International Journal of Advances in Medicine
Khanam FM. Int J Adv Med. 2023 Aug;10(8):653-659
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20232215

Review Article

Donepezil to lecanemab-advancements in targeted therapy of Alzheimer's disease so far

Fouqia Mahnaz Khanam*

Doctor of Pharmacy, Shadan College of Pharmacy, Hyderabad, Telangana, India

Received: 18 June 2023
Accepted: 12 July 2023

***Correspondence:**
Dr. Fouqia Mahnaz Khanam,
E-mail: fouqiakhanam@gmail.com

ABSTRACT

Alzheimer's disease (AD) first identified as Alois Alzheimer in 1907, is a slowly progressing dementia that affects cognition, behaviour and functional status. There is no cure for AD since precise pathophysiological mechanisms underlying it is not completely known. Drugs may temporarily reduce the symptoms associated with disorder, but condition is ultimately fatal. Objective of treatment of AD is to reduce behaviour issues associated with memory loss and improve cognition. Single acetylcholinesterase inhibitors donepezil and galantamine, as well as the dual AChE and butyrylcholinesterase (BuChE) inhibitor rivastigmine, are now utilized in treatment of AD. Cholinesterase inhibitors have shown dose-dependent impact on cognition and functional activities in clinical trials. Memantine NMDA receptor antagonist is used to minimize neurotoxicity that's suspected to contribute to conditions like Alzheimer's and other neurodegenerative disorders. Estrogen administration post menopause can result in modulation of synaptogenesis, enhanced cerebral blood flow, mediation of crucial neurotransmitters and hormones, protection against apoptosis. Aducanumab is 1st disease modifying drug and monoclonal antibody that targets beta-amyloid clusters in mild AD. Recent advancement in therapy, lecanemab, a recombinant IgG1 monoclonal antibody is targeted against aggregated soluble and insoluble forms of amyloid beta, thereby minimizing Aβ plaques and preventing Aβ deposition in the brain. As research advances, molecular basis of disease becomes more apparent leading to the advent of plausible targeted therapy.

Keywords: AD, Targeted therapy, Lecanemab, Donepezil, Galantamine, Memantine

INTRODUCTION

Alzheimer's disease (AD) first identified as Alois Alzheimer in 1907, is slowly progressing dementia that affects cognition, behaviour, and functional status. There is no cure for AD since the precise pathophysiological mechanisms underlying it is not completely known. Drugs may temporarily reduce the symptoms associated with the disorder, but the condition is ultimately fatal.[1]

EPIDEMIOLOGY

Fifth-leading cause of death, primary cause of dementia in senior population is AD. Around 44 million people worldwide suffer from it. By 2050, no. of patients should almost double as result of population's growing ageing. Recent epidemiological research discovered decline in prevalence of AD, which may be partially attributed to better management of specific risk factors for disease.[2]

GENETICS AND ETIOPATHOGENESIS

Majority of cases of early-onset AD show mutations in the PSEN1, PSEN2, and APP genes. Apolipoprotein E4 (ApoE4) gene mutations are mostly responsible for late-onset AD, particularly in non-Hispanic white people. In members of other racial/ethnic groups, there was no consistent relationship between ApoE4 and AD. Recently,

albeit without a conclusive generalization, evidence has emerged suggesting that other genes may also be associated with Alzheimer's.[3]

Amyloid plaques and neurofibrillary tangles

Plaques are spherical microscopic lesions that have enlarging axonal end and extracellular amyloid beta-peptide core. An amyloid precursor protein (APP), transmembrane protein, is source of beta-amyloid peptide. Alpha, beta, and gamma-secretases work as proteases to cleave beta-amyloid peptide from APP. Typically, alpha- or beta-secretase will cleave APP, and resulting minute pieces are not harmful to neurons. However, beta-secretase and gamma-secretase cleavages in succession produce 42 amino acid peptides (beta-amyloid 42). Increase in beta-amyloid 42 results in amyloid aggregation, which harms neurons. In contrast to typical APP degradation, beta-amyloid 42 favours development of aggregated fibrillary amyloid protein. On chromosome 21, one of locations connected to familial AD, is where APP gene is found. In AD, amyloid buildup surrounds meningeal, cerebral, and grey matter arteries. Multifocal grey matter deposits combine to produce plaques, which are milliary structures. However, some people with dementia found to have amyloid plaques on their brain scans whereas others did not, despite having dementia.

