ejpmr, 2025, 12(4), 264-273

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

ALZHEIMER DISEASE: A REVIEW

Karamjeet Kaur*, Shruti Thakur, Jyoti Gupta, Raman Gupta and Shallu Dhiman

Student Nalagarh, Distt. Solan HP Nalagarh Himachal Pradesh India 174101.

***Corresponding Author: Karamjeet Kaur**

Student Nalagarh, Distt. Solan HP Nalagarh Himachal Pradesh India 174101.

Article Received on 11/02/2025 **Article Revised on 03/03/2025** **Article Accepted on 23/03/2025**

ABSTRACT

Alzheimer's disease recognized as a complex and progressive neurodegenerative disorder. It is a primary case of the dementia in older adults. It is marked by the assistance of neurofibrillary tangles. Previously twenty years, progress in understanding the disease's pathogenesis has encouraged researches to explore new pharmacological treatments. Treatment for AD mainly strive to ease symptom and slow the advancement of the condition. . In addition to medication, non drug approaches like cognitive therapy, structured routine. Changes in environment can also enhance quality of life for individual for Alzheimer's .Recent progress in molecular biology, neuroimaging ,and biomarkers has enhanced our understanding of disease mechanisms and created new opportunities for diagnosis and treatment development. Although various treatment exist to help alleviate the symptom and also slow its progression and also enhance the quality of life. Additionally non medical strategies such as cognitive and physical therapy, such as modification, support for caregivers and play important role.

KEYWORD:- Alzheimer's disease, Neurodegenerative, Treatment.

Abbreviations: AD: Alzheimer's disease, NPs: Neuritic plaque, NFTs: Neurofibrillary tangles, CSF: cerebrospinal fluid, NSAIDS: Non Steriodal Antinflammatory Drugs.

INTRODUCTION

Memory loss is an overarching concept which describe a significant decline in cognitive function that impairs a person's capacity to carry out daily task. Alzheimer disease is most common cause of dementia. AD is a neurodegenerative disorder which is characterized by a gradual onset. Although Alzheimer disease does not directly result in death, it significantly increases the risk of other complication that may ultimately lead to death.[1]

Around 200,000 individuals under the age of 65 are diagnosed with younger 0nset. While 5 million are aged 65 and older. By 2050 it is projected that a new case of AD will be emerged in every 33 seconds, leading to nearly a million more new cases annually, with an anticipated amount of thirteen. eight million.[2]

Although the exact cause of Alzheimer's is still unknown, researches have discovered that those who suffer from the illness haven an old accumulation of specific death.[3]

Due to its complexity, AD is not predicted to effectively treated with a single medication for other intervention. Presentation methods concentrate on assisting individuals in the preserving mental function, controlling behavioral symptoms, and delaying or reducing disease symptoms. In order to treat or prevent the disease's true underlying cause, researches and neurodegeneration, the prevention of neuritic plaques (NPs) and neuroebrillary tangles (NFTs) is the key to working to develop therapeutics that target specific gene, molecular and cell pathways. With the potential to postpone future of AD treatment. The above review article give a quick overview of AD, including its causes Or diagnosis. The highlights and new developments in AD treatment will review in this article.[4]

AD involves a complicated interaction of various biochemical changes, such as alterations in the metabolism of protein known as tau amyloid beta progenitor protein, oxidative stress, problem with metabolism of energy.[5] A lot of medical condition is able to be straightly linked with chemical disparity, highlighting its significance in AD.[6] For instance, reduced uptake of glucose in brain happens ten years prior to cognitive deterioration and is a consistent characteristic of AD.[7] The well-established neurotoxicity linked to Aβ42 is believed to contribute to neuronal energy deficiencies by triggering a series of harmful events.

The interaction between Alzheimer's disease (AD) involves a complicated interaction of various biochemical changes, such as alterations in the

metabolism of protein known as tau amyloid beta progenitor protein, oxidative stress, problem with metabolism of energy. Many of these pathological aspects can be directly associated with metabolic dysfunction, highlighting its significance in AD. For instance, reduced uptake of glucose in the brain happens ten year prior to cognitive deterioration and is a consistent characteristic of AD.[8,9]

Individuals that have AD can face clinical and treatment difficulties in general medical treatment instances, in which they are often diagnosed or cured. Early investigation and diagnosis of Alzheimer's disease can lead to the initiation of symptomatic drug treatments, psychosocial support, and the management of concurrent health issues. In this article, we examine the identification and treatment of AD, based on data from control experiments whenever possible.[10]

Neuropathology of AD senile plaques are accumulation of amyloid that act as neuropathological marker in tangle nerve fibers and the degeneration process in AD individuals minds. Neurofibrillary tangles consist of hyperphosphorylated protein like tau found in axon, whereas beta pair organisms gathering in outside of cells cause degenerative plaque. The first signs of AD are observed in the badly formed neurons from the brain cortex and hippocampal tissue, that include associated with storage of memory. Conversely, neurons that are highly myelinated tend to be impacted only in the later stages of AD. Reduced myelination compromises neuron function as it raises the energy demands for transmission of neurons. A specific region of the prefrontal region and the portion of the parietal lobe are belong the final brain regions to myelinate, making them particularly susceptible to AD. Research on AD patients shows downregulation of synapse markers in different part of brain changes in molecular architecture or deterioration in cerebral cortex or brain fluid as revealed by brain resonance spectroscopy studies.[11-17]

