Update on the pharmacological management of neurodegenerative diseases: Alzheimer's disease

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Abstract

Neurodegenerative diseases (NDDs) are the most common causes of morbidity and cognitive impairment, particularly among the elderly population worldwide. Due to increasing life expectancy, there has been an increase in the prevalence of NDDs. One of the most common NDDs is Alzheimer's disease (AD), which is characterised by a complex, multifactorial irreversible aetiology, including the progressive loss of neurons. It is also the most common cause of dementia. Pathologically, AD is associated with the presence of amyloid plaques and intracellular neurofibrillary tangles. The management of AD focuses mainly on establishing an early, accurate clinical diagnosis, early drug administration, treatment of comorbidities and dementia-related complications, as well as treatment of behavioural and psychological symptoms. There is currently no cure for AD, and the currently United States Food and Drug Administration (US-FDA) approved drugs only offer symptomatic relief aiming to improve cognitive and behavioural symptoms; however, they do not target the underlying AD pathology or prevent neuronal degeneration. The current US-FDA approved drugs used for the management of AD include acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine), N-methyl-D-aspartate (NMDA) receptor antagonist (memantine), and monoclonal antibody against Aβ (Lecanemab). It should be noted that all these approved drugs only assist in the management of symptoms; however, they do not prevent neuronal loss, brain atrophy, and progressive deterioration of cognition associated with AD. To curb the increasing prevalence of AD, new therapeutic strategies are required, including the development of gene therapy, drugs targeting Aβ, and drugs targeting neuronal hyperexcitability among others.

Keywords: alzheimer's disease, cholinesterase inhibitors, dementia, lecanemab, memantine, neurodegenerative diseases

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Introduction

Neurodegenerative diseases (NDDs) are characterised by a gradual loss of neurons, resulting in progressive dysfunction of synapses, neurons, glial cells, and their networks.[1,2] NDDs are common causes of morbidity and cognitive impairment worldwide, particularly in the elderly population.[3] This is mainly due to the collapse of the structure and function of neural networks and loss of neurons in several areas of the central nervous system (CNS), resulting in the breakdown of the core communicative circuitry, culminating in impaired memory, cognition, behaviour, sensory, and/or motor function.[4] Thus, NDDs are associated with cognitive, psychiatric, and motor deficits due to atrophy of the affected regions.[5] The clinical manifestation of a particular NDD reflects the region of the brain that is involved and the specific population of cells that are affected.[6] Due to increased life expectancy and changing population demographics, NDDs have become more common, and they account for a significant and increasing proportion of morbidity and mortality.[7] NDDs encompass a broad range of neurological diseases, including, among others, Alzheimer's and Parkinson's diseases. However, the most prevalent form of NDD is Alzheimer's disease (AD). Thus, this review will provide an overview of the diagnosis and management of AD.

Alzheimer's disease

AD is defined as an irreversible and incurable progressive NDD characterised by memory impairment and cognitive decline that can affect behaviour, speech, visuospatial orientation, and motor function.[8,9] AD is pathologically defined by extensive neuronal loss and the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in the brain.[10] It is the most common cause of dementia, which accounts for approximately 50–70% of dementia cases.[11,12] Age is regarded as the main risk factor for AD, as its prevalence tends to increase exponentially with age.[8,12] It has been reported that the risk of AD doubles every five years after the age of 65 years, with those over the age of 85 years having a 50% chance of developing AD.[13] Due to an increase in life expectancy, the prevalence of AD has increased.[14] However, ageing alone may not be sufficient to induce AD. It has been reported that AD affects approximately 10% of people over the age of 65 years and 50% of those over the age of 85 years.[8] However, it has also been occasionally reported in individuals over the age of 20 years, mainly due to genetic predisposition.[8]