In neurons, protein called tau forms fibrillary intracytoplasmic formations known as neurofibrillary tangles. The stabilization of axonal microtubules is the tau protein's main purpose. Microtubules are necessary for intracellular transport and are found along neuronal axons. Tau protein holds together microtubule assembly. Tau is hyperphosphorylated in AD and forms tau clumps as result of extracellular beta-amyloid aggregation. Neurofibrillary tangles are twisted pairs of helical filaments made of tau clumps. They begin to appear in the hippocampus before spreading to other parts of the cerebral cortex. In the neurons, tau-aggregates are deposited. National institute on ageing and Reagan Institute neuropathological criteria for the diagnosis of Alzheimer disease include the Braak staging, which was devised by Braak and Braak and is based on the topographical staging of neurofibrillary tangles into 6 stages. In comparison to plaques, tangles have a stronger correlation with AD. [4]

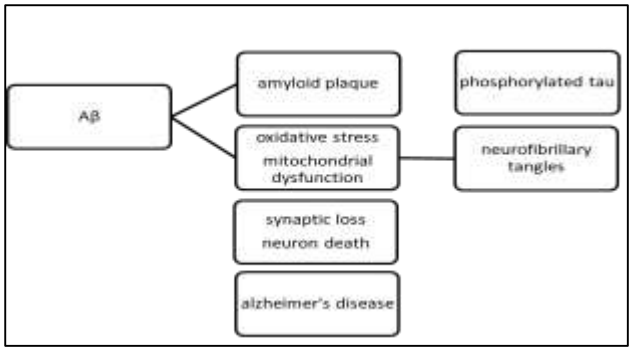

Figure 1: Progression of AD.

CLINICAL PRESENTATION

Mild AD

Memory loss and other cognitive problems get with the progression of Alzheimer's. Wandering and getting lost can be a problem, as can having difficulties managing money and paying bills, asking questions repeatedly, taking longer to do everyday duties, and changing their personality and behaviour. In this period, patients are frequently diagnosed.

Moderate AD

This stage of the disease involves brain damage to the regions responsible for language, cognition, conscious thought, and sensory processing, including the capacity to recognize sounds and odours. As disorientation and memory loss worsen, it gets harder for people to identify their loved ones. They might not be able to adapt to new circumstances, learn new things, or perform complex chores like getting dressed. Additionally, individuals in this stage may exhibit impulsive behaviour and have hallucinations, delusions, and paranoia.

Severe AD

Plaques and tangles eventually cover the entire brain, and the brain's tissue begins to dramatically diminish. People who have advanced AD are fully reliant on others for their care and are unable to communicate. As the body slows down at the end of life, the person may spend most of the time in bed.[5]

DIAGNOSIS

Inquiry about general health, usage of prescription and over-the-counter medications, food, prior medical issues, capacity to carry out daily activities, and changes in behaviour and personality from the person experiencing symptoms as well as a family member or friend is done. Tests for language, counting, problem-solving, and memory is administered. Blood, urine, and other common medical tests that can assist pinpoint further potential reasons of the issue should be done. To ascertain whether depression or another mental health disorder is causing or contributing to a person's symptoms, a psychiatric evaluation can be instated. Concentrations of the proteins linked to AD and other dementias in cerebrospinal fluid (CSF), which is obtained through a spinal tap, should be assessed. To confirm an Alzheimer's diagnosis or to rule out other potential causes of symptoms, brain scans using computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) are done.[6]

THERAPEUTIC MANAGEMENT

The objective of treatment is to reduce behaviour issues associated with memory loss, psychosis, delirium, paranoia and improve cognition.[7]