1. Genetic and Enviromental influences
ApoE4 gene variant
Age
Family history

2. Formation of amyloid plaques
Abnormal build up amyloid-beta protein
Development of the extracellular plaques between neurons

3. Tau protein tangles
Increased phosphorylation of tau protein
Creation of neurofibrillary tangles within neurons

4. Neuronal impairment
Interference with cellular communication
Deterioration of synaptic function

5. Neuroinflammatory response
Activation of microglia and astrocytes
Release o pro- inflammatory cytokines

6. Neuronal loss of cell death
Damage to neurons and synapses
Reduction in brain size, particularly in the hippocampus and cortex

7. Decline in cognitive Function
Loss of memory
Deteriorated reasoning and decision making abilities
Changes in language and behavior

Causes

1. Neurofibrillary tangles

One widely discussed and accepted explanation for the onset of Alzheimer's disease (AD) is the buildup of proteins, specifically Tau. Tau comprises a group of proteins crucial for maintaining the stability of neuronal cytoskeletons, which include all the organelles that support cellular structure. In neurons, microtubules, which are long tube-like structures made of tubulin, play a vital role in sustaining cell shape, especially in elongated sections such as the axon. Tau functions as a microtubule-associated protein by binding to these microtubules, preventing their shortening and deformation. While Tau is essential for cell stability, it can become problematic. In AD patients, cerebrospinal fluid (CSF) contains significantly higher levels of Tau proteins compared to healthy adults, as illustrated in. This increase is attributed to neurofibrillary tangles (NFTs) formed by proteins within neurons. As AD progresses, more Tau proteins disengage from the microtubules, compromising their structural integrity and aggregating into clumps within the neurons. These tangles inhibit the neurons' ability to transmit signals from dendrites to axons. The formation of tangles is due to a chemical abnormality, specifically hyperphosphorylation, which occurs when Tau proteins have additional phosphate groups attached. Normally, Tau undergoes cycles of phosphorylation and dephosphorylation regulated by a group of enzymes called kinases, which facilitate the transfer of phosphate groups between ATP and other molecules. However, when an imbalance favors phosphorylation, Tau tends to aggregate with itself rather than bind to the necessary microtubules. Additionally, the inherently long, rope-like structure of Tau, combined with hyperphosphorylation, enables it to form complex tangles similar to a ball of lint.[18-19]

2. Age

This age-related susceptibility is not limited to Alzheimer’s disease (AD); it is also a risk factor for various chronic illnesses, including other neurodegenerative disorders, cancer, atherosclerosis, arthritis, and emphysema. This suggests the potential for shared underlying causes that lead to different outcomes.

However, it remains uncertain whether AD is solely a result of aging, as has been proposed, and whether it

would be beneficial to distinguish "senile dementia," as it was referred to during Alzheimer's time, from "Alzheimer disease." Various studies have long suggested that the pathology of AD may be more severe in younger patients, although further evidence has consistently disproved this assertion.[20] The challenges of diagnosing Alzheimer's disease (AD) in the elderly have been recognized since the initial accounts of the condition. Specifically, the range of neuropathological changes in cognitively intact older adults can vary from minimal alterations to advanced stages of confirmed AD. In fact, one study found that neuropathologists, unaware of the clinical histories, identified AD in 76% of elderly individuals who did not exhibit clinical signs of dementia during their lives.[21]

3. Genetics

A considerable number of people with Alzheimer's disease (AD) exhibit a significant genetic component. First-degree relatives of those with AD face a greater lifetime risk of developing the condition compared to the general public, with 15–35% of AD patients having affected first-degree relatives.[22] Research using the now outdated classification of early (under 65 years) versus late (over 65 years) onset reveals that the familial early-onset version of the disease tends to be more aggressive and is linked to specific ages of onset.[23] Nonetheless, accurately determining the incidence of genetically linked AD can be complicated by several factors, including misdiagnosis as sporadic AD when other family members had shorter lifespans, the occurrence of 'familial Alzheimer's disease' in long-lived families, local environmental factors causing clusters of 'familial Alzheimer's disease' (as seen with Parkinsonism-dementia cases in Guam), interactions between multiple genes and environmental influences, and insufficient postmortem data leading to misdiagnosis of AD.[24]

4. Education

No other field related to aging and dementia involves as much speculation as the relationship between education and dementia risk. The notion that mental engagement can offer a protective benefit dates back to Cicero in the 2nd century B.C., who stated that it is our responsibility to combat old age by maintaining diligence and effort to preserve our mental abilities.[25] Santiago Ramon y Cajal built on this idea, proposing that intense mental activity could stimulate the growth of axonal branches, a concept he called "gymnastique cerebrale." The "use it or lose it" mantra has always resonated, possibly offering reassurance to those in academic and medical circles. Recently, epidemiological studies have emerged, indicating that lower educational levels may lead to a higher risk of dementia, while other research suggests that education might not significantly influence dementia risk.[26,27,28]

Anti inflammatory Drugs Given that the prevalence of AD in rheumatoid arthritis patients is lower than anticipated, long-term use of anti-inflammatory medications, such as non-steroidal anti-inflammatory medicines (NSAIDs), may help prevent the onset of AD.[28] In fact, anti-inflammatory medication use lowers the risk of AD, according to clinical research, and enhances cognitive test scores, such as the Mini-Mental Status Examination, for AD patients.[29]

