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A COMPREHENSIVE REVIEW ON ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) remains a significant global health challenge, with no cure and limited treatment options to halt its progression. This review explores the current therapeutic landscape for AD, including recently approved drugs and emerging treatments targeting key pathological features such as amyloid-beta plaques, tau protein tangles, and neuroinflammation. Monoclonal antibodies like aducanumab have shown potential by targeting amyloid aggregation, while tau-based therapies and neuroprotective agents are being actively developed to address other pathological hallmarks. Advances in small molecule drugs, gene therapy, and cell-based therapies are also examined for their potential to modify disease progression and improve cognitive function. Additionally, we discuss novel approaches utilizing precision medicine and biomarkers for individualized treatment strategies. By reviewing these therapeutic developments, this article highlights both the challenges and opportunities in achieving effective, disease-modifying treatments for Alzheimer's, offering a comprehensive view of potential pathways toward mitigating the impact of AD on patients and society.

Keywords- Alzheimer's disease, Emerging Therapeutics, Dementia, Pathophysiology.

1. INTRODUCTION

Dementia is a general term used to describe a significant decline in cognitive ability that interferes with a person's activities of daily living. Alzheimer disease (AD) is the most prevalent type of dementia, accounting for at least two-thirds of cases in individuals aged 65 and older. AD is a neurodegenerative condition with insidious onset and progressive impairment of behavioral and cognitive functions. Memory, comprehension, language, focus, logic, and judgment are some of these abilities. Although AD is not the primary cause of mortality, it significantly increases a person's susceptibility to other problems that may ultimately result in death. In 2022, AD was the seventh most common cause of death in the United States, while COVID-19 was the fourth, according to data from the Centres for Disease Control and Prevention (CDC). Before the COVID-19 pandemic, AD was the sixth leading cause of death following stroke [1]. AD typically manifests after age 65, referred to as late-onset AD (LOAD). However, early-onset AD (EOAD), occurring before 65, is less common and seen in about 5% of AD patients. EOAD often exhibits atypical symptoms, and its diagnosis is usually delayed, leading to a more aggressive disease course [2].

Alzheimer's disease (AD) is a progressive neurological condition that impairs speech, behaviour, motor function, visuospatial orientation, and memory. It is dementia's primary cause. Variant syndromes with early localized atrophy may not always follow the classic presentation, and pathological subgroups of AD have been identified [3].

ETIOLOGY

A slow and progressive neurodegeneration brought on by the death of neuronal cells is a hallmark of Alzheimer's disease. Usually, the entorhinal cortex in the hippocampal region is where the neurodegenerative process starts. Both early-onset and late-onset AD have been linked to genetic variables. An example of a risk factor for early-onset dementia is trisomy 21.

AD is a complex disorder with numerous established risk factors. Age is the most important component, and growing older is the main cause. Beginning at age 65, the frequency of AD about doubles for every five years of age gain.

A small percentage of cases (about 1-5%) are hereditary and linked to mutations in genes such as *APP* (amyloid precursor protein), *PSEN1* (presenilin 1), and *PSEN2* (presenilin 2). These mutations lead to early-onset Alzheimer's and often have an autosomal dominant inheritance pattern [4].

According to one prominent idea, Alzheimer's disease starts when amyloid-beta (Aβ) plaques build up abnormally in the brain. The breakdown of APP produces the peptide Aβ, which collects into plaques, impairing cell function and inducing neuroinflammation. Amyloid buildup contributes to chronic neuroinflammation by activating brain immune cells called microglia, which then produce inflammatory cytokines. Over time, this immune response contributes to neuronal damage [5].

Cerebrovascular disease and conditions like hypertension, diabetes, and atherosclerosis increase the risk of AD by impairing blood flow to the brain. This vascular insufficiency can lead to reduced nutrient supply and accelerate the accumulation of amyloid plaques [5].

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Neurons with mitochondrial malfunction produce less energy, which leaves them more susceptible to harm. Reactive oxygen species (ROS) cause accumulated oxidative stress, which further deteriorates cells and encourages the development of tau and amyloid disease.[6]. Cardiovascular diseases (CVD) are recognized as significant risk factors for AD. They increase the risk of developing AD and contribute to the risk of dementia caused by strokes or vascular dementia. CVD is increasingly recognized as a modifiable risk factor for AD [7].