Cholinesterase inhibitors

The aetiology of cognitive failure in AD is thought to involve a decrease in brain acetylcholine (ACh) levels. ACh levels in the brain may rise as a result of the inhibition of the ACh catabolic enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). AChE/BuChE inhibitors have been licensed by the FDA to treat AD symptoms. Although it has been hypothesised that blocking AChE and BuChE may help prevent the development of Aβ plaques and serve as a fundamental component of a disease-modifying strategy, this hypothesis has not been supported by any solid data. The development of new bio-oxidizable AChE and BuChE inhibitor prodrugs may be a creative way to enhance the therapeutic effects of this type of medication for AD.[8] Acetylcholinesterase (AChE)-selective inhibitors donepezil and galantamine, as well as the dual AChE and butyrylcholinesterase (BuChE) inhibitor rivastigmine, are now utilised in the treatment of AD.[9] Cholinesterase inhibitors show a dose-dependent impact on cognition and functional activities in clinical trials. Behavioural symptoms also improve, but there is no dose-response association. Adverse gastrointestinal effects are dosage dependent. When cholinesterase is inhibited between 40 and 70%, clinical improvement ensues.[10] For mild to moderate AD, two galantamine dosages of 24 mg and 32 mg daily is used. The most effective treatment for moderate to severe AD is a combination of donepezil 10 mg and memantine 20 mg, followed by donepezil 23 mg on its own. None of the cognitive boosters, however, were expected to change behaviour. The transdermal patch with a greater dose of rivastigmine (15 cm^2) was probably the best choice when considering the advantages of both function and clinical overall impression.[11] With 10-mg of donepezil per day, cholinergic side effects like diarrhoea, nausea, and vomiting are more prominent when compared to 5-mg of donepezil per day.[12] AChE inhibitors cannot totally stop AD's progression, and the single-target drugs that have made it to clinical trials weren't successful in treating AD either. Therefore, there is a need to create drugs that are multi-functional to target all AD symptoms.[13]

NMDA receptor antagonist/ glutamate receptor antagonist

The principal excitatory neurotransmitter in the human brain, glutamate, is a receptor for the N-methyl-D-aspartate (NMDA) receptor. It is crucial to synaptic plasticity, a neuronal process thought to constitute the foundation of memory formation.[14] Memantine is an antagonist of the glutamate receptor subtype known as the NMDA (N-Methyl-D-Aspartate)-receptor. It's used to minimise the neurotoxicity that's suspected to contribute to conditions like Alzheimer's and other neurodegenerative disorders.[15] Memantine prevents overactivation of glutamine receptors while letting normal action by blocking the NMDA-receptor subtype of glutamate receptors. Its blocking properties counteract the central nervous system's (CNS) hyperactive glutaminergic pathway, which is responsible for the neurotoxicity found in Alzheimer disease.[16] The receptor is pathologically overstimulated in AD, which makes it persistently active. Memantine aids in reducing the overstimulation.[17] Memantine is safe and well tolerated when given at a dosage of 20 mg/d to patients receiving consistent dosages of donepezil.[18] According to Annweiler and colleagues, taking vitamin D supplements in addition to MEM improved overall cognition more than AD symptoms, both statistically and clinically.[19] The most notable adverse effects include dizziness, headache, confusion, diarrhea, and constipation.[20] At present, the only approved choice for the treatment of moderate to severe AD is memantine, an efficient pharmacotherapeutic drug.[21]

