-related receptor . Furthermore, studies on functional cell biology show that lipid raft cholesterol is involved in the control of Ab precursor protein processing by b-secretase and g-secretase, resulting in altered Ab synthesis. Epidemiological studies, on the other hand, provide contradictory findings, with no or ambiguous links between the two [25].

**5.6.Traumatic brain injury:** Individuals having a history of traumatic brain injury (TBI) had a greater risk of dementia than those who had not. Men had a higher risk of dementia than women in two meta-analyses of TBI patients. While prospective research on the association between TBI and AD have been inconclusive, postmortem and experimental investigations show a correlation between the two disorders [6].

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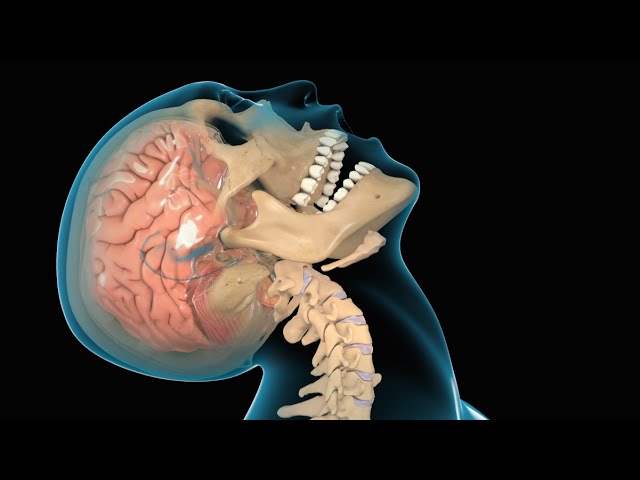


Figure 04: Traumatic brain injury

**5.1.1:** **Protective & non-genetic factors**

**5.1.2. Diet:** There is evidence that a mediterranean diet,which consists of fruits & vegetables from the mediterranean,can helo lose weight .A high fat diet consisting primarily of plant foods & seafood’s with olive oil as the predominant monounsaturated fat source, a moderate wine intake & a low intake of red meat & poultry, is linked to a lower outbreak of alzheimer’s disease & MCI, regardless of vascular comorbidity or physical activity. Antioxidants and polyunsaturated fatty acids abound in diets rich in fish, fruits, and vegetables (PUFAs). Although reactive oxygen species have been linked to neuronal damage in Alzheimer's disease, it's unclear if in the neurotoxic process is a primary or subsequent event. Furthermore, vitamin C & carotenes protect against lipid peroxidation & vitamin C inhibits nitrosamine production and may alter catecholamine synthesis. Antioxidant intake may potentially lessen the risk of Alzheimer's disease through lowering the chance of cerebrovascular illness. PUFAs have beneficial impacts on neuronal and vascular functioning, as well as inflammatory processes, in addition to lowering oxidative stress [28].

**5.1.3. Physical activity:** Physical activity may boost brain health, according to epidemiological and experimental evidence. While physical activity has been shown to improve brain function, some studies have shown no link between the two. Exercise impact on cognitive performance in healthy elderly persons has been studied in RCTs ,with varied results. Physical activity has the potential to affect cognition through causing anatomical changes in the brain like capillary density. Furthermore, animal studies show that physical activity slows the production of amyloid plaques [30].

**5.1.4. Intellectual activity:** Variant following studies in the future & RCTs demonstrate which individuals who engage in cognitively stimulating activities such as studying, reading, or playing games, at both early and old ages, are less likely to develop dementia than those who do not. However, the impact of cognitive training appears to be domain specific and more obvious in people who do not have memory problems [12].