Factor affecting AD

Cardiovascular disease Cardiovascular alterations, including , such as vaculpathies, minor and big infraction cortex infraction, and bleeding infraction or alteration in white cells, decrease the risk of AD, although the mechanisms involved are not well understood. These infarcts or regions of white matter hyperintensity may directly harm critical brain areas for memory, such as the thalamus and its connections to the cortex. Additionally, these changes might promote the accumulation of amyloid-beta (Aβ), which can contribute to failing cognitive or inciting an autoimmune reaction that hinder cognitive abilities. Moreover, decreased blood flow could result in the overactivity of cyclin-dependent kinase 5 (CDK5), an important enzyme for brain development and flexibility.[30] Abnormal activation of CDK5 is linked to neuronal death and apoptosis[31] and may also play a role in the abnormal phosphorylation of tau, leading to the formation of neurofibrillary tangles (NFTs), possibly serving as a critical link between NFT pathology and amyloid plaques.[33]

Type 2 diabetes Observational studies indicate that this diabetes nearly doubles the danger of developing AD.[33,34] The exact pathways connecting T2D to late-onset Alzheimer's disease (LOAD) remain unclear, but they may involve both cerebrovascular and noncerebrovascular factors.[35] T2D is known to increase the risk of stroke and is often associated with other vascular issues such as hypertension and dyslipidemia.[36] Additionally, research has shown that while T2D is linked to infarcts, it does not necessarily show the same association with AD pathophysiology in individuals with clinical LOAD. This suggests that the presence of infarcts, which lowers the threshold of amyloid needed to cause cognitive decline, could be a key mechanism linking T2D to LOAD.[37]

Body weight Research has indicated a weight of a person or risk of developing dementia have a U like in shape relationship and AD, suggesting that both low and high body weight can increase this risk.[38] This relationship appears to vary depending to the years at which weight of a person is assessed and is likely influenced by central obesity.[39] Furthermore, there is proof of opposite causal relationship prior to the onset of AD, where weight loss due to malnutrition occurs in the initial phases of illness.[40]

Clinical features

Alzheimer's disease (AD) primarily affects older adults, manifesting as progressively worsening temporal thinking problems. Initially, this may align with amnestic

mild cognitive impairment (MCI). As the condition progresses, individuals face difficulties with spatial orientation, multitasking, and decreased self-confidence. In later stages, cognitive decline intensifies and impacts daily life, resulting in a diagnosis of AD dementia, with increased dependence on others. Advanced symptoms may include behavioral changes, mobility challenges, hallucinations, and seizures, with an average life expectancy of around 8.5 years[41] following diagnosis. Besides these typical memory-related symptoms, atypical clinical syndromes, particularly in early-onset cases, are also observed. These encompasses the rear atrophy of cortex, logopenic aphasia (LPA), and the frontal kinds of AD. In atrophy of cortex is marked by widespread amyloid plaques and tau pathology affecting the parieto-occipital lobes, causing significant visuospatial and visuoperceptual difficulties while leaving memory largely intact.[42] LPA is defined by prominent identifying words issues, anomia, and working memory deficits.[43] The frontal kinds of AD, though rare, can closely resemble behavioral kinds frontotemporal dementia. Familial AD usually presents with the classic amnestic symptoms but at a significantly younger age.[44]

Diagnostic criteria Recognizing that pathological changes can occur years before symptoms appear, along with the introduction of measurement of atrophy and markers for beta amyloid and protein like tau disease, has led to the evolution of diagnostic criteria aimed at facilitating earlier and more molecularly specific diagnoses. The latest recommendation from the working committee of national institute of aging now include one at least one preliminary studies of AD, meaning biomarkers indicating AD pathology can be present without symptoms.[45,46] Although a definitive AD diagnosis diagonistic assuramce is needed, the working committee of national institute criteria enable dementia or mild cognitive impairment to be linked to AD pathology by varying degrees of likelihood based on biomarker data. Additionally, both sets of criteria acknowledge the presence of atypical, non-amnestic presentations.[47,48]

Treatment of AD

Medications

Acetylcholineserase inhibitors Currently, acetylcholinesterase inhibitors are considered the primary treatment for mild to moderate Alzheimer's disease.[49,50,51,52,53,54,55] Most systematic reviews and randomized controlled trials have found no significant differences in the effectiveness of the various acetylcholinesterase inhibitors.[56] While these medications operate through slightly different mechanisms, they each have distinct profiles of side effects.[56,57,58,59] The most common adverse effects include nausea, vomiting, and diarrhea, with cardiovascular and neurological issues being similar among the different medications. The likelihood of experiencing side effects is directly influenced by the dosage administered. Oral rivastigmine may be less tolerated compared to rivastigmine patches. Additionally, due to concerns regarding safety and tolerability, tacrine is no longer available.[60]

Memantine Memantine acts to inhibit excessive glutamatergic activity. A Cochrane study found that individuals with moderate to severe Alzheimer's disease who took twenty mg of memantine daily for six months experienced a slight enhancement in their ability to carry out daily activities and cognitive function. While this effect on cognition may not be clinically significant, it was statistically meaningful for those with mild to moderate dementia. Additionally, patients taking memantine exhibited a minor reduction in agitation. To prevent one instance of agitation, six months of treatment would be necessary for patients with moderate to severe Alzheimer's disease.[61]

The meta-analysis revealed that memantine was not effective for individuals with mild AD, and the benefits for those with moderate Alzheimer's disease varied.[62]

Selegiline Selegiline (Eldepryl) is a type B monoamine oxidase inhibitor that has limited anticolinergic effects. A Cochrane review examined seventeen two fold-blind, experiments with random placebo control assessing selegiline administered at a dose of ten mg daily for Alzheimer's disease treatment. The review found that cognitive improvements were noted in some trials at four to six weeks, but no noticeabe changes were find after the six-week mark.[63]

