IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES
ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 3, 2022

ANALYSIS OF BEHAVIOURAL PATTERNS IN ALZHEIMER'S DISEASE: A COMPREHENSIVE INSIGHT

Deepak Sai Ram Punaku[*1], Niranjan Bavu Mudduluru[2], Pooja Mavuluru[3]

[1]Department of Pharmaceutical Analysis, Seven Hills College of Pharmacy, Tirupati, A.P., India
[2]Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, A.P., India
[3]Department of Pharmaceutical Analysis, Seven Hills College of Pharmacy, Tirupati, A.P., India

Corresponding Author
P. Deepak Sai Ram
Assistant Professor, Department of Pharmaceutical Analysis, Seven Hills College of Pharmacy, Tirupati, A.P., India – 517561, Contact: 7337408402, Email: dheepaksai@gmail.com

Abstract

Alzheimer's disease, known as AD, is the most common form of dementia, affecting approximately 35 million people globally and progressing over time. Effective treatments and preventive measures are currently lacking, despite significant advancements in understanding its molecular pathways since its initial description in 1907. Research has highlighted connections between cognitive function, caregiver burden, and Behavioral and Psychological Symptoms of Dementia (BPSD). However, the relationship between caregiver burden and BPSD in community-dwelling Alzheimer's patients remains unclear. This review aims to explore the pathophysiology of Alzheimer's disease, behavioral manifestations in affected individuals, and its comorbidities. Additionally, it examines the impact of COVID-19 on Alzheimer's patients and underscores the importance of digital health, clinical outcomes, policy frameworks, and basic science. Recommendations for future research and challenges in leveraging gender and sex differences in Alzheimer's research are also addressed, alongside insights into disease biomarkers, drug targets, and network biology methodologies for identifying new biomarkers and therapies.

KEYWORDS: - Alzheimer's disease, Neurology, BPDS, Sex difference, gender, Alzheimer's disease caregiver, AD, cerebral, Psychology, Future prospectus.

INTRODUCTION:

Alzheimer's disease is a devastating neurological condition primarily affecting the brain, characterized by progressive cognitive decline, memory loss, and significant impairments in daily functioning. It is the leading cause of dementia among older adults and a major global health concern. Less than 10% of Alzheimer's cases manifest as early-onset, occurring before age 65, which is rare[1]. Currently, there is no known cure for Alzheimer's disease. AD is widely regarded as a paradigmatic neurodegenerative disorder influenced by various factors, including the accumulation of amyloid deposits, vascular abnormalities, and changes in cerebrospinal fluid (CSF) dynamics. These factors collectively contribute to brain

hypoperfusion, inflammation, increased amyloid deposition, and eventual disruption of neural networks.

Symptoms of Alzheimer's disease: -
• pre-symptomatic,
• mild, and
• Depending on the severity of cognitive impairment, Alzheimer's disease stage

According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for categorizing Alzheimer's disease, several stages are identified. The earliest symptom is often amnesia with relatively preserved long-term memory, which can manifest in many patients even if it is not initially noticeable. Following amnesia, there is a decline in executive functioning, motivation, problem-solving abilities, and organizational skills, which impairs multitasking and abstract thinking. Executive function impairment in the early stages can range from mild to severe[2].

In the medium to late stages of Alzheimer's disease, neuropsychiatric symptoms become prominent. These may include apathy, social withdrawal, disinhibition, anxiety, agitation, psychosis, and wandering. Other symptoms such as dyspraxia (difficulty with coordinated movement), olfactory dysfunction (loss of smell), sleep disturbances, extrapyramidal motor signs like dystonia and akathisia, and symptoms resembling Parkinson's disease can also occur[3].

BACKGROUND:
German scientist Dr. Alois Alzheimer first documented Alzheimer's disease in 1907, identifying it as a neurodegenerative condition characterized by cognitive decline and significant behavioral abnormalities such as restlessness, disorientation, depression, and anxiety[4].