Obesity and diabetes are also important modifiable risk factors for AD. Obesity can impair glucose tolerance and increase the risk of developing type II diabetes. Chronic hyperglycemia can lead to cognitive impairment by promoting the accumulation of beta-amyloid (A-beta) and neuroinflammation. Obesity further amplifies the risk by triggering the release of pro-inflammatory cytokines and promoting insulin resistance [8].

Other risk factors for LOAD have been identified by genome-wide association studies, including as TREM2, ADAM10, and PLD3. Along with their known functions, they also have an impact on immunological response, cholesterol metabolism, endocytosis, and hormonal changes, especially the postmenopausal fall in estrogen in women, which may raise the risk of AD because estrogen is believed to have neuroprotective properties. This is part of why women experience a higher incidence of AD compared to men [9, 10].

EPIDIOMILOGY

AD is predominantly observed in older individuals. The global prevalence of dementia was reported to be 20.3 million in 1990, and it significantly increased to 43.8 million in 2016, representing a remarkable rise of 116%. From 1990 to 2019, the incidence and prevalence of Alzheimer disease and other dementias rose by 147.95% and 160.84%, respectively. Projections indicate that the number of people affected by dementia is expected to reach 150 million by 2050, representing a 4-fold increase [11].

After age 65, the prevalence of Alzheimer's disease increases every five years. Before age 65, age-specific incidence rates were less than 1% annually; beyond age 85, they increased to 6% annually. After age 65, prevalence rates rise to 10%, and after age 85, they reach 40%. Women have a somewhat higher incidence of Alzheimer's disease, particularly after the age of 85. [12].

By 2050, over 131 million people are estimated to be impacted by these financially destructive diseases, as the population ages [8]. Alzheimer's disease is mostly caused by aging, with the incidence doubling every 6.3 years from 3.9 per 1000 for ages 60-90 to 104.8 per 1000 over 90 [10]. The prevalence is estimated at 10% for people over the age of 65 and 40% for people older than 80 years [13].

To reduce personal and financial expenses, efficient pre-clinical diagnosis and therapy are necessary to prevent disease progression before symptoms appear.

PATHOPHYSIOLOGY

Alzheimer disease is characterized pathologically by an accumulation of abnormal neuritic plaques and neurofibrillary tangles in the brain. These pathological changes are accompanied by a loss of neurons, particularly cholinergic neurons in the basal forebrain and the neocortex. [14].

Two prominent pathophysiological hypotheses have been proposed based on these pathological findings:

1. **The Cholinergic Hypothesis** proposes that the reduced levels of acetylcholine (ACh) in the brain, resulting from neuronal loss in the Nucleus Basalis of Meynert, play a significant role in AD development. The initial degeneration of cholinergic neurons in AD, which emphasizes the significance of ACh in cognitive activities, is the basis for this theory. By impairing ACh release and cholinergic synaptic loss, beta-amyloid is thought to have a detrimental effect on cholinergic function. Anticholinergics also adversely affect memory in elderly patients clinically [15].
2. **The Amyloid Hypothesis** is currently the most widely accepted pathophysiological mechanism for AD, especially in cases of inherited AD. According to the amyloid hypothesis, β- and γ-secretase enzymes work to convert amyloid precursor protein (APP) into amyloid beta (Aβ) peptide. Alpha or beta-secretase may often cleave APP, and the resulting little fragments are not harmful to neurons. However, if beta and gamma secretase cleave APP sequentially, 42 amino acid peptides (Aβ42) are produced. Neuronal toxicity results from amyloid aggregation caused by elevated Aβ42 levels. Aβ42 favours the formation of aggregated fibrillary amyloid protein over normal APP degradation [16].

Along with the above, other different hypotheses are also included which are as follows-

Impaired mitochondrial function decreases energy production and further contributes to ROS production, compounding cellular damage and promoting neurodegeneration.

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The brain's native immune cells, known as microglia, are triggered when tau and amyloid build-up occurs. Although they initially aid in the removal of plaque, prolonged activation causes pro-inflammatory cytokines to be released, which worsens neuronal damage.