Antipsychotics While antipsychotics are commonly prescribed to manage behavioral symptoms of Alzheimer's disease, the U.S. Food and Drug Administration has not authorized their use specifically for this condition. Studies show that haloperidol and clozapine can reduce psychosis in individuals with Alzheimer's, with olanzapine also being effective in decreasing violent behavior.[64] The effects of antipsychotics drugs on behavioral and psychological symptoms were assessed through the Clinical Antipsychotic Trials of Intervention Effectiveness protocol for AD.[65]

Possible pharmacological treatment in future

Anti amyloid therapy Up till just latelly, several prominent clinical trials aimed at altering the amyloid cascade through pharmacological agents were conducted, but they mostly yielded unsatisfactory outcomes. These agents typically focused on three distinct target sites.[66]

Beta secretase enzyme Inhibitors of beta-secretase in small molecules have shown a decrease in CSF beta-amyloid levels when compared to control groups. Current Phase second and third clinical trials are ongoing for 2 compounds, AZD3293 and MK-8931, with completion expected in 2019.[67]

Tau targeted therapy Current clinical trials focusing on Tau-targeted therapies are testing agents that aim to inhibit hyperphosphorylation as well as those that stabilize microtubules and prevent aggregation.[68] Although lithium and valproic acid have the potential to reduce tau phosphorylation,[69] randomized controlled trials for these medications have not shown favorable outcomes.[70] Recently, a phase II clinical trial of methylthioninium, which acts as a tau aggregation inhibitor, indicated modest cognitive improvements in patients with mild to moderate Alzheimer's disease following fifty weeks of treatment, and there are intentions to move forward with phase III trials.[71]

Other medication drugs for treatment of AD

Antiasthmatic compounds Zileuton is believed to have effects that combat Alzheimer's disease by inhibiting 5-lipoxygenase, which is found at elevated levels in patients with the condition.[72] In mice lacking this enzyme due to genetic modifications, there was a decrease in Aβ levels. Likewise, the inhibition of 5-lipoxygenase by zileuton led to lower levels of cerebral Aβ accumulation in treated transgenic mice.

Antiinflammatory Medication Ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAIDs) like naproxen may offer various anti-inflammatory benefits, which are thought to contribute to neuroprotection in AD. Recent human reaseacrh of epidemiology indicate the NSAIDs might have protective effects in this context.[73]

Antipsychotics Atypical antipsychotics are frequently used to treat behavioral symptoms and psychosis in AD and other dementias. According to certain animal models, they might also have an impact on the pathophysiology of the disease. Risperidone may inhibit mitochondrial-complex-1 while simultaneously protecting against Aβ-induced apoptosis.[74]

Future directions

Most of the therapeutics currently in development aim to address the two primary pathologies associated with Alzheimer's Disease (AD): beta-amyloid plaques and tau neurofibrillary tangles. As of two thousand nineteenth of the feb, there are 132 drugs in the AD pipeline, of which 96 (73%) are designed for disease modification. Among these, 38 focus primarily or in combination on amyloid, while 17 concentrate on tau.[75]

One therapeutic class targeting amyloid is monoclonal antibodies, which aim to promote the removal of amyloid from the brain. However, despite significant reductions in amyloid levels, these treatments have not demonstrated improvements in clinical symptoms. Notably, aducanumab, an antibody that targets both amyloid fibrils and soluble oligomers, initially failed Phase III futility tests but later showed positive results in some patients. Its developer, Biogen, plans to seek Food and drug administration (FDA) approval in two thousand twenty.[76] Another category of drugs targets the enzyme beta-site APP-cleaving enzyme 1 (BACE-1), which cleaves beta-amyloid from its precursor, amyloid precursor protein (APP). These drugs also reduce amyloid levels but have been linked to worse cognitive decline compared to placebo, suggesting that BACE-1 activity may play a role in maintaining normal synaptic function.[77]

In addition, various therapeutics targeting tau are under development, as it is considered to directly contribute to the symptoms of AD and build up within neurons. Research indicates that protein like tau can spread between neurons in a “prion-like” manner, presenting a potential target for therapy.[78] LMTX, a tau aggregation inhibitor, did not show cognitive improvement over placebo in a Phase third trial, though a new Phase second and third trial is testing a lower dosage.[79] Additionally, early clinical trials are investigating several anti-tau antibodies and two or more active tau vaccinations aimed at stimulating antibody production in patients of Alzheimer disease.[80]

Due to the disappointing outcomes of treatments targeting amyloid and tau, drug development efforts are increasingly concentrating on the “pre-dementia” phase, which includes individuals with preliminary AD and those danger of cognitive deteroration. Numerous therapeutic trials, supported by public as well as private financing, are currently going in high-risk asymptomatic high risk person, such as genetic mutation carriers or persons with amyloid-positive PET scans or elevated biomarker levels.[81] Findings from these trials over the next few years may shed light on effective interventions to slow or prevent the progression to symptomatic AD.

Preventions of AD

It is estimated that in high-income countries, 40% of all cases of dementia could be prevented or postponed by addressing factors such as insufficient early education, obesity during midlife, hypertension, excessive alcohol intake , diabetes, depression, lack of physical exercise, smoking, brain injuries, hearing loss in later life, ar exposure to air pollution.[82]

In 2019, the World Health Organization released well-regarded guidelines aimed at reducing risks associated with cognitive deteroration and dementia.[83] These regulation give essential information for healthcare professionals, governments, policymakers, ar relevant stokeholders to help mitigate the danger of cognitive deteroration and AD.