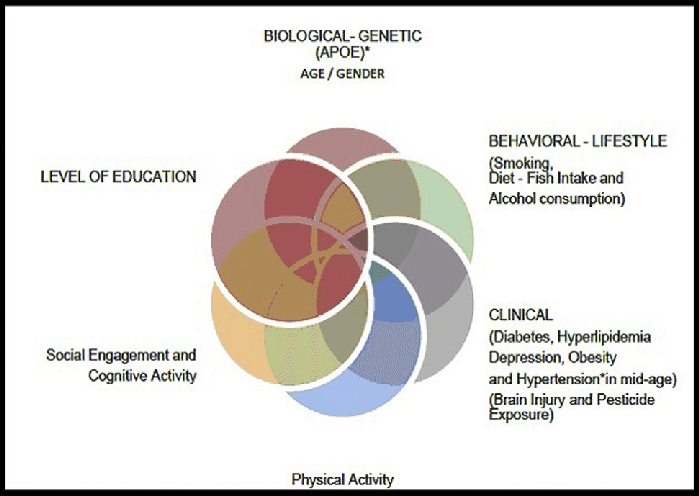


Figure 05: Risk and protective factors for Alzheimer’s disease

**Chapter 6**

**Pathophysiology of Alzheimer’s Disease**

**6. Pathophysiology of AD:**

**6.0. Neuropathological of mild congnitive impairment and early AD:** Patients with AD-type dementia generally have a Braak stage V or VI of neurofibrillary degeneration and significant and extensive synaptic and neuronal loss at the time of clinical diagnosis, according to clinicopathological correlation studies. A novel clinical framework was required to predict the clinical diagnosis of Alzheimer's disease before it progressed to the level of full-blown dementia. The notion of "mild cognitive impairment" (MCI) was presented by Petersen et al. as a novel diagnostic entity for the transition between normal aging and Alzheimer's disease dementia. Patients with MCI already have certain cognitive complaints that may be detected with appropriate cognitive tests and indicate a drop from a previous higher baseline level, but which, unlike dementia, do not impede with everyday activities. Patients with MCI have a unique set of challenges.There are few autopsy studies on MCI patients, but they have consistently found a stage of AD pathology intermediate between cognitively intact subjects and demented patients, particularly in terms of neurofibrillary degeneration, which is consistent with the idea of a transition phase between normal aging and definite AD. MCI patients had an intermediate amount of synapses in the hippocampus compared to nondemented controls and moderate AD patients, implying that many people with MCI symptoms have early AD. Despite the fact that AD was the most common pathological diagnostic underlying MCI in the above case series, there was a high degree of pathological heterogeneity underpinning the clinical diagnosis of MCI, with vascular disease. A big number of the participants in the largest study [34].

**6.1: Neuropathological alteration in AD:** The neuropathological alterations in the brain of people with Alzheimer's disease (AD) have both positive and unfavorable aspects. Traditional "positive" lesions including amyloid plaques and cerebral amyloid angiopathy, neurofibrillary tangles, and glial responses, as well as "negative" lesions like neuronal and synaptic loss. Postmortem studies have enabled the staging of the advancement of both amyloid and tangle diseases and, as a result, the establishment of diagnostic criteria that are now utilized worldwide, despite their intrinsic cross-sectional nature. Importantly, longitudinal in vivo studies employing current imaging biomarkers such as amyloid PET and volumetric MRI have largely supported this cross-sectional neuropathological results [34-35]

**6.1.1. Macroscopic features:** Although a thorough visual examination of the AD brain is not diagnostic, a characteristic symmetric pattern of cortical atrophy affecting the medial temporal lobes but sparing the primary motor, sensory, and visual cortices is extremely suggestive of AD. The lateral ventricules, especially their temporal horns, can seem notably dilated as a result of this pattern of cortical thinning. This pattern is stereotypical, and MRI scans can detect it early in the disease's clinical history. Chronic hypertension and other vascular risk factors induce cerebrovascular illness, which typically manifests as small vessel occlusive disease. The substantia nigra has normal coloring unless there is also Parkinson's disease or dementia with Lewy bodies; nevertheless, the locus coeruleus is altered in the early stages of Alzheimer's disease [38].

**6.1.2. Microscopic features:** Intraneuronal filamentous aggregates within the perikaryal area of pyramidal neurons were first identified as neurofibrillary tangles (NFTs) by Alois Alzheimer in his original postmortem case report. A tiny percentage of fibrils in NFTs do not form pairs and appear as straight filaments with no periodicity like PHFs. NFTs occasionally contain hybrid filaments with a sharp transition between a paired helical segment and a straight segment. The presence of twisted ribbon-like assemblages of tau fibrils in vitro has recently been discovered using new high-resolution molecular microscopy techniques, casting doubt on the PHF idea. The microtubule-associated protein tau, which is abnormally misfolded and hyperphosphorylated, has been discovered to be the primary constituent of NFTs, regardless of the shape of their structural units. NFTs are a type of non-crystalline semiconductor [34].