Down Syndrome, a genetic condition caused by trisomy 21, is strongly linked to the amyloid hypothesis in the context of AD research. In Down Syndrome, individuals have an extra copy of chromosome 21, leading to an additional copy of the APP gene.

Due to this genetic duplication, individuals with Down Syndrome have higher levels of APP, which increases the production of amyloid-beta (Aβ) peptides. As a result, individuals with Down Syndrome are at a significantly increased risk of developing AD. It is estimated that approximately 40% to 80% of patients with Down Syndrome experience clinical AD by the fifth to sixth decade of life, and nearly 100% of them exhibit AD pathology, such as amyloid plaques and neurofibrillary tangles.

AD can be inherited as an autosomal dominant disorder with nearly complete penetrance. This form of the disease is linked to mutations in 3 genes: the AAP gene on chromosome 21, Presenilin1 (PSEN1) on chromosome 14, and Presenilin 2 (PSEN2) on chromosome 1. [17].

HISTOPATHOLOGY

The histopathology of Alzheimer's disease (AD) is characterized by distinct microscopic changes in brain tissue, including the accumulation of amyloid-beta (Aβ) plaques, tau neurofibrillary tangles, neuronal loss, and other cellular changes. These pathological features are primarily observed in brain regions involved in memory and cognition, such as the hippocampus and cerebral cortex. Here's an overview of the major histopathological features of AD [18-20]:

Amyloid-Beta (Aβ) Plaques- Extracellular deposits known as amyloid plaques are mostly made up of aggregated Aβ peptides, especially Aβ42, which are extremely prone to aggregating. In AD patients, the Aβ deposits are seen in the cortical gray matter, near the meningeal and cerebral arteries. Multifocal gray matter deposits that consolidate to create milliary structures known as plaques are mostly seen in the cerebral cortex, hippocampus, and other regions related to memory and cognition.

Neurofibrillary Tangles- A protein known as tau makes up neurofibrillary tangles, which are fibrillary intracytoplasmic formations that develop inside neurons. Stabilizing axonal microtubules is the tau protein's main job. Microtubules are vital for intracellular transport and travel along neuronal axons. Tau facilitates the formation of microtubules along neural axons and helps to preserve their integrity.

Tau becomes hyperphosphorylated in AD as a result of extracellular beta-amyloid accumulation. Tau becomes misfolded and accumulates inside the neurons as a result of this aberrant phosphorylation. Neurofibrillary tangles are tau aggregates that resemble twisted paired helical filaments.

Neuropil Threads- Neuropil threads are thread-like extensions of hyper phosphorylated tau found within the neuropil, the dense network of neuronal processes, which are often seen in regions with high NFT density, contributing to the disruption of local circuitry and neural connectivity.

Microglial Activation and Astrocytosis- Around amyloid plaques, activated microglia form clusters in an effort to remove Aβ and debris. Chronic activation, on the other hand, causes neuroinflammation by generating reactive oxygen species and cytokines, which can worsen damage to neurons. Reactive astrocytes are frequently observed close to plaques and tangles, where they try to buffer extracellular glutamate, which is neurotoxic at high concentrations, and produce inflammatory mediators. These cells are thought to be responsible for the persistent neuroinflammation that speeds up neurodegeneration in AD.

Hirano Bodies- Hirano bodies are eosinophilic, rod-shaped, cytoplasmic inclusions composed of actin and other cytoskeletal proteins. They are primarily found in the hippocampus and other vulnerable brain regions. Although Hirano bodies are not specific to AD, they are frequently seen in affected brain regions and are associated with cellular degeneration.

Cortical Neuronal Degeneration: Granulovacuolar degeneration of hippocampus pyramidal neurons is a frequently reported degenerative alteration. A decrease in the number of presynaptic boutons originating pyramidal neurons in particular layers of the cerebral cortex, especially in laminae III and IV, seems to be more directly linked to cognitive decline in AD. The reduction in their density may have a more significant impact on cognitive function than the mere increase in the number of plaques characteristic of AD.