Alzheimer's disease is the most severe form of dementia. Currently, 50 million people worldwide are affected by this illness, and without effective treatment or prevention, this number is projected to sharply increase to 152 million by the year 2050[5].
Further information on Alzheimer's disease and its impact includes:

- AD ranks as the 6th leading cause of death in the US and globally.
- Elderly individuals with Alzheimer's disease account for one in three deaths.
- Caregivers are expected to provide 18.4 billion unpaid hours of care, involving over 16.1 million caregivers.
- A new case of Alzheimer's disease is identified every 65 seconds, according to recent surveys.

Epidemiology of Alzheimer's Disease: Globally, it is projected that there will be 152 million people with dementia by the end of the century, with low- and middle-income countries expected to experience the largest increase [6]. According to recent data from 2020, the

number of Alzheimer's disease (AD) patients under 65 years old could rise significantly from 5.8 million to 13.8 million in the United States and globally by 2050 [7]. Community-based studies conducted in China and Japan over recent decades have shown a clear increase in the prevalence of AD [8]. Specifically, women exhibit a higher age-standardized death rate compared to men, and their age-specific global prevalence is 1.17 times higher than that of men, suggesting factors beyond longer life expectancies contribute to this disparity [9].
Moreover, AD mortality increased by 146.2% between 2000 and 2018, ranking it seventh among all causes of mortality in the elderly[10]. Caregivers face increased mental strain and emotional impact due to the demands of caregiving for AD patients, which can place an unsustainable burden on society and families. The primary goal of AD care is to promote well-being, as patients may experience complex issues and symptoms across multiple domains.

Furthermore, epidemiological studies provide strong evidence that environmental and behavioral factors play crucial roles in the pathophysiology and progression of the disease. Pre-existing conditions are more prevalent among AD patients compared to peers of similar age, highlighting the importance of maintaining physical health to protect cognitive function. Additionally, several risk factors may both contribute to AD development and manifest as symptoms simultaneously, as suggested by the theory of reverse causality. Therefore, accurate diagnosis is essential for individuals with cognitive impairment, although pre-symptomatic diagnosis remains challenging, as some cognitively normal individuals with AD biomarkers (A and tau) do not develop the disease[11].

Pathophysiology

Pathophysiology of Alzheimer's Disease: Alzheimer's disease is characterized by the accumulation of abnormal neurotic plaques and neuronal tangles. Plaques are small circular lesions composed of an amyloid beta-peptide core surrounded by an expanding axonal end. The beta-amyloid peptide originates from the amyloid precursor protein (APP), a transmembrane protein. Proteases, including alpha, beta, and gamma secretases, cleave the beta-amyloid peptide from APP. Normally, APP is cleaved by alpha- or beta-secretase, producing small fragments that are safe for neurons to absorb. However, sequential cleavages by beta-secretase and gamma-secretase lead to the production of a 42 amino acid peptide (beta-amyloid 42), which increases beta-amyloid 42 levels and forms amyloid aggregates that are detrimental to neurons. Abnormal accumulation of fibrillary amyloid proteins predominates over normal APP degradation by beta-amyloid 42. APP is located on chromosome 21, one of the chromosomal regions associated with familial Alzheimer's disease[12].

In Alzheimer's disease, amyloid accumulates around the meningeal, cerebral, and grey matter arteries. These accumulations form consolidated deposits known as plaques in multifocal grey matter areas. Interestingly, some individuals with dementia do not display amyloid plaques during brain scans, while others do. Neurofibrillary tangles are fibrillary intracytoplasmic structures formed in neurons by tau protein. Tau's primary role is to stabilize

axonal microtubules, essential for intracellular trafficking along neuron axons. In Alzheimer's disease, tau protein becomes hyperphosphorylated due to extracellular beta-amyloid aggregation, leading to the formation of tau clumps. These abnormal helical filament pairs composed of tau clumps are termed neurofibrillary tangles. Initially appearing in the hippocampus before spreading throughout the cerebral cortex, tau aggregates accumulate inside neurons[13].