Pathologically, AD is characterised by neurodegeneration, neuronal loss, and atrophy, particularly in the temporal and parietal lobes of the brain.[13] However, the key pathological hallmarks of AD are the presence of amyloid plaques and neurofibrillary tangles.[13,15,16] The pathogenesis of AD is complex and multifactorial; however,

the most common factors are amyloid plaques and intracellular neurofibrillary tangles, which contain abnormally phosphorylated tau protein aggregated into filaments.[17,18] The amyloid plaques first develop in brain areas associated with cognition and spread to other cortical areas as the disease progresses.[19] AD has been associated with the accumulation of insoluble forms of amyloid-β (Aβ) plaques extracellular spaces and blood vessel walls and aggregation of the microtubule protein, tau in neurofibrillary tangles in neurons.[20]

The second distinguishing feature of AD is the accumulation of neurofibrillary tangles in neurons, which are mostly formed by chemically altered (abnormally folded and phosphorylated) tau protein.[19] In addition, neuropil threads, dystrophic neurites, associated astrogliosis, microglial activation, and cerebral amyloid angiopathy that frequently coexist, have been reported.[21] These pathological processes may induce neurodegeneration with synaptic and neuronal loss, resulting in macroscopic atrophy.[21] The neuronal loss tends to regularly appear in the neocortex, hippocampus, amygdala, and basal nucleus of Meynert thus, impairing the function of these brain regions.[22] This in turn may result in progression from episodic memory loss to a slow global decline of cognitive function, which characterises AD.[23] In addition, these pathological changes in AD are accompanied by decreased acetylcholine concentrations in the basal forebrain, which results in reduced cognitive function, as well as glutamate excitotoxicity, and ultimately in neuronal apoptosis.[18]

Diagnosis of Alzheimer's disease

Early diagnosis plays a crucial role in the management of AD and may be a determinant of the disease outcome. However, clinical diagnosis has been challenging, especially in the early stages of AD due to symptoms being mistakenly associated with the normal consequences of aging.[8] It has been reported that the earliest and most salient aspect of AD is episodic memory impairment, which reflects an inability to effectively encode and store new information.[24] This memory impairment may be associated with the normal ageing consequences. Thus, it is important to confirm AD diagnosis. The diagnosis of AD is based on a comprehensive assessment that includes a thorough medical history, as well as clinical, neurological, biofluid (cerebrospinal fluid (CSF) and blood) testing, and psychiatric examinations.[8,25] Thus, the diagnostic assessment of patients suspected of having AD comprises the following: i) history (family, medical, neurological, and neuropsychiatric) from a reliable source; ii) physical and neurological examination; iii) routine laboratory examinations (complete blood count, sequential multiple analysis-21, thyroid function test, vitamin B_{12}, folate, and rapid plasma regain); optional laboratory examinations (erythrocyte sedimentation rate, human immunodeficiency virus (HIV) serology, serology for Lyme's disease, urinalysis, urine drug screening, lumbar puncture, and electroencephalography); and iv) neuroimaging (computed tomography (CT) or magnetic resonance imaging (MRI) scan).[8,19]

Currently, only a probable diagnosis of AD can be made clinically, with a definite diagnosis only achievable after postmortem through several neuropathological assessments.[15,26] Clinical diagnosis of AD involves a detailed history of the type and course of symptoms from both the patient and another source (partner or family member) to assess whether there is cognitive impairment and whether social, occupational, or other instrumental functions are affected, and also involves neuropsychological assessments such as orientation, memory, and concentration tests.[15] The commonly used diagnostic criteria for AD were initially outlined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) joint task force in 1984.[14] These criteria primarily depend on the exclusion of other dementias; however, relative accuracy is low.[25] It is important to note that not all dementias are caused by AD and can be differentiated by their signs and symptoms.[8] Criteria for probable AD include dementia with cognitive deficits in at least two cognitive domains including progressive memory loss, normal level of consciousness, including, onset between ages 40–90 years, and the absence of another plausible medical explanation.[14,27,28]