EVALUATION

From a primary care provider standpoint, when evaluating a patient suspected to be suffering from AD, the following tasks are essential:

- Review and confirm the medical and family history.
- Review the patient's medication list for medications that may potentially cause or worsen cognition.
- Perform a bedside cognitive assessment test, either an MMSE or MOCA, to evaluate the patient's cognitive function.
- Request blood tests to rule out any reversible causes of dementia

Cognitive and Neuropsychological Testing-

Mini-Mental State Examination (MMSE)**:** A widely used screening tool that assesses orientation, recall, attention, calculation, language, and visual-spatial skills.

Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)**:** A detailed test specifically designed to assess cognitive deficits in AD, often used in clinical trials to track disease progression.

Clock Drawing Test and Verbal Fluency Test**:** Simple tools to assess executive function, visual-spatial ability, and language skills, which can be impaired in AD [21].

Neuroimaging Techniques

Magnetic Resonance Imaging (MRI)**:** MRI scans are used to assess brain atrophy, particularly in the hippocampus and medial temporal lobe, which are early indicators of AD. MRI can also help rule out other causes of dementia, such as stroke or tumors.

Computed Tomography (CT)**:** Although less sensitive than MRI, CT scans may be used if MRI is unavailable, mainly to exclude other causes of cognitive decline.

Functional brain imaging methods including Positron Emission Tomography (PET), Single-Photon Emission Computed Tomography (SPECT), and functional magnetic resonance imaging (fMRI) are becoming more and more useful for mapping dysfunctional patterns in the medial temporal and parietal lobes. The importance of these functional brain imaging methods in the final diagnosis of AD is still unclear, despite the fact that they show promise for early identification and monitoring of the disease's clinical development [22].

Biomarker Analysis

Cerebrospinal Fluid (CSF) Biomarkers-

Amyloid-beta (Aβ42): Reduced levels of Aβ42 in CSF are indicative of plaque deposition in the brain.

Total Tau (t-tau) and Phosphorylated Tau (p-tau): Elevated levels of t-tau and p-tau are markers of neurofibrillary tangles and neuronal damage.

Blood Biomarkers**:** Blood-based biomarkers, though less established, are emerging as a less invasive alternative to CSF tests. Tests measuring plasma Aβ42/40 ratio, p-tau, and neurofilament light chain (NfL) are increasingly promising for AD diagnosis and monitoring.

Genetic Testing: In cases of early-onset or familial AD, genetic testing for mutations in *APP*, *PSEN1*, *PSEN2*, and *APOE ε4* may be recommended, though genetic testing is generally not used for late-onset AD diagnosis.

Some patients may exhibit subjective cognitive complaints that can be objectively assessed but do not yet reach the level of impairment that interferes with their daily functioning. In such cases, the classification may be mild cognitive impairment (MCI) instead of dementia. [23-25].

MANAGEMENT

The treatment and management of Alzheimer's disease (AD) focus on slowing disease progression, managing symptoms, and improving the quality of life for patients and caregivers. Although there is no cure for AD, current treatment options include pharmacological therapies, lifestyle modifications, supportive care, and emerging therapeutic approaches. Here's an overview of key strategies [26-30]:

Pharmacological Treatments

Cholinesterase Inhibitors: These drugs increase acetylcholine levels by inhibiting its breakdown, which helps improve communication between neurons. Common cholinesterase inhibitors include:

Donepezil (for all stages)

Rivastigmine (for mild to moderate stages)

Galantamine (for mild to moderate stages)

It causes modest improvement in cognition, function, and behaviour; side effects may include nausea, diarrhoea, and sleep disturbances.

NMDA Receptor Antagonists:

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Memantine is used for moderate to severe AD and works by blocking NMDA receptors to reduce excitotoxicity caused by excessive glutamate, which can damage neurons.

It Can help with memory and learning and is often used in combination with cholinesterase inhibitors.

Amyloid-Targeting Drugs:

Amyloid-beta plaques, a defining feature of AD pathology, are the target of recently developed monoclonal antibodies such as aducanumab and lecanemab. The goal of these medications is to lessen the buildup of amyloid plaque in the brain. Although these medications are controversial with may have adverse effects like brain bleeding and swelling (ARIA), they have demonstrated some promise in decreasing cognitive decline.