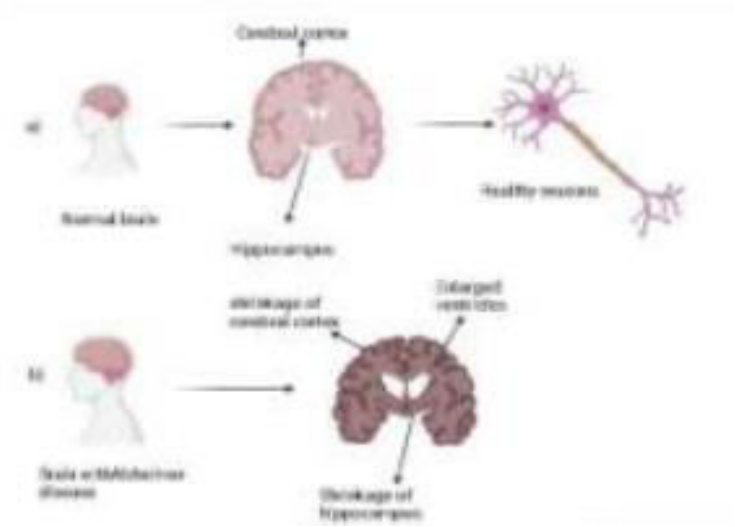


Figure1.1: - The physiology of neurons and the brain (a) healthy brain and (b) brain with Alzheimer's disease.

FDA-approved Medications for Alzheimer's Disease: The only treatments for Alzheimer's disease approved by the FDA include acetylcholinesterase inhibitors (AChEIs) such as donepezil, galantamine, rivastigmine, and the NMDA receptor antagonist memantine.

Donepezil:

Donepezil is a piperidine-derived cholinergic drug that inhibits acetylcholinesterase, an enzyme responsible for breaking down acetylcholine in the central nervous system. It acts reversibly and non-competitively. In addition to its role in acetylcholine regulation, donepezil impacts AD pathogenesis by mitigating glutamate-induced excitotoxicity, reducing early inflammatory cytokine expression, promoting a neuroprotective form of acetylcholinesterase, and attenuating oxidative stress effects.

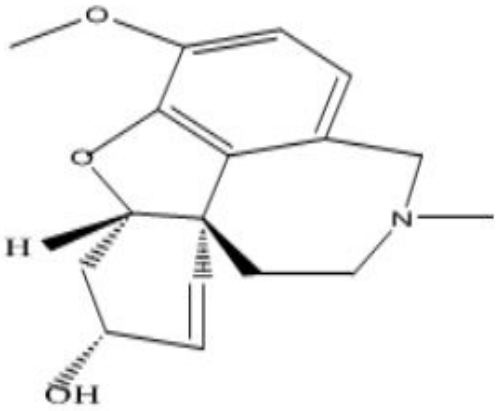
Approved in 1996 for treating mild to moderate Alzheimer's disease (AD), donepezil is administered orally as a pill, liquid, or orally disintegrating tablet. Treatment typically begins with 5 mg/day, which can be increased to 10 mg/day over four to six weeks. For patients with moderate to severe dementia who have been on 10 mg/day for at least three months, the dosage may be further increased to 23 mg/day. Research has shown that 10 mg/day of donepezil improves cognitive function, activities of daily living, and clinician-rated overall impression, though it does not significantly impact behavior or quality of life. Studies comparing higher doses, up to 23 mg/day, have not shown substantial additional benefits over the 10 mg/day dose. However, none of the doses investigated have been able to halt the

ISSN PRINT 2319 1775 Online 2320 7876
 UGC CARE Listed (Group -I) Journal Volume 11, Iss 3, 2022

progression of AD . Despite this, donepezil is well-regarded for its high patient compliance and minimal side effects, particularly affecting the brain and gastrointestinal systems.

Galantamine:

Galantamine is a tertiary is quinoline alkaloid that acts as a selective, reversible acetylcholinesterase inhibitor. It also enhances the natural functioning of acetylcholine on nicotinic receptors (114). It is administered orally, with doses ranging from 4 mg to 24 mg, either as immediate-release solutions twice daily or as an extended-release capsule once daily. The recommended starting dose of galantamine is 8 mg/day, which may be increased to 16 mg/day twice daily after 4–8 weeks as a maintenance dose.