Estrogen

AD is more likely to affect women than men because oestrogen, which is necessary for healthy memory function, drops as women approach menopause. The analysis of factors causing this elevated risk in women is crucial for AD research since women, particularly APOE4 carriers, have a considerably higher chance of acquiring AD than males.[22] Studies on oestrogen therapy, however, reveal that while some menopausal women benefit from the hormone, others do not. Taxier et al conducted a study in mice with one or two copies of E3 and estradiol was directly injected into the hippocampus, one of the first areas of the brain to degenerate in Alzheimer's, thereby improving memory and increasing the density of dendritic spines.[23] Modulation of synaptogenesis, enhanced cerebral blood flow, mediation of crucial neurotransmitters and hormones, protection against apoptosis, anti-inflammatory effects, and antioxidant qualities are few of the many impacts of estrogen on the brain.[24] Using conditional logistic regression with age and education level adjustments, the degree of the connection between estrogen use and early-onset AD was examined by Slooter et al. Estrogen consumption and early-onset AD had an inverse relationship (adjusted odds ratio 0.34; 95% confidence range 0.12-0.94). Therefore, the study suggests estrogen use is advantageous for AD that manifests early.[25] Episodic memory which is an important early symptom of AD, is not improved by estrogen-containing hormone therapy when it is started in the late postmenopausal stage, on the contrary this can increase the risk of dementia.[26]

Non-steroidal anti-inflammatory drugs

Pathogenesis of AD has been linked to inflammatory processes. In AD, interactions between protein complexes of β-amyloid and hyper-phosphorylated tau with microglia and astrocytes cause the release of cytokines and chemokines, which are indicators of activated inflammation.[27] Nonsteroidal anti-inflammatory drugs (NSAIDs) may lessen the inflammatory response by inhibiting cyclooxygenase-1 and cyclooxygenase-2 and by activating the peroxisome proliferator g nuclear transcription factor (PPAR).[28] Use of celecoxib,

diclofenac, ibuprofen, paracetamol, aspirin, and naproxen was all linked to a significantly lower prevalence of AD.[29] In comparison to individuals who did not take NSAIDs, meta-analysis conducted by Zhang et al showed that current NSAID use was substantially related with a lower risk of AD (RR, 0.81, 95% CI0. 70 to 0.94).[30]

Lipid lowering agents

The theory that having elevated cholesterol levels raises the risk of AD has amassed a lot of research. Subsequently, a lot of research has been put into the potential use of lipid-lowering medications, in particular statins, as preventative or therapeutic agents for AD.[31] By lowering intracranial A and phosphorylated tau, enhancing cerebral blood flow and the blood-brain barrier, reducing inflammation and oxidative stress, and through other mechanisms, statins may reduce the risk of development of AD. The most significant genetic risk factor for AD is the apolipoprotein E 4 allele (APOE 4). According to a longitudinal trial that lasted more than 6 years, statins appear to slow the deterioration of memory in people with heart disease and APOE4 carriers.[32] Simvastatin 80 mg/day, rather than the standard dose of 20 mg/day, was used in the clinical investigation to lower total cholesterol, lathosterol, and 24S-OH levels in cerebrospinal fluid.[33] A study conducted by Masse et al suggests that lipid lowering agents may decrease cognitive decline associated with AD by exhibiting neuroprotective effect.[34]

Vitamin E

Vitamin E is a potential clinical intervention for AD (AD) given the association of its various biological functions influencing the neurodegenerative processes. The vitamin E isoforms, tocopherol and tocotrienol provide a wide range of benefits, including strong antioxidant and anti-inflammatory properties, effects on immunological response, cellular signaling, and cholesterol reduction. A number of these roles provide a theoretical justification that help in treating AD-related disease.[35] One of the most significant antioxidants is vitamin E, and studies have shown that it can reduce Aβ-induced oxidative stress. Preclinical trials provided evidence that vitamin E supplementation may help AD. Furthermore, vitamin E has the ability to restore memory and cognitive deficits in addition to reducing oxidative stress.[36] A randomized trial conducted by Dysken et al showed that Alpha tocopherol at a dosage of 2000 IU/d proved successful in delaying the functional deterioration of mild to moderate AD.[37]

Ginkgo biloba

One of the well-known herbal remedies for AD is Ginkgo biloba leaves, which are listed in the Chinese Pharmacopoeia (2015 edition). One of the main active components of EGb, ginkgolide B, has the ability to reduce the neurotoxicity brought on by β-amyloid.[38] Modern pharmacological research has demonstrated that the combination of donepezil and G. biloba extract may be effective in treating AD in rats and mice.[39] A meta-analysis conducted by Xie et al suggest that the early stages of AD may benefit from the long-term (over 24 weeks) and high dose (240 mg/day) of ginkgo biloba extract.[40] Headaches or gastrointestinal issues could be the potential adverse effects. Ginkgo's tendency to interact with other drugs cannot be completely disregarded. For instance, it may intensify the effects of blood-thinning drugs like warfarin and acetylsalicylic acid.[41]