**6.1.3. Morphological Characteristics:**The designations "primitive," "classical," and "burn-out" plaques came about as a result of attempts to comprehend the evolution of the amyloid plaque after its formation based on morphological parameters. Based on their staining with dyes specific for the beta pleated sheet conformation such as Congo Red and Thioflavin-S, a more practical and frequently used morphological classification distinguishes only two types of amyloid plaques: diffuse vs dense-core plaques. Thioflavin-S positive dense-core plaques are associated with deleterious effects on the surrounding neuropil, including increased neurite curvature and dystrophic neurites, synaptic loss, neuron loss, and recruitment and activation of both astrocytes and microglial cells, unlike diffuse Thioflavin-S negative plaques.In the brains of cognitively intact older persons, diffuse amyloid plaques are typically found. The pathological distinctions between normal aging and AD dementia are blurry, and many cognitively normal older persons have significant amyloid burdens in their brains, as we will explore further below. The ultrastructure of dense-core plaques is revealed by electron microscopy studies to be made up of a center mass of extracelullar filaments that radially expand toward the periphery, where they are intermingled with neuronal, astrocyte, and microglial processes. Dystrophic neurites are neuronal processes that frequently comprise packets of paired helical filaments, as well as a large number of aberrant mitochondria and dense bodies of mitochondrial and lysosomal origin. [37].

**6.1.4. clinical pathological correlation:** The amyloid burden does not appear to be related to the severity or duration of dementia, according to clinicopathological investigations. The amyloid load hits a plateau early after the onset of cognitive symptoms or even in the preclinical period of the disease in an area of early amyloid deposition, such as the temporal associative isocortex, and the plaque size does not change much with disease development. It's probable that when the distribution of amyloid deposits "spreads" after the previous stages, the amount of amyloid assessed across the entire cortical mantle increases during the clinical course of the disease.

This notion has recently been reinforced by preliminary results from longitudinal amyloid PET imaging studies in live individuals [40].

**6.2. Oxidation stress and AD:** Alzheimer's disease (AD) is a type of dementia that affects a considerable section of the elderly population. The histological alterations of Alzheimer's disease, such as widespread neuronal cell death, the production of amyloid plaques, and neurofibrillary tangles, have received a lot of attention. Oxidative stress is defined as an imbalance in radical production of reactive oxygen species (ROS) and antioxidative defense, both of which are thought to have a role in age-related neurodegeneration and cognitive decline. High levels of oxidised proteins, advanced glycation end products, lipid peroxidation end products, formation of toxic species such as peroxides, alcohols, aldehydes, free carbonyles, ketones, cholestenone, and oxidative modifications in nuclear and mitochondrial DNA are all signs of oxidative stress in Alzheimer's disease. Memory loss with age is linked to a drop in brain and plasma volume [5].

**6.2.1. protein oxidation in AD:** The oxidation of protein side chains by reactive oxygen species (ROS) has been studied, and it results in the introduction of hydroxyl groups or the creation of protein-based carbonyls. Carbonyl groups are incorporated into proteins by oxidizing side-chain hydroxyls in amino acid residues to ketone or aldehyde derivatives. Proteins are carbonylated by a variety of oxidative processes. Direct oxidation of lysine, arginine, proline, and threonine residues can also add carbonyl groups to proteins [42].