Galantamine:

Galantamine's unique ability to predominantly act within the central nervous system while minimally affecting the peripheral system makes it particularly compelling for Alzheimer's disease (AD) treatment. Various formulations have been developed to enhance its brain distribution, such as chitosan, solid lipid nanoparticles, and hydroxyapatite particles containing cerium. According to a recent meta-analysis by Li et al., galantamine is considered one of the most effective medications for AD, not only addressing behavioral symptoms but also improving cognitive function, activities of daily living, and overall health assessments by clinicians. While generally well-tolerated, galantamine can cause side effects such as seizures, severe nausea, stomach cramps, vomiting, irregular breathing, confusion, muscle weakness, and watery eyes.

Rivastigmine:

Introduced in Switzerland in 1997 and approved by the FDA in 2000, rivastigmine is indicated for mild to moderate AD and mild to severe Parkinson's dementia. It acts as a pseudo-irreversible inhibitor of both butyrylcholinesterase and acetylcholinesterase (AChE), binding to their anionic and esteric sites. Rivastigmine is available in transdermal patches that allow for continuous release over 24 hours, avoiding gastrointestinal side effects associated with oral administration due to intestinal and hepatic metabolism. This makes transdermal patches particularly beneficial for AD patients who may experience memory loss and swallowing difficulties. However, side effects such as nausea, vomiting, diarrhea, loss of appetite, and abdominal pain can affect patient adherence to treatment. Overdosing on

rivastigmine may lead to symptoms like rapid or slow breathing, chest pain, and irregular heartbeat.

N-Methyl D-Aspartate (NMDA) Antagonists: Memantine: Memantine is a voltage-dependent, intermediate affinity, non-competitive antagonist of the NMDA receptor. Pathologically elevated levels of glutamate prevent neuronal dysfunction, influencing both the symptom manifestation and progression of Alzheimer's disease (AD) into neurodegenerative dementia, particularly through dysfunction in glutamate-mediated neurotransmission at NMDA receptors. It was the first medication authorized by the US FDA for treating moderate to severe Alzheimer's symptoms.

Additionally, the FDA has approved the combination therapy of memantine and donepezil (Namzaric®) for managing symptoms in moderate to severe Alzheimer's disease. However, the European Medicines Agency has not approved Acescent®, a medication combining memantine and donepezil hydrochlorides, citing insufficient evidence to support its efficacy in treating this condition.This combination therapy targets both the adverse effects of excessive glutamate and the degradation of acetylcholine in the brain. Scientific studies indicate that memantine + donepezil is more effective than either treatment alone or placebo in improving cognition as assessed by scales such as ADAS-Cog and SIB, overall clinical assessment, daily functioning, and symptoms of neuropsychiatric disorders.

Complementary Therapies: Managing behavioral symptoms, depression, or anxiety—common clinical manifestations in AD patients—has been shown effective through alternative healthcare approaches like aromatherapy and music therapy, in addition to conventional treatments. Physical therapy is also integral in Alzheimer's disease care, employing cognitive and behavioral exercises to improve both patients' and caregivers' quality of life.

Recent Advances in Alzheimer’s Disease Psychology: Advancements in neuroimaging are providing novel insights into Alzheimer's disease (AD), aiding in early detection by identifying pathology and neurodegeneration in individuals with or without cognitive impairment.

Epigenetic Alterations in Alzheimer's Disease: The development of AD has been associated with various epigenetic changes, including histone posttranslational modifications, DNA methylation and hydroxymethylation, mitochondrial epigenetics (Mitoepigenetics), and the translation of noncoding RNA. Disorders such as AD, categorized as neuropathologies, have shown disruptions in DNA methylation and hydroxymethylation processes. Research also indicates that histone signatures like H3K27me3 and H3K4me3 at Polycomb-repressed (poised) promoters overlap with specifically methylated DNA sites in AD.

DNA Methylation: DNA methylation plays a crucial role in cognitive processes and maintains essential cellular activities and synaptic flexibility in the central nervous system.