Criteria for possible AD include all those listed for probable AD; however, these are often accompanied by another illness that might be contributing to the symptoms but not necessarily the primary cause of dementia and progressive focal cognitive deficit.[14,27,28] Therefore, the inclusion of laboratory analyses such as CSF testing is essential to confirm the diagnosis.[29,30] It has been recommended that the diagnosis should incorporate biomarkers associated with the pathophysiological processes of AD.[27,28] Research suggests that the early stages of AD may induce changes in CSF levels of multiple markers, including Aβ and tau proteins,[30] which are the most established AD fluid biomarkers.[28] It has been reported that the biomarkers of brain Aβ protein deposition are low CSF Aβ and positive positron emission tomography (PET) amyloid imaging, and the biomarkers of downstream neuronal degeneration are elevated CSF tau (total and phosphorylated), decreased fluorodeoxyglucose (FDG) uptake on PET in the temporo-parietal cortex, and disproportionate atrophy on structural MRI.[27,28] The diagnosis of definite AD is regarded as the gold standard and requires neuropathological assessments such as an autopsy or brain tissue biopsy, which can only be conducted by a neuropathologist.[14,25] An autopsy is mainly used to confirm clinical assessment and to assess any comorbidities that may have contributed to cognitive impairment.[31]

AD progresses slowly into three clinical stages, i.e. mild, moderate, and severe; however, these often overlap with the normal ageing process.[8] In the mild stage of AD, patients exhibit short-term memory impairment, often accompanied by symptoms of anxiety and depression, and this stage usually lasts for approximately 2–3 years.[32] The moderate stage of AD is mainly characterised by neuropsychiatric manifestations such as hallucinations, delusions, and reversal of sleep patterns, while the severe stage of AD is mainly characterised by motor signs such as motor rigidity and prominent cognitive decline.[32]

Table I: Approved drugs for the treatment of AD

Class	Drug	Indication	Notes
Acetylcholinesterase inhibitors	Donepezil	Mild to moderate AD.[18,35]	Well tolerated but may have GIT effects. May be combined with Memantine.[18,35]
	Galantamine	Mild to moderate AD.[18]	Well tolerated but, may have GIT effects.[35]
	Rivastigmine	Mild to moderate AD.[18,35]	Well tolerated but, may have GIT effects.[35]
N-methyl-D-aspartate receptor antagonist	Memantine	Moderate to severe AD.[18,35]	Use with caution in patients with renal or liver diseases. May be combined with Donepezil.[18,35]
Monoclonal antibody against Aβ	Lecanemab	Early AD (mild cognitive impairment/ dementia).[45-47]	Elevated levels of Aβ plaques should be confirmed before initiating it.[46,47] Monitor amyloid-related imaging abnormalities (ARIA). May also cause headache.[45]

AD, Alzheimer's disease; Aβ, Beta-amyloid; GIT, Gastrointestinal tract; ARIA, Amyloid-related imaging abnormalities

Pharmacological management of Alzheimer's disease

The management of AD focuses mainly on establishing an early, accurate clinical diagnosis, early drug administration, treatment of comorbidities and dementia-related complications, and treatment of behavioural and psychological symptoms.[33] However, the management of AD has long been challenging as its pathogenesis is complex, making it an area of research interest.[34] As previously mentioned, AD is an irreversible and progressive disease. Thus, there is currently no cure. Both non-pharmacological and pharmacological strategies have been employed in the management of AD; however, this review focuses on the pharmacological strategies. The currently approved treatments for AD are only symptomatic in nature with the aim of improving cognitive and behavioural symptoms; however, they do not target the underlying pathology, nor have they been shown to completely protect neurons.[35-39] Most drug development programs target disease modification with agents that prevent or delay the onset or slow down the progression of AD.[36] Thus, the main objectives of AD management are to relieve cognitive, behavioural, and psychological symptoms; and to slow down progression of the disease.[40] There are currently five individual drugs and one drug combination that have been approved by the United States Food and Drug Administration (US-FDA) for the treatment of AD (Table I).[18] For the treatment of mild to moderate AD, the following acetylcholinesterase inhibitors (ChEIs) have been approved, i.e. donepezil, galantamine, and rivastigmine, while memantine (an N-methyl-D-aspartate (NMDA) receptor antagonist) has been approved for the treatment of moderate to severe AD.[18,35,41]