Understanding dangerous factors also crucial for designing interventions that prevent targeting individuals at risk in order to maintain or enhance cognitive function and delay or prevent dementia.[84] However prior earlier therapies that have been studied often pay attention to the danger element at the moment, newer multidomain interventions aim to tackle several modifiable risk factors

at once for those vulnerable to cognitive decline and dementia. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGERS) exhibited positive effects on cognitive function through a several domains lifestyle intervention over two years.[85] Other European trials, like the French several domain Alzheimer Preventive Trial and the Dutch Prevention of Dementia by Intensive Vascular Care Trial, have shown less definitive results, though there have been suggestions of benefits for certain high-risk adult subgroups.[86,87] These mixed findings have contributed to the establishment of World-Wide FINGERS, a global, interdisciplinary network that aims to share knowledge, harmonize data, and coordinate international initiatives focused on preventing cognitive impairment and dementia. This network includes culturally tailored lifestyle trials from over 40 countries, addressing factors such as diet, physical activity, cognitive training, social engagement, and the administration of vascular or metabolic risks. These trials vary in terms of the populations targeted, risk factors considered, and the cultural, geographical, and economic contexts involved. A notable ongoing multidomain lifestyle trial is the German AgeWell.de study, a pragmatic, clustered randomized controlled trial that focuses on cognitive decline in a primary care audience at heightened risk for dementia.[88]

While several domain interventions appear encouragement for selective Avoidance in high-risk populations, the results thus far are inconclusive. Uncertainties persist regarding the necessary intensity of interventions to instigate behavioral changes, the ideal timeframe in a person's life for these interventions, the most effective target groups, preferred methods for delivering interventions (in-person versus virtual), and suitable settings for implementation (such as primary care).[89,90] Alzheimer's disease prevention remains an evolving research area, with significant potential for combating dementia that is still far from fully understood.

CONCLUSION

Research indicates that participating in physical activity, even at low to moderate intensity, can lower the risk of developing dementia and Alzheimer's disease (AD). While it remains uncertain whether this connection is dependent on exercise levels, evidence suggests that higher physical activity correlates with reduced risk. This information is particularly important for individuals with risk factors for AD or those suffering from early mild cognitive impairment (MCI). Moreover, for patients already diagnosed with AD, engaging in exercise may offer various benefits. Systematic reviews and meta-analyses have shown potential enhancements in cognitive functions, a decrease in neuropsychiatric symptoms, and a slower decline in the ability to perform daily activities (ADLs). Additionally, a comprehensive systematic review revealed that exercise tends to have fewer side effects and better compliance compared to medications. It also provides significant advantages for cardiovascular health and overall well-being. Considerable advancements have occurred in understanding AD since its initial diagnosis, with numerous studies focused on finding cures and improving diagnostic strategies. These research efforts have deepened insight into the symptoms, diagnosis, and progression of the disease. Substantial funding has been directed towards these studies aimed at uncovering new treatment options and medications. Links have been established concerning the disease's progression, which include factors such as diet, cardiovascular risks, and the influence of pharmaceuticals. While a definitive cure remains elusive, the enhanced understanding of the disease allows for earlier diagnosis and more effective management.

REFERENCES

1. Ahmad FB, Cisewski JA, Xu J, Anderson RN. Provisional Mortality Data - United States, 2022. MMWR Morb Mortal Wkly Rep, 2023; 05, 72(18): 488-492. [PMC free article] [PubMed].
2. Ramirez-BermudeZ Alzheimer's disease: critical notes on the history of a medical concept.
3. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, et al. Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. Proc Natl Acad Sci U S A, 2005; 102: 8299-8302.
4. Mar□nez A Emerging drugs and targets for Alzheimer's disease; Beta-Amyloid, Tau protein and glucose metabolism. Cambridge: The Royal Society of Chemistry, 2010; 1.
5. R. Kaddurah-Daouk, H. Zhu, S. Sharma, M. Bogdanov, S.G. Rozen, W. Matson, N.O. Oki, A.A. Motsinger-Reif, E. Churchill, Z. Lei, D. Appleby, M.A. Kling, J.Q. Trojanowski, P.M. Doraiswamy, S.E. Arnold, Alterations in metabolic pathways and networks in Alzheimer's disease, Transl. Psychiatry, 2013; (3): 244.
6. H. Cai, W.N. Cong, S. Ji, S. Rothman, S. Maudsley, B. Martin, Metabolic dysfunction in Alzheimer's disease and related neurodegenerative disorders, Curr. Alzheimer Res, 2012; (9): 5–17.
7. Z.Chen, C. Zhong, Decoding Alzheimer's disease from perturbed cerebral glucose metabolism: implications for diagnostic and therapeutic strategies, Prog. Neurobiol, 2013; (108): 21-43.
8. C. Caspersen, N. Wang, J. Yao, A. Sosunov, X. Chen, J.W. Lustbader, H.W. Xu, D. Stern, G. McKhann, S.D. Yan, Mitochondrial abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease, FASEB J, 2005; (19): 2040–2041.
9. X. Chen, S.D. Yan, Mitochondrial abeta: a potential cause of metabolic dysfunction in Alzheimer's disease, IUBMB Life, 2006; (58): 686–694.
10. Matthews FE, McKeith I, Bond J, Brayne C; MRC CFAS. Reaching thepopulationwith dementia