This importance is underscored by the concentration of DNA hydroxymethylation in the central nervous system, critical for neurodevelopment. While some studies indicate a general decrease in DNA methylation in AD patients, others have not found significant differences in DNA methylation compared to age-matched healthy individuals. Research has explored DNA methylation patterns in genes associated with AD, including GSK3b (glycogen synthase kinase 3 beta, ANK1 (ankyrin 1) , and brain-derived neurotrophic factor (BDNF). Decreased DNA methylation has been observed in the prefrontal cortex and locus coeruleus in AD, as well as in blood samples. Additionally, studies have shown alterations in noncoding RNA CpG patterns in AD patients, significantly increasing 5mC levels at these specific genetic loci.

Methylation of Mitochondrial DNA: Research has identified significant deletions in mitochondrial DNA (mtDNA) linked to the pathophysiology of AD. Low levels of mtDNA have been observed in presymptomatic individuals with PSEN1 mutations and in AD patients with low Aβ and elevated tau in their cerebrospinal fluid (CSF). Reduced CSF mtDNA levels correlate with abnormal mitochondrial propagation and low mtDNA copy number, potentially serving as a preclinical biomarker for AD. Furthermore, studies have found a negative association between CSF mtDNA levels and phosphorylated tau protein, alongside a positive correlation with Aβ and CSF mtDNA content. Low CSF mtDNA levels, combined with low Aβ and high phosphorylated tau, distinguish AD from other neurological disorders. Notably, AD blood samples show a significant reduction in mtDNA methylation.
DNA Hydroxymethylation: Studies have identified elevated levels of 5-hydroxymethylcytosine (5hmC) in intragenic regions, associated with hundreds of distinct hydroxymethylated regions (DhMRs) in AD brains. Genomic research has highlighted the F-box and leucine-rich motif protein 16 (FBXL16) gene, which shows increased 5hmC levels . FBXL16 has been implicated as a potential gene associated with AD, with reduced expression observed in microglial cells of mouse AD models. Another study found decreased 5hmC levels in four CpG sites within the ANK1 gene.

Further investigations have shown a decrease in astrocyte distribution and an increase in tau protein deposition in AD brains. However, one study reported the absence of 5hmC in the AD cerebellum and entorhinal cortex. In the hippocampal CA1 region, glial cells from AD patients exhibited reduced 5hmC deposition, according to another study. Subsequent research focused on TREM2's role in AD pathogenesis, revealing a positive correlation between TREM2 expression and 5hmC levels in exon 2. This suggests that increased TREM2 gene expression may aid in tissue repair, as TREM2 is essential for microglial function, maintaining tissue homeostasis, and supporting the brain's immune response.

Histone Modifications: Histones are highly basic proteins rich in arginine and lysine residues (H1, H2A, H2B, H3, and H4) that play a crucial role in DNA condensation into nucleosomes within eukaryotic nuclei. Changes in histone modifications affect various processes such as brain aging, AD pathogenesis, neuronal growth, and differentiation. Studies in tau transgenic models of Drosophila, mice, and human AD have frequently shown deficits in

heterochromatin. This relaxation of heterochromatin has been linked to oxidative damage and DNA degradation in the presence of transgenic tau (158). Aberrant acetylation of histones has also been associated with signaling abnormalities, apoptosis, inflammation, immunological responses, and neuroplasticity.

MicroRNA: MicroRNAs (miRNAs) play a significant role in AD pathophysiology, targeting various genes involved in the disease process. Approximately 161 miRNAs have been implicated in AD pathogenesis, including those regulating genes like SIRT1, BACE1, APP, and those involved in myelin sheath formation. MiRNAs are involved in the regulation of APP degradation and Aβ metabolism by controlling enzymes like BACE1.

Research indicates that the expression of miRNA-132 and miRNA-212 is inhibited in early AD stages. Increased Aβ and APP expression have been correlated with overexpression of specific miRNAs such as miRNA-155, miRNA-146, and miRNA-124. Lower levels of AD CNS miRNA-181 have been observed, correlating with increased Aβ expression and affecting the MAPK signaling pathway. Additionally, elevated levels of miRNA-206 have been detected in AD cerebrospinal fluid (CSF) and blood samples in various studies.