Huperzine A

In Chinese traditional medicine, dementia has historically been treated with huperzine A (HupA), an alkaloid derived from the club moss Huperzia serrata.[42] This alkaloid's effects have been related to its capacity to operate as an acetylcholinesterase inhibitor (AChEI), inhibiting the cholinergic enzyme acetylcholinesterase (AChE). HupA's biological functions have been investigated both in vitro and *in vivo*, and its involvement in neuroprotection seems to make it a promising therapeutic target for AD with potency much higher than huperzine B, donepezil or rivastigmine.[43] It has also been noted that HupA possesses neuroprotective qualities against Aβ injury, oxygen-glucose deprivation, glutamate, and free radical-induced cytotoxicity.[44] Although HA is one of the safest AChE inhibitors, it takes a high dosage (between 0.2 and 0.8 mg per day) to noticeably improve cognition.[45] This frequently causes cholinergic reactions, which can have adverse effects like sweating, nausea, vomiting, dizziness, hypertension, headaches, tachycardia, and insomnia.[46] In patients with AD, huperzine A appears to have positive impacts on improvement of cognitive function, daily living activities, and overall clinical assessment.[47]

Aducanumab

The U.S. FDA has granted conditional permission for the use of aducanumab, the first disease modifying drug and monoclonal antibody that targets beta-amyloid clusters in mild AD.[48] Accelerated approval by the FDA is linked to the drug's effect on a surrogate endpoint which is the reduction of amyloid beta plaque.[49] It is a human immunoglobulin gamma 1 (IgG1) monoclonal antibody serving as an immunotherapeutic. It works by bridging the blood-brain barrier, preferentially targeting and binding aggregated soluble oligomers and insoluble fibril conformations of Aβ plaques in the brain.[50] It is administered intravenously through a 45-to-60-minute infusion every 4 weeks. The most frequent adverse effects include headaches, falls, and amyloid-related imaging abnormalities (ARIA). An allergic reaction is another adverse effect that could be quite harmful.[51] In the clinical trials, 41% of the patients had brain haemorrhage or edoema. While the majority of instances were minor and treated by reducing the dose, 1% to 2% of individuals needed to be hospitalised or had lasting effects. The cause of a recent patient death connected to aducanumab is being investigated. In order to determine whether aducanumab

provides a significant patient benefit, the FDA has mandated that a new trial be finished by 2030.[52]

Lecanemab

A recombinant humanised immunoglobulin gamma 1 (IgG1) monoclonal antibody known as lecanemab is targeted against aggregated soluble and insoluble forms of amyloid beta (Aβ), which are believed to have a role in the pathogenesis of AD. With a high level of selectivity for Aβ protofibrils, lecanemab helps to minimize Aβ plaques and prevent Aβ deposition in the brain.[53] Patients receiving the recommended dose of lecanemab, 10 milligram/kilogram every two weeks, had a statistically significant reduction in brain amyloid plaque from baseline to week 79 compared to the placebo arm, which had no reduction in amyloid beta plaque. The FDA used the accelerated approval process to approve lecanemab following a clinical trial conducted by Dyck et al because it demonstrated an impact on a surrogate endpoint that is reasonably likely to predict a therapeutic benefit for patients.[54] Lecanemab selectively targets the forms of amyloid protein thought to be the most harmful to brain cells in the study by Dyck et al involving 1,795 individuals with early-stage, symptomatic Alzheimer's, and found to slow clinical decline by 27% after 18 months of treatment compared to those who received a placebo. The most frequent adverse reaction to the medication is an infusion-related reaction, which can involve momentary symptoms like flushing, chills, fever, rash, and body aches (26.4% of participants vs. 7.4% in the placebo group). 75% of these responses occurred after the first dose, and 96% of them were mild to moderate.[55] Randomized trial by McDade et al suggests amyloid plaques were significantly reduced after receiving lecanemab therapy, and the rate of clinical decline was also slowed. The possibility of using plasma biomarkers to track the effects of lecanemab treatment is suggested by the data, which also shows that rapid and dramatic amyloid reduction correlates with clinical benefit and possible disease-modifying effects.[56]