drugs:what are the challenges? IntJ Geriatr Psychiatry, 2007; 7: 627-31.
11. Archer T, Garcia D Selective diets for dementia disorders. ClinExpPsychol, 2016; 2: 127.
12. Garden G Theimpact of advance care planning for care home residents with dementia on hospital admission and death in preferred place of care. J Palliat Care Med, 2016; 6: 261.
13. Tobe EH (2016) Geriatric traumatic brain injury: relationship to dementia and neurodegenerative disease. J Gerontol Geriatr Res., 5: 292.
14. Sherzai D, Sherzai A, Sahak M, Ani C (2016) Age and race specific trends and mortality for dementia hospitalization in the US. J Neurol Neurophysiol, 7: 358.
15. Tsuno N Thepotential role of donepezil for the treatment of dementia with lewy bodies. J Alzheimers Dis Parkinsonism, 2016; 6: 214.
16. Suzuki H, Inoue Y Acomparison of lamotrigine or sodium valproate on the efficacy in Alzheimer's disease with behavioral and psychological symptoms of dementia: A retrospective open-label study running title: Efficacy of anticonvulsants for BPSD. J GerontolGeriatr Res, 2015; 4: 253.
17. Schwartz M, Serrano G, Beach TG, Tsai A, Malek-Ahmadi M, et al. Neurofibrillarytangle predominant dementia: Clinical and pathological description in a case series. J Alzheimers Dis Parkinsonism, 2016; 6: 204.
18. Kadavath, H., Hofele, R. V., Biernat, J., Kumar, S., Tepper, K., Urlaub, H., Mandelkow, E., & Zweckstetter, M. Tau stabilizes microtubules by binding at the interface between tubulin heterodimers. Proceedings of the National Academy of Sciences of the United States of America, 2015; 112(24): 7501–7506.
19. Zhang, H., Cao, Y., Ma, L., Wei, Y., & Li, H. Possible Mechanisms of Tau Spread and Toxicity in Alzheimer's Disease. Frontiers, 2021; 9. https://doi.org/10.3389/fcell.2021.707268.
20. Berrios G. Alzheimer's disease: A conceptual history. International Journal of Geriatric Psychiatry, 1990; 5: 355–365. [Google Scholar]
21. Brayne C, Richardson K, Matthews FE, Fleming J, Hunter S, Xuereb JH, et al. Neuropathological correlates of dementia in over-80-year-old brain donors from the population-based Cambridge city over-75s cohort (CC75C) study. J Alzheimers Dis, 2009; 18: 645–658. doi: 10.3233/JAD-2009-1182. [DOI] [PubMed] [Google Scholar]
22. Breitner JC, Folstein MF. Familial Alzheimer Dementia: a prevalent disorder with specific clinical features. Psychol Med, 1984; 14: 63–80. doi: 10.1017/s0033291700003081. [DOI] [PubMed] [Google Scholar]
23. Bondareff W, Mountjoy CQ, Roth M, Rossor MN, Iversen LL, Reynolds GP. Age and histopathologic heterogeneity in Alzheimer's disease. Evidence for subtypes. Arch Gen Psychiatry, 1987; 44: 412–417. doi: 10.1001/archpsyc.1987.01800170026005. [DOI] [PubMed] [Google Scholar]
24. Rodgers-Johnson P, Garruto RM, Yanagihara R, Chen KM, Gajdusek DC, Gibbs CJ., Jr Amyotrophic lateral sclerosis and parkinsonism-dementia on Guam: a 30-year evaluation of clinical and neuropathologic trends. Neurology, 1986; 36: 7–13. doi: 10.1212/wnl.36.1.7. [DOI] [PubMed] [Google Scholar]
25. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. Neurobiol Aging, 1998; 19: 173–189. doi: 10.1016/s0197-4580(98)00052-9. [DOI] [PubMed] [Google Scholar]
26. Katzman R. Education and the prevalence of dementia and Alzheimer's disease. Neurology, 1993; 43: 13–20. doi: 10.1212/wnl.43.1_part_1.13. [DOI] [PubMed] [Google Scholar]
27. Beard CM, Kokmen E, Offord KP, Kurland LT. Lack of association between Alzheimer's disease and education, occupation, marital status, or living arrangement. Neurology, 1992; 42: 2063–2068. doi: 10.1212/wnl.42.11.2063. [DOI] [PubMed] [Google Scholar]
28. Bonaiuto S, Rocca WA, Lippi A, Giannandrea E, Mele M, Cavarzeran F, et al. Education and occupation as risk factors for dementia: a population-based case-control study. Neuroepidemiology, 1995; 14: 101–109. doi: 10.1159/000109785. [DOI] [PubMed] [Google Scholar]
29. Jenkinson ML, Bliss MR, Brain AT, Scott DL. Rheumatoid arthritis and senile dementia of the Alzheimer's type. Br J Rheumatol, 1989; 28: 86–88. doi: 10.1093/rheumatology/28.1.86-b. [DOI] [PubMed] [Google Scholar]
30. Rich JB, Rasmusson DX, Folstein MF, Carson KA, Kawas C, Brandt J. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. Neurology, 1995; 45: 51–55. doi: 10.1212/wnl.45.1.51. [DOI] [PubMed] [Google Scholar]
31. Cheung ZH, Gong K, Ip NY. Cyclin-dependent kinase 5 supports neuronal survival through phosphorylation of Bcl-2. J Neurosci., 2008; 7, 28(19): 4872–7. doi: 10.1523/JNEUROSCI.0689-08.2008. [DOI] [PMC free article] [PubMed] [Google Scholar]
32. Weishaupt JH, Kussmaul L, Grotsch P, Heckel A, Rohde G, Romig H, et al. Inhibition of CDK5 is protective in necrotic and apoptotic paradigms of neuronal cell death and prevents mitochondrial dysfunction. Mol Cell Neurosci, 2003; 24(2): 489–502. doi: 10.1016/s1044-7431(03)00221-5. [DOI] [PubMed] [Google Scholar]
33. Wen Y, Yang SH, Liu R, Perez EJ, Brun-Zinkernagel AM, Koulen P, et al. Cdk5 is involved in NFT-like tauopathy induced by transient cerebral ischemia in female rats. Biochimica et biophysica acta, 2007;