Other Management Strategies in AD

In managing AD, addressing accompanying symptoms such as anxiety, depression, and psychosis is essential, especially in the mid to late stages of the disease.

Tricyclic antidepressants should be avoided due to their anticholinergic action, which might exacerbate cognitive impairment. When all other options have been exhausted and the patient's or caregiver's safety is in jeopardy, antipsychotic drugs should be used with caution to treat acute agitation. Antipsychotics are typically considered after other drugs have been tried. These often consist of anticholinesterase medications like donepezil and SSRI antidepressants like citalopram.

Second-generation antipsychotics are generally favoured over first-generation antipsychotics because of their safety and less extrapyramidal side effects. FDA just approved Brexpiprazole in May 2023 for treating agitation associated with dementia due to AD. However, their limited benefits should be weighed against the small risks of stroke and increased mortality.

Cognitive Stimulation**:** Activities like puzzles, reading, memory games, or engaging in social activities can help maintain cognitive functions and reduce cognitive decline.

Sleep Management**:** Encouraging good sleep hygiene and addressing sleep issues can reduce cognitive decline and improve daytime functioning.

Immunotherapy**:** Research is ongoing into other monoclonal antibodies targeting amyloid and tau, with hopes of halting or reversing disease progression.

Gene Therapy**:** Early-stage research is exploring gene therapy to correct or influence genes associated with AD, particularly in familial forms of the disease.

Regular aerobic exercise has been shown to slow the progression of AD [31, 32].

NOVEL APPROACH

Artificial intelligence (AI) tools are increasingly becoming valuable in managing Alzheimer's disease (AD), helping with early diagnosis, predicting disease progression, developing personalized treatment strategies, and even aiding in patient care. Here are some key areas where AI tools are making an impact [33-36]:

Early Diagnosis and Detection

Medical Imaging Analysis**:** Early indicators of AD can be found by using AI algorithms to evaluate brain imaging data, including MRI and PET scans. Often before symptoms appear, deep learning models can accurately detect patterns of atrophy, amyloid plaques, as well as tau protein deposits.

Biomarker Analysis**:** AI can analyze complex biomarker data from cerebrospinal fluid (CSF), blood, and imaging to identify subtle changes linked to AD. Machine learning models are being used to process these large datasets to detect early-stage Alzheimer’s.

Cognitive Testing**:** Cognitive assessment technologies with AI capabilities, including smartphone apps, monitor a person's language, memory, and problem-solving skills over time. These techniques evaluate minor language and cognitive changes that can indicate early AD by utilizing natural language processing (NLP).

Predicting Disease Progression

Prognostic Models**:** Machine learning models trained on large patient datasets can predict the rate of cognitive decline and disease progression in individuals. These models can incorporate data such as age, genetic factors (e.g., APOE status), lifestyle, and clinical biomarkers to give personalized predictions.

Patient Stratification**:** AI tools can help classify patients based on the severity of their symptoms and projected progression rates, aiding clinicians in planning and tailoring interventions for individual needs.

Developing and Personalizing Treatments

Precision Medicine**:** AI can analyze genetic and biomarker data to create personalized treatment plans for patients. For example, it may identify patients who are likely to respond well to certain drugs or lifestyle interventions, thereby maximizing treatment effectiveness and minimizing side effects.

Drug Discovery**:** By evaluating enormous datasets from biomedical research, AI speeds up the process of finding new medication candidates. Compounds that may target tau or amyloid-beta or alter neuroinflammatory responses can be found via algorithms. By identifying which patients are most likely to gain advantages from experimental treatments, AI is now being used to design clinical trials.

Monitoring and Managing Symptoms

Wearable Devices and Sensors: Wearables with AI capabilities, such fitness trackers and smartwatches, may keep an eye on patients' heart rates, sleep habits, and physical activity, among other things. AI may examine this data to find any anomalies that would point to a deterioration in symptoms or other health issues, enabling prompt treatment.

Digital Health Tools**:** Cognitive and behavioral symptoms, like wandering, sleep disturbances, and agitation, can be tracked using AI-driven apps. These apps can alert caregivers to unusual behavior or predict behavioral changes, providing crucial support in real time.