**6.2.2. Lipid Oxidation in AD:** Membrane lipoperoxidation and lipid peroxidation products are two different types of lipid peroxidation. ROS changes lipids, and there's a link between lipid peroxides, antioxidant enzymes, amyloid plaques, and NFTs in Alzheimer's brains. When comparing AD brains to age-matched controls, several oxidative stress breakdown products such as 4-hydroxy-2,3-nonenal (HNE), acrolein, malondialdehyde, and F2-isoprostanes were found. HNE has the ability to alter proteins, causing a variety of consequences such as inhibition of neuronal glucose and glutamate transporters, inhibition of Na-K ATPases, activation of kinases, and dysregulation of intracellular calcium signaling, all of which lead to an apoptotic cascade. Because malondialdehyde and HNE adducts are present in NFTs, they show signs of oxidative membrane degradation.Furthermore, membrane damage is greater in dystrophic neurites of senile plaques with NFTs filaments than in those without filaments.Lipid peroxidation produces HNE, which are the most cytotoxic compounds. The only currently known "advanced" adduct that arises from HNE modification of proteins in AD patients is lipid peroxidation, which is a 2-pentylpyrrole modification of lysine. The discovery that HNE is neurotoxic and inhibits the function of membrane proteins, particularly the neuronal glucose transporter GLUT 3, suggests that HNE is a biomarker and toxin linked to neurodegeneration in Alzheimer's disease [50].

**6.2.3.DNA Oxidation in AD:** Hydroxylation, protein carbonylation, and nitration are all forms of oxidative stress that can damage DNA bases. In Alzheimer's disease, brain ROS causes calcium influx through glutamate receptors, which causes an excitotoxic reaction that results in cell death. When oxygen combines with redox-active metals that are not under control, reactive oxygen species (ROS) are produced. 8-hydroxy-2-deoxyguanosine (8OHdG) and 8-hydroxyguanosine (8OHg) levels rise when DNA and RNA are oxidized (8OHD).In Alzheimer's disease, higher levels of DNA strand breaks have been discovered. They were once thought to be a part of apoptosis, but it is now commonly known that DNA strand breaks are caused by oxidative damage, which is compatible with the increased free carbonyls in the nuclei of neurons and glia in AD. In AD brains, the elevation of heme oxygenase-1, an antioxidant enzyme involved in the conversion of heme to bilirubin, is higher, and it's linked to NFTs [44].

**6.2.4.Glycoxidation in AD:** Advanced glycation end products (AGEs) are neurotoxins and proinflammatory chemicals that are produced by a non-enzymatic interaction of sugars with long-lived protein deposits. The spontaneous condensation of ketone or aldehyde groups of sugars with a free aminoacid group of proteins initiates glycation of proteins as a nonenzymatic process. The production of AGEs, which are heterogeneous protein aggregates that are irreversibly cross-linked. AGEs are one way that long-lived proteins can get cross-linked. Extracellular AGEs accumulation in senile plaques has been demonstrated in primitive plaques and coronas of classic plaques in several cortical regions. The microtubuli-associated protein tau, which is a significant component of NFTs, has been found to generate intracellular AGEs. In vitro, MAP-tau can be glycated, which prevents it from binding to microtubules [15].

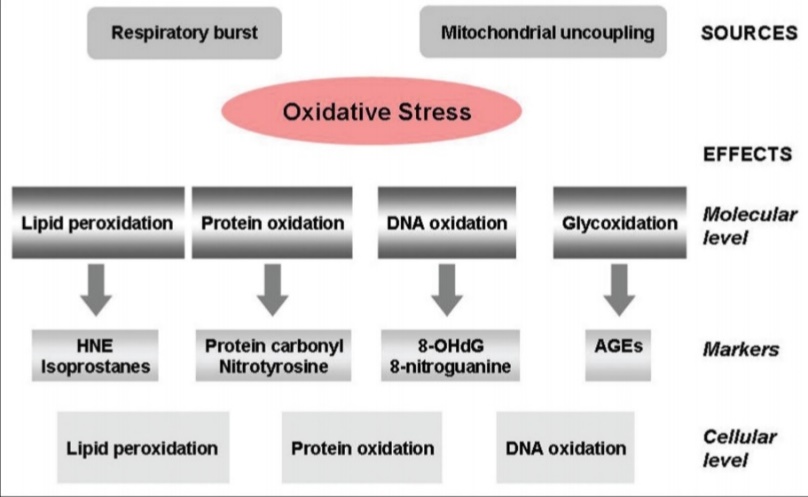


Figure 06: Oxidative stress and Alzheimer’s disease

**6.3. Molecular genetics and pathogensis:** Although mutations account for less than 5% of all cases of Alzheimer's disease, they have shown to be extremely useful in research into the disorder's pathophysiology. Autosomal dominant inheritance with virtually total penetrance is caused by mutations in the amyloid precursor protein, presenilin 1 gene, and presenilin 2 gene. The amyloid protein generated from APP is formed in neuritic plaques and appears to be crucial to the pathophysiology of AD. The buildup of beta amyloid triggers a cascade of events that lead to cell death, including cell death programs activation, lipid oxidation and membrane rupture, an inflammatory response, and the creation of tangles. The production of beta amyloid protein is elevated in all of the recognized mutations that cause AD. Injury to the head, educational level, and other factors all increase the risk of death [36].