Biomarkers of Alzheimer's Disease: Biomarkers play a crucial role in accurately diagnosing various disorders, including Alzheimer's disease (AD). Despite recent diagnostic advancements, distinguishing Alzheimer's dementia from other forms of dementia remains challenging. Cerebrospinal fluid (CSF) analysis of Aβ-42, total tau protein, and phosphorylated tau (p-tau) is currently considered the most reliable biological marker for AD diagnosis and differentiation from other types of dementia and mild cognitive impairment. Key indicators for AD include reduced Aβ levels in CSF and the presence of Aβ or tau deposits in the brains of AD patients.

Additionally, PET biomarker data can link underlying AD pathology to clinical dementia symptoms or mild cognitive impairment with varying degrees of certainty (168). Diagnosis in living patients typically involves family history of cognitive disorders, the patient's clinical progression over time, and observed symptomatology (169). Prior to the early 2000s, autopsy was the only definitive method to diagnose AD post-mortem.

Currently, there are 12,073 identified biomarkers associated with AD. Among these, approximately 441 biomarkers are either approved or in late-stage clinical trials for AD diagnosis, prognosis, staging, and disease progression monitoring. The most commonly utilized biomarkers include tau, phospho-tau, and Aβ42, which are primary components of tau tangles and amyloid plaques in the brain, respectively. CSF, the fluid surrounding the brain and spinal cord, is used to measure these biomarkers. In May 2022, the US FDA approved the LumiPulse G beta-Amyloid Ratio (142/1-40) in vitro diagnostic test for evaluating beta-amyloid pathology in CSF samples.

Conclusion:

In conclusion, individuals with Alzheimer's disease exhibit complex and diverse behavioral patterns. Effective care and support require collaboration among family members, caregivers, and medical professionals to better understand these patterns. A comprehensive approach that considers individual needs, underlying triggers, and the progressive nature of the disease is crucial to enhance the quality of life for patients and caregivers alike.

Furthermore, there is a critical need for increased research and collaboration within the medical community to develop more effective interventions and treatments for managing the behavioral manifestations of Alzheimer's disease. Recent advancements in biomarker diagnostics and understanding of symptomatology have revolutionized early diagnosis outside of clinical settings. This progress facilitates earlier enrollment of patients in studies and potentially offers accessible blood biomarkers for early disease detection.

REFERENCES: -

[1]. Tang Y, Lutz MW, Xing Y. A systemsbased model of Alzheimer's disease. Alzheimers Dement. 2019 Jan;15(1):168-171. [PubMed]
[2]. Zilberzwige-Tal S, Gazit E. Go with the Flow-Microfluidics Approaches for Amyloid Research. Chem Asian J. 2018 Nov 16;13(22):3437-3447. [PubMed]
[3]. Maccioni RB, González A, Andrade V, Cortés N, Tapia JP, Guzmán-Martínez L.Alzheimer´s Disease in the Perspective of Neuroimmunology. Open Neurol J. 2018; 12:50-56. [PMC free article] [PubMed]
[4]. Hippius, H.; Neundörfer, G. The discovery of Alzheimer's disease. Dialogues Clin. Neurosci. 2003, 5, 101–108.
[5]. Christina Patterson. World Alzheimer report 2018: the state of the art of dementia research. New Frontiers. 2018.
[6]Alzheimer's Association, 2018 Alzheimer's Disease Infographic (2018), Retrieved from https://www.alz.org/media/Documents/alzheimers-facts-and-figures-infographic.pdf, Accessed on July 1, 2018.
[7]. C. P World Alzheimer report 2018. London: Alzheimer's Disease International, 2018.
[8]. 2020 Alzheimer's disease facts and figures. Alzheimer's & Dementia 2020;16: 391-460.
[9]. Ohara T, Hata J, Yoshida D, et al. Trends in dementia prevalence, incidence, and survival rate in a Japanese community. Neurology 2017;88: 1925-1932.
[10]. Chan KY, Wang W, Wu JJ, et al. Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet (London, England) 2013;381: 2016-2023.
[11]. Global, regional, and national burden of Alzheimer's disease and other dementias, 19902016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. Neurology 2019;18: 88-106.
[12]. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet (London, England) 2020;396: 413446.
[13]. Edwards Lee T, Miller B, Cummings J, et al. The temporal lobe variant of frontotemporal dementia. Neurology 1996;46(Suppl. 1): A178.Google Scholar