1772(4): 473–83. doi: 10.1016/j.bbadis.2006.10.011. [DOI] [PubMed] [Google Scholar]
34. Leibson CL, Rocca WA, Hanson VA, Cha R, Kokmen E, O'Brien PC, et al. The risk of dementia among persons with diabetes mellitus: a population-based cohort study. Ann N Y Acad Sci, 1997; 26, 826: 422–7. doi: 10.1111/j.1749-6632.1997.tb48496.x. [DOI] [PubMed] [Google Scholar]
35. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. American journal of epidemiology, 2001; 1, 154(7): 635–41. doi: 10.1093/aje/154.7.635. [DOI] [PubMed] [Google Scholar]
36. Luchsinger JA. Adiposity, hyperinsulinemia, diabetes and Alzheimer's disease: an epidemiological perspective. Eur J Pharmacol, 2008; 6, 585(1): 119–29. doi: 10.1016/j.ejphar.2008.02.048. [DOI] [PMC free article] [PubMed] [Google Scholar]
37. Sacco RL, Benjamin EJ, Broderick JP, Dyken M, Easton JD, Feinberg WM, et al. American Heart Association Prevention Conference. IV. Prevention and Rehabilitation of Stroke. Risk factors. Stroke, 1997; 28(7): 1507–17. doi: 10.1161/01.str.28.7.1507. [DOI] [PubMed] [Google Scholar]
38. Arvanitakis Z, Schneider JA, Wilson RS, Li Y, Arnold SE, Wang Z, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology, 2006; 12, 67(11): 1960–5. doi: 10.1212/01.wnl.0000247053.45483.4e. [DOI] [PubMed] [Google Scholar
39. Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Archives of neurology, 2005; 62(1): 55–60. doi: 10.1001/archneur.62.1.55. [DOI] [PubMed] [Google Scholar]
40. Gustafson DR, Backman K, Waern M, Ostling S, Guo X, Zandi P, et al. Adiposity indicators and dementia over 32 years in Sweden. Neurology, 2009; 10, 73(19): 1559–66. doi: 10.1212/WNL.0b013e3181c0d4b6. [DOI] [PMC free article] [PubMed] [Google Scholar]
41. Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, et al. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Archives of neurology, 2005; 62(1): 55–60. doi: 10.1001/archneur.62.1.55. [DOI] [PubMed] [Google Scholar]
42. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology, 2008; 30, 71(14): 1057–64. doi: 10.1212/01.wnl.0000306313.89165.ef. [DOI] [PubMed] [Google Scholar]
43. Jost BC, Grossberg GT. The natural history of Alzheimer's disease: a brain bank study. J.Am. Geriatr. Soc, 1995; 43: 1248–55.
44. Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol, 2012; 11: 170–8.
45. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. American Academy of Neurology, 2011; 76: 1006–14.
46. Lam B, Masellis M, Freedman M, Stuss DT, Black SE. Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. Alzheimers. Res. Ther, 2013; 5: 1.
47. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers. Dement, 2011; 7: 280-92.
48. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimer's Dement, 2016; 12: 292–323.
49. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 2011; 7: 2639.
50. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias. 2nd ed. Arlington, Va.: American Psychiatric Association, 2007.
51. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev, 2006; 1: CD005593.
52. National Institute for Health and Clinical Excellence (Great Britain); Social Care Institute for Excellence (Great Britain); National Collaborating Centre for Mental Health (Great Britain). Dementia: supporting people with dementia and their carers in health and social care. NICE clinical guideline 42. London, United Kingdom: National Institute for Health and Clinical Excellence, 2006.
53. Qaseem A, Snow V, Cross JT, et al.; American College of Physicians/American Academy of Family Physicians Panel on Dementia. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med, 2008; 148(5): 370-378.
54. American Geriatrics Society. A guide to dementia diagnosis and treatment. http://dementia.americangeriatrics.org/. Accessed June 1, 2010.