**Chapter 7**

**Drug delivery strategics for AD treatment**

**7. Drug delivery strategics for AD treatment:** Treatment techniques are categorized by route of administration and active principle to be supplied, with a focus on medication delivery systems that can lead to reduced dosing regimens and improved patient quality of life. The most often used treatment for Alzheimer's disease is a symptomatic strategy involving cholinesterase inhibitors and NMDA receptor antagonists. Extended-release, orally dissolving, or sublingual formulations, intranasal or short- and long-acting intramuscular or transdermal forms, and a range of nanotechnology-based drug delivery methods are all possible alternatives to traditional oral formulations. Until disease-modifying medicines become available, further efforts in drug delivery technology are needed to carry therapeutic molecules to the CNS more effectively while still meeting the requirements of ease of administration and reasonable treatment persistence [52].

**7.1: Traditional oral-based AD therapies:** ChEIs and NMDA receptor antagonists are the only two kinds of medicines licensed to treat Alzheimer's disease.

The ChEIs (oral versions of tacrine, donepezil, rivastigmine, galantamine, and the rivastigmine patch) are the first-line treatment for Alzheimer's disease because they prevent the breakdown of acetylcholine in the synaptic cleft and compensate for its deficit.

Tacrine was the first ChEI to be licensed for the treatment of mild to severe Alzheimer's disease, but its hepatotoxic side effects have limited its use.

Excitotoxic neuronal dysfunction is thought to be induced by prolonged and non-physiological activation of NMDA receptors mediated by the neurotransmitter glutamate, which is thought to be involved in the pathophysiology of Alzheimer's disease.

Memantine, a mild and non-competitive NMDA receptor antagonist, was licensed by the FDA in the United States in 2003 for the treatment of depression [49].

**7.1.1. Donepezil:** Donepezil (Aricept, Pfizer, NY, USA) is a reversible, non-competitive, and selective ChEI that inhibits brain acetylcholinesterase (AChE) for a long time without altering AChE activity in the peripheral nervous system. Donepezil was licensed for the treatment of Alzheimer's dementia in the United States in 1996, and it comes as 5 and 10 mg conventional instant release tablets. Lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate are among the inactive components found in the 5 and 10 mg tablets. Talc, polyethylene glycol, hypromellose, and titanium dioxide are among the ingredients used in the film coating. The most serious side effects are gastrointestinal in nature, and some patients have experienced sleep disturbances [27].



Figure 07: Donepezil

**7.1.2. Rivastigmine:** Rivastigmine (Exelon, Novartis, Switzerland) has been marketed in the EU since 1998, and the FDA approved it for use in the US in 2000. During the titration period, it is a dual inhibitor of AChE and butyrylcholin-esterase, with the most common adverse effects being gastrointestinal issues. Rivastigmine tartrate is available as 1.5 mg, 3 mg, 4.5 mg, and 6 mg (orange and red) capsules, as well as a 2 mg/ml oral solution for traditional oral administration [57].



Figure 08: Rivastigmine

**7.1.3. Galantamine:** Galantamine was the latest of the three major ChEIs to be approved by the FDA, but it was also the first to go off-patent and become generic. Galantamine is available in the form of biconvex film-coated quick release tablets in a circular shape. Galantamine is available as a 4 mg (off-white), 8 mg (pink), and 12 mg (orange-brown) galantamine free base circular biconvex film-coated instant release tablet, as well as a 4 mg/ml galantamine hydro-bromide oral solution for traditional distribution. Colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, propylene glycol, talc, and titanium dioxide are just a few of the inactive components. Yellow ferric oxide is present in the 4 mg tablet, red ferric oxide is present in the 8 mg tablet, and red ferric oxide is present in the 12 mg tablet. Galantamine has been given the go light [61].