AI-Assisted Clinical Trials

Patient Recruitment: AI helps identify and recruit patients for clinical trials based on criteria such as genetic data, biomarker status, or disease stage. This streamlines trial recruitment, ensures diverse participation, and improves study results.

Trial Monitoring**:** AI-driven tools can continuously monitor patients' health data during clinical trials, enabling real-time analysis and adjustments to trial protocols if needed, increasing the chances of identifying effective treatments faster.

Assistive Technologies for Patients

Speech and Language Tools**:** AI tools using NLP can assist patients with memory and communication difficulties. Speech recognition software, for instance, can simplify communication and engage patients in cognitive exercises.

Cognitive Therapy Applications: AI-powered apps can provide cognitive exercises tailored to each patient's abilities, helping maintain cognitive function and slowing decline.

2. CONCLUSION

Alzheimer’s disease (AD) remains a complex and challenging neurodegenerative disorder, affecting millions globally and placing a significant burden on individuals, families, and healthcare systems. Despite extensive research, AD’s multifactorial nature—characterized by amyloid plaques, tau tangles, neuroinflammation, oxidative stress, and synaptic loss—continues to present difficulties in developing effective treatments.

Though they are still in their infancy, recent developments in our knowledge of the genetic, biochemical, and environmental variables that contribute to AD have accelerated the establishment of targeted therapies, such as medications that target tau and amyloid, as well as neuroprotective techniques. Better care tactics and research toward a potential cure are made possible by emerging sectors like artificial intelligence as well as precision medicine, which are showing potential in early diagnosis, individualized treatment, and patient management. To halt progression and enhance patient quality of life, managing AD calls for a comprehensive strategy that incorporates medication, lifestyle changes, caregiver support, and cutting-edge technologies. Going forward, addressing the intricacies of AD and eventually attempting to lessen its effects on people and society will require sustained study, international cooperation, and investment in innovative therapy techniques.

3. REFERENCES

[1] Ahmad FB, Cisewski JA, Xu J, Anderson RN. Provisional Mortality Data - United States, 2022. MMWR Morb Mortal Wkly Rep. 2023 May 05;72(18):488-492.
[2] Mendez MF. Early-Onset Alzheimer Disease. Neurol Clin. 2017 May;35(2):263-281.
[3] Therriault J, Zimmer ER, Benedet AL, Pascoal TA, Gauthier S, Rosa-Neto P. Staging of Alzheimer's disease: past, present, and future perspectives. Trends Mol Med. 2022 Sep;28(9):726-741.
[4] Therriault J, Zimmer ER, Benedet AL, Pascoal TA, Gauthier S, Rosa-Neto P. Staging of Alzheimer's disease: past, present, and future perspectives. Trends Mol Med. 2022 Sep;28(9):726-741.
[5] Tang Y, Lutz MW, Xing Y. A systems-based model of Alzheimer's disease. Alzheimers Dement. 2019 Jan;15(1):168-171.
[6] Zilberzwige-Tal S, Gazit E. Go with the Flow-Microfluidics Approaches for Amyloid Research. Chem Asian J. 2018 Nov 16;13(22):3437-3447.