55. California Workgroup on Guidelines for Alzheimer's Disease Management. Guideline for Alzheimer's disease management: final report. Los Angeles, Calif.: Alzheimer's Association, 2008.
56. Chertkow H. Introduction: the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, 2006. Alzheimers Dement, 2007; 3(4): 262-265.
57. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol, 2007; 14(1): e1-e26.
58. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol, 2007; 14(1): e1-e26.
59. Caltagirone C, Bianchetti A, Di Luca M, et al. Guidelines for the treatment of Alzheimer's disease from the Italian Association of Psychogeriatrics. Drugs Aging, 2005; 22(1): 1-26.
60. Raina P, Santaguida P, Ismaila A, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med, 2008; 148(5): 379-397.
61. Thomson Reuters. Micromedex Healthcare Series: Drug Point Summary: Memantine. http://www.thomsonhc.com (subscription required).
62. Lockhart IA, Mitchell SA, Kelly S. Safety and tolerability of donepezil, rivastigmine and galantamine for patients with Alzheimer's disease: systematic review of the 'real-world' evidence. Dement Geriatr Cogn Disord, 2009; 28(5): 389-403.
63. Rainer M, Mucke HA, Krüger-Rainer C, Kraxberger E, Haushofer M, Jellinger KA. Cognitive relapse after discontinuation of drug therapy in Alzheimer's disease: cholinesterase inhibitors versus nootropics. J Neural Transm, 2001; 108(11): 1327-1333.
64. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Database Syst Rev, 2006; 2: CD003154.
65. Schneider LS, Dagerman KS, Higgins JP, McShane R. Lack of evidence for the efficacy of memantine in mild Alzheimer Disease [published ahead of print April, 2011; 11]. Arch Neurol. http://archneur.ama-assn.org/cgi/content/abstract/archneurol.2011.69 Accessed May 20, 2011.
66. Birks J, Flicker L. Selegiline for Alzheimer's disease. Cochrane Database Syst Rev, 2003; 1: CD000442.
67. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev, 2006; 1: CD003476.
68. Sultzer DL, Davis SM, Tariot PN, et al.; CATIE-AD Study Group. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. Am J Psychiatry, 2008; 165(7): 844-854.
69. L Ghezzi, E Scarpini, D GalimbertiDisease-modifying drugs in Alzheimer's diseaseDrug Des Dev Ther, 2013; 7: 1471-1478.
70. R. VassarBACE1 inhibitor drugs in clinical trials for Alzheimer's diseaseAlzheimers Res Ther, 2014; 6: 89.
71. CM Wischik, CR Harrington, JM StoreyTau-aggregation inhibitor therapy for Alzheimer's diseaseBiochem Pharmacol, 2014; 88: 529-539.
72. PN Tariot, PS AisenCan lithium or valproate untie tangles in Alzheimer's disease?J Clin Psychiatry, 2009; 70: 919-921.
73. H Hampel, M Ewers, K Bürger, et al.Lithium trial in Alzheimer's disease: a randomized, single-blind, placebo-controlled, multicenter 10-week studyJ Clin Psychiatry, 2009; 70: 922-931.
74. CM Wischik, RT Staff, DJ Wischik, et al.Tau aggregation inhibitor therapy: an exploratory phase 2 study in mild or moderate Alzheimer's diseaseJ Alzheimers Dis, 2015; 44: 705-720.
75. Chu J, Praticò D: Pharmacologic blockade of 5-lipoxygenase improves the amyloidotic phenotype of an Alzheimer's disease transgenic mouse model. Am J Pathol, 2011; 178: 1762-1769.
76. In t' Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, et al: Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N Engl J Med, 2001; 345: 1515–1521.
77. Lauterbach EC, Victoroff J, Coburn KL, Shillcutt SD, Doonan SM, Mendez MF: Psychopharmacological neuroprotection in neurodegenerative disease: assessing the preclinical data. J Neuropsychiatry Clin Neurosci, 2010; 22: 8–18.
78. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2019; 1, 5: 272-93.
79. Schneider L. A resurrection of aducanumab for Alzheimer's disease. The Lancet Neurology, 2020; 1, 19(2): 111-2.
80. Knopman DS. Lowering of amyloid-beta by β-secretase inhibitors—some informative failures. The New England Journal of Medicine, 2019; 11, 380(15): 1476-1478.
81. DeVos SL, Corjuc BT, Oakley DH, Nobuhara CK, Bannon RN, Chase A, et al. Synaptic tau seeding precedes tau pathology in human Alzheimer's disease brain. Frontiers in Neuroscience, 2018; 24, 12: 267.
82. Gauthier S, Feldman HH, Schneider LS, Wilcock GK, Frisoni GB, Hardlund JH, et al. Efficacy and safety of tauaggregation inhibitor therapy in patients with mild or moderate Alzheimer's disease: a randomised, controlled, double-blind, parallel-arm, phase 3 trial. The Lancet, 2016; 10, 388(10062): 2873-84.

83. Aisen P, Touchon J, Amariglio R, Andrieu S, Bateman R, Breitner J, et al. EU/US/CTAD task force: lessons learned from recent and current Alzheimer's prevention trials. The Journal of Prevention of Alzheimer's Disease, 2017; 4(2): 116.
84. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet, 2020; 396: 413–446. CrossRefPubMedGoogle Scholar]
85. Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines. World Health Organization, 2019. Google Scholar
86. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet, 2015; 385: 2255–2263. CrossRefPubMedGoogle Scholar
87. Moll van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet, 2016; 388: 797–805. CrossRefPubMedGoogle Scholar
88. Chhetri JK, de Souto Barreto P, Cantet C, et al. Effects of a 3-year multi-domain intervention with or without omega-3 supplementation on cognitive functions in older subjects with increased CAIDE dementia scores. J Alzheimers Dis, 2018; 64: 71–78. Google Scholar
89. Zülke A, Luck T, Pabst A, et al. AgeWell.de: study protocol of a pragmatic multi-center cluster-randomized controlled prevention trial against cognitive decline in older primary care patients. BMC Geriatr, 2019; 19: 203. Google Scholar
90. Hussenoeder FS, Riedel-Heller SG. Primary prevention of dementia: from modifiable risk factors to a public brain health agenda? Soc Psychiatry Psychiatr Epidemiol, 2018; 53: 1289–1301. Google Scholar.