Figure 09: Galantamine

**7.1.4. Memantine:** In the United States, the NMDA antagonist memantine was licensed in October 2003 for the treatment of moderate to severe stages of Alzheimer's disease. Several large-scale, controlled clinical trials back up its safety and efficacy. For traditional memantine hydrochloride dosing, 5 and 10 mg film-coated tablets and a 2 mg/ml oral solution are available [39].



Figure 10: Memantine

**7.2: Current treatment and future perspective:** Alzheimer's disease is a slowly progressive neurodegenerative illness that, according to biomarker and autopsy research, begins decades before symptoms appear clinically. Alzheimer's disease diagnostic criteria are developing, and recent modifications also include criteria for diagnosing the disease before the beginning of dementia.

There is a critical need for a better knowledge of disease transitions – from normal aging to moderate cognitive impairment and dementia – as well as more effective therapies at different stages of the degenerative process. Lifestyle habits like physical activity, mental stimulation, and nutrition, in addition to oral medications, transdermal patches, and intravenous infusions, are potential intervention methods. Three controlled studies are included in this edition of the journal, each of which provides insight into different types of treatment at various stages of neurodegeneration. This is the first study to provide such information [57]. Add-on studies are not the same as combination trials; in combination therapy trials, two medications are examined separately, in combination, and in contrast to placebo, usually in a 22 trial design.In add-on therapy, a new medication is compared to a placebo in patients who are already on a background therapy. The majority of studies for new therapeutic drugs in Alzheimer's disease take place in individuals who are already taking cholinesterase inhibitors, memantine, or both, and are thus new types of add-on treatment. The advantage of combination trials over add-on studies is that they allow investigators to compare the effects of each therapy separately and in combination with others, allowing them to discern between individual and synergistic effects of the experimental therapies.Pharmacodynamic and pharmacokinetic treatment combinations exist. Pharmacokinetic combinations alter a drug's absorption, distribution, metabolism, or elimination; pharmacodynamic combinations are designed to have numerous effects on disease biology [21].For the treatment of Parkinson's disease, pharmacokinetic combinations include levodopa plus a dopamine decarboxylase inhibitor [22].Treatment of pseudobulbar effect with dextromethorphan and quinidine [23]. This review will not go into detail about pharmacokinetic combinations.Symptomatic agents that address the behavioral and cognitive symptoms of AD without changing the underlying disease biology or disease-modifying therapies (DMTs) that change disease course by addressing the underlying biology that leads to nerve cell death can be used in pharmacodynamic combinations for the treatment of Alzheimer's disease [24].To treat Alzheimer's disease, pharmacodynamic combinations allow for the use of two symptomatic medicines, two DMTs, or complex combinations of symptomatic therapy and DMTs. Multifunctional molecules single drugs that combine many activities or targets—are another type of combination therapy. Rasagiline, a monoamine oxidase (MAO) B inhibitor used to treat Parkinson's disease, exhibits neuroprotective and amyloid processing benefits in addition to MAO B inhibition [27,28].Brexpiprazole, a dopamine D2 receptor partial agonist licensed for the treatment of schizophrenia and as add-on therapy for major depressive disorder, is currently being tested in phase III trials for the treatment of agitation in people with Alzheimer's disease. Two phase III trials in patients with mild to severe Alzheimer's disease [60] recently came to a close [46].

**Chapter 8**

**Worldwide situation of AD**

**8.1. Worldwide of AD situation:** Since its inception in 2004, the Alzheimer's Disease Neuroimaging Initiative (ADNI) has aimed to speed drug development by verifying imaging and blood/cerebrospinal fluid biomarkers for Alzheimer's disease clinical trials. ADNI is a multisite longitudinal research with a naturalistic approach. The ADNI campaign in North America isn't the only one taking place around the world. The Alzheimer's Association recognized these international efforts and established the Worldwide Alzheimer's Disease and Neurodegenerative Disease Initiative (Worldwide ADNI) (WW-ADNI). WW-goals ADNI's are to harmonize projects and findings across geographical regions, as well as to make data management and availability easier for researchers all over the world, by building a platform for international collaboration and cooperation. North American, European, Japanese, Australian, Korean, and Argentina-based WW-ADNI projects are included [55].