The rationale for the use of ChEIs is based on the cholinergic hypothesis, which states that cognitive dysfunction and other symptoms of AD may be due to the loss of cholinergic neurons.[35] The ChEIs inhibit the acetylcholine esterase enzyme, which breaks down acetylcholine in the synaptic cleft. In so doing, ChEIs prevent acetylcholine hydrolysis, thus increasing its synaptic levels resulting in enhanced cholinergic transmission.[35] All three US-FDA approved ChEIs are well tolerated by patients; however, the most common adverse events have been linked with the gastrointestinal (GIT) effects such as nausea, vomiting, diarrhoea, and anorexia.[35] The efficacy of these ChEIs are comparable, and their selection is merely based on cost, individual patient tolerance, and physician experience.[42] It has been shown that excessive activation of NMDA receptors by glutamate (main excitatory neurotransmitter in the CNS) increases the vulnerability of CNS neurons to neuronal degeneration.[34,43] Excessive activation of NMDA receptors results in the intracellular accumulation of calcium (Ca^{2+}), which initiates a cascade of events resulting in neuronal death.[44] Memantine is a non-competitive, moderate-affinity, phencyclidine-site, NMDA antagonist that protects neurons from glutamate mediated excitotoxicity without preventing the physiological activation thereof.[34,39,44]

Furthermore, monoclonal antibodies that target Aβ are currently under investigation. Aducanumab (Aduhelm) was the first therapy to demonstrate the reduction of cognitive and functional impairment by removing Aβ from the brain.[45] As a result, it received accelerated approval in 2021, however it has since been discontinued by the manufacturer (Biogen).[45] However, this decision was not prompted by concerns regarding safety or efficacy. Fortunately, recent approval by the US-FDA has paved the way for Lecanemab (Leqembi), a recombinant humanised immunoglobulin gamma 1 (IgG1) anti-amyloid monoclonal antibody that binds to amyloid oligomers, protofibrils and insoluble fibrils, and also targets Aβ in the brain.[45,46] Leqembi has been shown to reduce Aβ and improve cognitive function.[45,46] Thus, it is empirical to first confirm elevated levels of Aβ plaques prior to prescribing Leqembi. However, the only drug combination that has been approved by the US-FDA is donepezil and memantine.[18] All these approved drugs only assist in the management of symptoms; however, they do not prevent neuronal loss, brain atrophy, and progressive deterioration of cognition.[35]

Conclusion

NDDs like AD present ongoing challenges globally. Despite a rising prevalence associated with increased life expectancy, advancements in AD management have been limited. Furthermore, the complex and heterogeneous nature of the disease poses significant hurdles in the management thereof. There is currently no cure for AD, and the currently US-FDA approved drugs are only symptomatic in nature with the aim of improving cognitive and behavioural symptoms, they do not target the underlying

AD pathology. The current US-FDA approved drugs used in the management of AD include ChEIs (donepezil, galantamine, and rivastigmine), NMDA receptor antagonist (memantine), and monoclonal antibody against Aβ (Lecanemab). It should be noted that while these drugs only assist in the management of symptoms, they do not prevent neuronal loss, brain atrophy, and progressive deterioration of cognition associated with AD. Agents targeting the underlying pathology of AD are required, including combination therapy. To curb the increasing prevalence of AD, novel therapeutic strategies are required, including the development of gene therapy, drugs targeting Aβ, and drugs targeting neuronal hyperexcitability, among others. Continued improvements in current therapies may lead to the development of effective agents that enhance cognitive function and protect against neuronal loss to address the unmet needs of AD patients.

Conflict of interest

The authors declare no financial or other competing interests that might have influenced the performance or presentation of this work.