[7] Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimers Dement (Amst). 2017;7:69-87.
[8] Anjum I, Fayyaz M, Wajid A, Sohail W, Ali A. Does Obesity Increase the Risk of Dementia: A Literature Review. Cureus. 2018 May 21;10(5):e2660.
[9] Karch CM, Goate AM. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biol Psychiatry. 2015;77:43–51.
[10] Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, Sealock J, Karlsson IK, Hagg S, Athanasiu L, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet. 2019;51:404–13.
[11] Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. Front Aging Neurosci. 2022;14:937486.
[12] Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci. 2009;11(2):111-28.
[13] Schultz C., Del Tredici K.H.B: Neuropathology of Alzheimer’s Disease. In Alzheimer’s Disease Current Clinical Neurology. Edited by R. R, B. R. Totowa, NJ: Humana Press; 2004.
[14] Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 08;25(24).
[15] Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, Khachaturian AS, Vergallo A, Cavedo E, Snyder PJ, Khachaturian ZS. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain. 2018 Jul 01;141(7):1917-1933.
[16] Paroni G, Bisceglia P, Seripa D. Understanding the Amyloid Hypothesis in Alzheimer's Disease. J Alzheimers Dis. 2019;68(2):493-510.
[17] Salehi A, Ashford JW, Mufson EJ. The Link between Alzheimer's Disease and Down Syndrome. A Historical Perspective. Curr Alzheimer Res. 2016;13(1):2-6.
[18] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med. 2011 Sep;1(1):a006189.
[19] Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 2011 Nov;70(11):960-9.
[20] Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol. 2014 Apr;71(4):505-8.
[21] Haapasalo A, Hiltunen M. A report from the 8th Kuopio Alzheimer Symposium. Neurodegener Dis Manag. 2018 Oct;8(5):289-299.
[22] Kim H. Detection of severity in Alzheimer's disease (AD) using computational modeling. Bioinformation. 2018;14(5):259-264.
[23] Petersen RC. How early can we diagnose Alzheimer disease (and is it sufficient)? The 2017 Wartenberg lecture. Neurology. 2018 Aug 28;91(9):395-402.
[24] Sobański M, Zacharzewska-Gondek A, Waliszewska-Prosół M, Sąsiadek MJ, Zimny A, Bladowska J. A Review of Neuroimaging in Rare Neurodegenerative Diseases. Dement Geriatr Cogn Disord. 2020;49(6):544-556.
[25] Bottino CM, Castro CC, Gomes RL, Buchpiguel CA, Marchetti RL, Neto MR. Volumetric MRI measurements can differentiate Alzheimer's disease, mild cognitive impairment, and normal aging. Int Psychogeriatr. 2002 Mar;14(1):59-72.
[26] Hussein W, Sağlık BN, Levent S, Korkut B, Ilgın S, Özkay Y, Kaplancıklı ZA. Synthesis and Biological Evaluation of New Cholinesterase Inhibitors for Alzheimer's Disease. Molecules. 2018 Aug 14;23(8).
[27] Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study. Curr Alzheimer Res. 2018;15(12):1106-1113.
[28] Adlimoghaddam A, Neuendorff M, Roy B, Albensi BC. A review of clinical treatment considerations of donepezil in severe Alzheimer's disease. CNS Neurosci Ther. 2018 Oct;24(10):876-888.
[29] Kumar A, Gupta V, Sharma S. StatPearls [Internet]. StatPearls Publishing; Treasure Island (FL): Aug 17, 2023. Donepezil.
[30] Kandiah N, Pai MC, Senanarong V, Looi I, Ampil E, Park KW, Karanam AK, Christopher S. Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia. Clin Interv Aging. 2017;12:697-707.

[31] Rashad A, Rasool A, Shaheryar M, Sarfraz A, Sarfraz Z, Robles-Velasco K, Cherrez-Ojeda I. Donanemab for Alzheimer's Disease: A Systematic Review of Clinical Trials. Healthcare (Basel). 2022 Dec 22;11(1)

[32] Sperling RA, Jack CR, Black SE, Frosch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, Black RS, Brashear HR, Grundman M, Siemers ER, Feldman HH, Schindler RJ. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement. 2011 Jul;7(4):367-85.

[33] Surr CA, Gates C, Irving D, Oyebode J, Smith SJ, Parveen S, Drury M, Dennison A. Effective Dementia Education and Training for the Health and Social Care Workforce: A Systematic Review of the Literature. Rev Educ Res. 2017 Oct;87(5):966-1002.

[34] Jackson M, Pelone F, Reeves S, Hassenkamp AM, Emery C, Titmarsh K, Greenwood N. Interprofessional education in the care of people diagnosed with dementia and their carers: a systematic review. BMJ Open. 2016 Aug 16;6(8):e010948.

[35] Burgio L. Interventions for the behavioral complications of Alzheimer's disease: behavioral approaches. Int Psychogeriatr. 1996;8 Suppl 1:45-52.

[36] Paterson DH, Warburton DE. Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. Int J Behav Nutr Phys Act. 2010 May 11;7:38.