**8.2. Japanese ADNI:** ADNI was founded in 2007 with support from the Japanese Ministries of Health, Labor, and Welfare, as well as the New Energy and Industrial Technology Development Organization. This effort, like NA-ADNI and E-ADNI before it, aims to promote global clinical trials of disease-modifying medicines for Alzheimer's disease. The J-ADNI clinical study protocol includes structural MRI, fluorodeoxyglucose and amyloid PET, CSF collection and APOE genotyping, as well as clinical and psychometric testing. The MRI center at J-ADNI has developed an algorithm to standardize MRI scanning across various MRI machines. The three-dimensional magnetization-prepared rapid gradient-echo methodology was used to create this algorithm. To allow reliable and repeatable volumetric analysis of structural MRI data, programs to improve picture quality and other parameters were implemented. The PET is an acronym for "Petition [49].

**8.3. Other worldwide sites:** The Chinese government and various industrial partners are supporting China ADNI, with the government providing initial start-up funding that are distributed to each participating site. Since then, a number of new facilities have opened, and participant registration has begun. C-ADNI plans to recruit and assess between 800 and 1000 people, with 200 to 250 cognitively normal controls, 400 to 500 people with MCI, and 200 to 250 people with dementia. The Taiwan Dementia Society was the first to establish Taiwan ADNI, with five locations throughout northern Taiwan. It planned to enroll 200 people, with an equal number of people with eMCI, late MCI, and Alzheimer's disease. ADNI activities are spreading to other countries of the world, including India and Brazil, in their early stages [59].

**8.4. The journey of AD diagnosis in Bangladesh and current perspective:** Alzheimer's disease (AD) is a terrible pathologic process that is responsible for the majority of dementia cases. The current global projected prevalence is 26.6 million, with the number expected to treble by 2040. Because there is no effective medication to slow or stop the advancement of the disease, the patient becomes dependant on others for help. For patients and carers, this translates into a severe social, psychological, physical, and financial burden. The prevalence of dementia is increasing at an alarming rate across Asia, especially Bangladesh, as people live longer. Dementia care is given the lowest priority in Bangladeshi healthcare policy, and many people living with the disease go untreated or suffer from poor management. Globally, 58 percent of the 35 million people living with dementia live in the United States.Although Alzheimer's disease is the most common cause of dementia, it is sometimes used as a catch-all word for a variety of disorders that cause dementia (including stroke, Parkinson's disease, and other neurological diseases). As developing countries proceed in their transition to noncommunicable diseases, AD appears to be growing in relevance, putting even more strain on many low-middle-income countries' already overburdened health care systems. Additionally, additional non-communicable diseases such as diabetes, hypertension, and others are on the rise in developing countries. Brain imaging, both functional and structural, has advanced quickly. It is critical in the differential diagnosis of dementia, the early detection of progressive dementia, and the monitoring of disease progression and treatment effectiveness. Structured brain abnormalities that may cause cognitive impairment can be detected using computed tomography (CT) or magnetic resonance imaging (MRI). Structural MRI is a type of MRI that examines the structure of a structure 58[-60].

**Chapter 9**

**Conclusion**

**9. Conclusion:** The rising prevalence of Alzheimer's disease in our aging society has far-reaching socioeconomic ramifications. This has sparked a surge of interest in the field of pharmaceuticals, particularly disease-modifying therapies. Treatments targeted at slowing cognitive decline will remain the standard of therapy until these therapies are proven to be safe and effective [64].  
Over the last few decades, significant progress has been achieved in the knowledge of Alzheimer's disease. Genetic studies have specifically pointed to certain mechanistic processes such as APP metabolism, immunological response, inflammation, lipid metabolism, and intracellular endocytosis. It is necessary to map the specific causal variations in known susceptibility genes as well as genes that have yet to be identified. Large-scale whole exome and whole genome sequencing initiatives are under underway, with the goal of identifying causal common and unusual variations linked to LOAD. Although the variants identified by this effort will need to be functionally confirmed, these studies have the potential to lead to a better understanding of the genetic risk factors in these ethnic groups, as well as refinement of risk estimates and diagnostic and predictive testing protocols specific to these ethnic groups [66].

**Chapter 10**

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