CONCLUSION

The world health organization has recently declared that about 139 million people worldwide will be affected with dementia which is typical in AD by the end of 2050. We are witnessing a growing epidemic of AD among the older population which contributes to the social and economic burden while the progression of the disease remains without cure. Since, the exact etiopathogenisis of AD is unknown, the screening process of the disease is only 80-90% accurate and the treatment was symptomatic at best until recently as the research progresses on the molecular basis of the neurodegenerative disease. Though single target drugs under acetylcholinesterase inhibitors and NMDA receptor antagonist have shown clinical improvements in patients over the years, the advent of lecanemab, an immunoglobulin gamma 1 (IgG1) monoclonal antibody that targets amyloid proteins, has shown promising disease-modifying results among the study participants when compared to placebo, granting it an accelerated approval by the FDA. The only drawback to lecanemab therapy is that it is not cost effective, thereby limiting its availability and use. Nonetheless, as the research on targeted treatment of AD advances, there is still hope in the horizon for a possible cure someday.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, L. Michael Posey, Pharmacotherapy: A Pathophysiological Approach, 8th Edition, Alzheimer's Disease. 2010;947-59.
2. Dumurgier J, Sabia S. Epidemiology of Alzheimer's disease: latest trends. Rev Prat. 2020;70(2):149-51.
3. Patel HH. Alzheimer's Disease Epidemiology. News-Medical. Available at: https://www.news-medical.net/health/Alzheimers-Disease-Epidemiology.aspx. Accessed on 25 March, 2023.
4. Kumar A, Sidhu J, Goyal A. Alzheimer Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
5. Alzheimer's Disease Fact Sheet, National Institute of Aging, April 5, 2023. Available at: https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet#:~:text=As%20Alzheimer's%20worsens%2C%20people%20experience,and%20personality%20and%20behavior%20changes. Accessed on 25 March, 2023.
6. Symptoms and Diagnosis of Alzheimer's Disease, National Institute of Aging, December 08, 2022, Available at: https://www.nia.nih.gov/health/how-alzheimers-disease-diagnosed. Accessed on 25 March, 2023.
7. Practice guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. American Psychiatric Association. Am J Psychiatr. 1997;154(5):1-39.
8. Marucci G, Buccioni M, Ben DD, Lambertucci C, Volpini R, Amenta F. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. Neuropharmacology. 2020;190.
9. Grossberg GT. Cholinesterase inhibitors for the treatment of Alzheimer's disease: getting on and staying on. Curr Ther Res Clin Exp. 2003;64(4):216-35.
10. Jann MW, Shirley KL, Small GW. Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. Clin Pharmacokinet. 2002;41(10):719-39.
11. Dou KX, Tan MS, Tan CC. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. Alz Res Therapy. 2018;10:126.

12. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology. 1998;50(1):136-45.
13. Sharma K. Cholinesterase inhibitors as Alzheimer's therapeutics. Molecular Med Rep. 2019;20:1479-87.
14. Jewett BE, Thapa B. Physiology, NMDA Receptor. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2023.
15. Rogawski MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. CNS Drug Rev. 2003;9(3):275-308.
16. Cacabelos R, Takeda M, Winblad B. The glutamatergic system and neurodegeneration in dementia: preventive strategies in Alzheimer's disease. Int J Geriatr Psychiatr. 1999;14(1):3-47.
17. Brianne Kuns, Alan Rosani, Memantine, Stat Pearls. 2022. Available at: https://www.statpearls.com/ArticleLibrary/viewarticle/24945#:~:text=Memantine%20is%20an%20antagonist%20of,disease%20and%20other%20neurodegenerative%20diseases. Accessed on 25 March, 2023.
18. Tariot PN, Farlow MR, Grossberg GT. Memantine Treatment in Patients with Moderate to Severe Alzheimer Disease Already Receiving Donepezil: A Randomized Controlled Trial. JAMA. 2004;291(3):317-24.
19. Annweiler C, Karras SN, Anagnostis P, Beauchet O. Vitamin D supplements: a novel therapeutic approach for Alzheimer patients. Front Pharmacol. 2014;28;5-6.
20. Ditzler K. Efficacy and tolerability of memantine in patients with dementia syndrome. A double-blind, placebo-controlled trial. Arzneimittel Forschung. 1991;41(8):773-80.
21. Robinson DM, Keating GM. Memantine: a review of its use in Alzheimer's disease. Drugs. 2006;66(11):1515-34.
22. Altmann A, Tian L, Henderson VW, Greicius MD; Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann Neurol. 2014;75(4):563-73.
23. Taxier LR, Philippi SM, Fleischer AW, York JM, LaDu MJ, Frick KM. APOE4 homozygote females are resistant to the beneficial effects of 17β-estradiol on memory and CA1 dendritic spine density in the EFAD mouse model of Alzheimer's disease. Neurobiol Aging. 2022;118:13-24.
24. Cholerton B, Gleason CE, Baker LD, Asthana S. Estrogen and Alzheimer's disease: the story so far. Drugs Aging. 2002;19(6):405-27.
25. Slooter AJC, Bronzova J, Witteman JCM. Estrogen use and early onset Alzheimer's disease: a population-based study. J Neurol Neurosurg Psychiatr. 1999;67:779-81.
26. Henderson VW. Estrogens, episodic memory, and Alzheimer's disease: a critical update. Semin Reprod Med. 2009;27(3):283-93.
27. Hershey LA, Lipton LB. Naproxen for pre-symptomatic Alzheimer disease. Is this the end, or shall we try again? Neurology. 2019;92(18):829-30.
28. John Hopkins Arthritis Center, Role of NSAIDS in Alzheimer's Disease. Available at: https://www.hopkinsarthritis.org/arthritis-news/role-of-nsaids-in-alzheimers-disease/. Accessed on 25 March 2023.
29. Rivers-Auty J. Alzheimer's Disease Neuroimaging Initiative, Anti-inflammatories in Alzheimer's disease-potential therapy or spurious correlate? Brain Communications. 2020;2(2):fcaa109.
30. Zhang C, Wang Y, Wang D, Zhang J, Zhang F. NSAID Exposure and Risk of Alzheimer's Disease: An Updated Meta-Analysis From Cohort Studies. Front Aging Neurosci. 2018;10:83.
31. Shepardson NE, Shankar GM, Selkoe DJ. Cholesterol Level and Statin Use in Alzheimer Disease: II. Review of Human Trials and Recommendations. Arch Neurol. 2011;68(11):1385-92.
32. Li Q, Chu-Na L, Jing-Long C. Statins Effects on Alzheimer's Disease, Statins - From Lipid-Lowering Benefits to Pleiotropic Effects. Intech Open. 2023;1.
33. Cibičková L. Statins and their influence on brain cholesterol. J Clin Lipidol. 2011;5(5):373-9.
34. Masse I, Bordet R, Deplanque D, Lipid lowering agents are associated with a slower cognitive decline in Alzheimer's disease. J Neurol Neurosur Psychiatr. 2005;76:1624-9.
35. Browne D, McGuinness B, Woodside JV, McKay GJ. Vitamin E and Alzheimer's disease: what do we know so far? Clin Interv Aging. 2019;14:1303-17.
36. Gugliandolo A, Bramanti P, Mazzon E. Role of Vitamin E in the Treatment of Alzheimer's Disease: Evidence from Animal Models. Int J Mol Sci. 2017;18(12):2504.
37. Dysken MW, Sano M, Asthana S. Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease: The TEAM-AD VA Cooperative Randomized Trial. JAMA. 2014;311(1):33-44.
38. Haolong L, Min Y, Hongzhu G, An Updated Review of Randomized Clinical Trials Testing the Improvement of Cognitive Function of Ginkgo biloba Extract in Healthy People and Alzheimer's Patients, Frontiers in Pharmacol. 2020;10.
39. Stein C, Hopfeld J, Lau H, Klein J. Effects of Ginkgo biloba Extract EGb 761, donepezil and their combination on central cholinergic function in aged rats. J Pharm Pharm Sci. 2023;4:634-46.
40. Xie L, Zhu Q, Lu J. Can We Use Ginkgo biloba extract to Treat Alzheimer's Disease? Lessons from Preclinical and Clinical Studies. Cells. 2022;11(3):479.
41. InformedHealth.org. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG);

2006. Alzheimer's disease: Do Ginkgo products help? 2009.
42. Friedli MJ, Inestrosa NC. Huperzine A and Its Neuroprotective Molecular Signaling in Alzheimer's Disease. Molecules. 2021;26(21):6531.
43. Wang Z, Tang L, Yan H, Wang Y, Tang X. Effects of Huperzine A on Memory Deficits and Neurotrophic Factors Production after Transient Cerebral Ischemia and Reperfusion in Mice. Pharmacol Biochem. Behav. 2020;83(4):603-11.
44. Zhang HY, Tang XC. Neuroprotective Effects of Huperzine A: New Therapeutic Targets for Neurodegenerative Disease. Trends Pharmacol Sci. 2006;27(12):619-25.
45. Little JT, Walsh S, Aisen PS. An Update on Huperzine A as a Treatment for Alzheimer's Disease. Expert Opin. Investig. Drugs. 2008;17(2):209-15.
46. Callizot N, Campanari ML, Rouvière L, Jacquemot G, Henriques A, Garayev E, et al. Huperzia serrata Extract 'NSP01' With Neuroprotective Effects-Potential Synergies of Huperzine A and Polyphenols. Front Pharmacol. 2021;12:681532.
47. Yang G, Wang Y, Tian J, Liu JP. Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. PLoS One. 2013;8(9):e74916.
48. Beshir SA, Aadithsoorya AM, Parveen A, Goh SSL, Hussain N, Menon VB. Aducanumab Therapy to Treat Alzheimer's Disease: A Narrative Review. Int J Alzheimers Dis. 2022;2022:9343514.
49. Aducanumab (marketed as Aduhelm) Information, U. S. Food and Drug Administration. 2021. Available at: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information. Accessed on 25 March 2023.
50. Padda IS, Parmar M. Aducanumab. In: StatPearls. Treasure Island (FL): StatPearls. 2023.
51. Aducanumab Approved for Treatment of Alzheimer's Disease, Alzhimer's Association. Available at: https://www.alz.org/alzheimers-dementia/treatments/aducanumab. Accessed on 25 March, 2023.
52. Woloshin S, Kesselheim AS. What to Know About the Alzheimer Drug Aducanumab (Aduhelm). JAMA Intern Med. 2022;182(8):892.
53. Shi M, Chu F, Zhu F, Zhu J. Impact of Anti-amyloid-beta Monoclonal Antibodies on the Pathology and Clinical Profile of Alzheimer's Disease: A Focus on Aducanumab and Lecanemab. Front Aging Neurosci. 2022;14:870517.
54. FDA Grants Accelerated Approval for Alzheimer's Disease Treatment, U. S. Food Drug Administration, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment. Accessed on 25 March 2023.
55. Van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023;388(1):9-21.
56. McDade E, Cummings JL, Dhadda S. Lecanemab in patients with early Alzheimer's disease: detailed results on biomarker, cognitive, and clinical effects from the randomized and open-label extension of the phase 2 proof-of-concept study. Alz Res Therapy. 2022;14:191.

Cite this article as: Khanam FM. Donepezil to lecanemab-advancements in targeted therapy of Alzheimer's disease so far. Int J Adv Med 2023;10:653-9.