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References

1. Mendez MF, McMurtray AM. Neurodegenerative disorders. In: Fink G, editor. Encyclopedia of Stress (Second Edition). New York: Academic Press. 2007;840-4.
2. https://doi.org/10.1016/B978-012373947-6/00575-4.
3. Kovacs GG. Molecular pathology of neurodegenerative diseases: principles and practice. Journal of Clinical Pathology. 2019;72(11):725-35. https://doi.org/10.1136/jclinpath-2019-205952.
4. Erkkinen MG, Kim MO, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. Cold Spring Harbor Perspectives in Biology. 2018;10(4):a033118. https://doi.org/10.1101/cshperspect.a033118.
5. Wilson DM, Cookson MR, Van Den Bosch L, et al. Hallmarks of neurodegenerative diseases. Cell. 2023;186(4):693-714. https://doi.org/10.1016/j.cell.2022.12.032.
6. Mortada I, Farah R, Nabha S, et al. Immunotherapies for neurodegenerative diseases. Frontiers in Neurology. 2021;12:654739. https://doi.org/10.3389/fneur.2021.654739.
7. Fu H, Hardy J, Duff KE. Selective vulnerability in neurodegenerative diseases. Nature Neuroscience. 2018;21(10):1350-8. https://doi.org/10.1038/s41593-018-0221-2.
8. Skovronsky DM, Lee VM, Trojanowski JQ. Neurodegenerative diseases: new concepts of pathogenesis and their therapeutic implications. Annu Rev Pathol Mech Dis. 2006;1:151-70. https://doi.org/10.1146/annurev.pathol.1.110304.100113.
9. Zvěřová M. Clinical aspects of Alzheimer's disease. Clinical Biochemistry. 2019;72:3-6.
10. https://doi.org/10.1016/j.clinbiochem.2019.04.015.
11. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Molecular Neurodegeneration. 2019;14(1):32. https://doi.org/10.1186/s13024-019-0333-5.
12. Karch CM, Goate AM. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biological Psychiatry. 2015;77(1):43-51. https://doi.org/10.1016/j.biopsych.2014.05.006.
13. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell. 2019;179(2):312-39. https://doi.org/10.1016/j.cell.2019.09.001.
14. Bernardini S, Zima T. Alzheimer's disease: Making the point. Clinical Biochemistry. 2019;72:1-2. https://doi.org/10.1016/j.clinbiochem.2019.05.007.
15. Oboudiyat C, Glazer H, Seifan A, Greer C, Isaacson RS. Alzheimer's disease. Seminars in Neurology. 2013;33(04):313-329. https://doi.org/10.1055/s-0033-1359319.
16. Caselli RJ, Beach TG, Yaari R, Reiman EM. Alzheimer's disease a century later. Journal of Clinical Psychiatry. 2006;67(11):1784. https://doi.org/10.4088/JCP.v67n1118.
17. Ballard C, Gauthier S, Corbett A, et al. Alzheimer's disease. The Lancet. 2011;377(9770):1019-31. https://doi.org/10.1016/S0140-6736(10)61349-9.
18. Trejo-Lopez JA, Yachnis AT, Prokop S. Neuropathology of Alzheimer's disease. Neurotherapeutics. 2023;19(1):173-85. https://doi.org/10.1007/s13311-021-01146-y.
19. Tariot PN, Federoff HJ. Current treatment for Alzheimer's disease and future prospects. Alzheimer Disease & Associated Disorders. 2003;17:S105-13. https://doi.org/10.1097/00002093-200307004-00005.
20. Knorz AL, Quante A. Alzheimer's disease: efficacy of mono-and combination therapy. A systematic review. Journal of Geriatric Psychiatry and Neurology. 2022;35(4):475-86.
21. https://doi.org/10.1177/08919887211044746.
22. Schachter AS, Davis KL. Alzheimer's disease. Dialogues in Clinical Neuroscience. 2000;2(2):91-100. https://doi.org/10.31887/DCNS.2000.2.2/asschachter.
23. Masters CL, Bateman R, Blennow K, et al. Alzheimer's disease. Nature Reviews Disease Primers. 2015;1(1):1-8. https://doi.org/10.1038/nrdp.2015.56.
24. Lane CA, Hardy J, Schott JM. Alzheimer's disease. European Journal of Neurology. 2018;25(1):59-70. https://doi.org/10.1111/ene.13439.
25. Wenk GL. Neuropathologic changes in Alzheimer's disease. Journal of Clinical Psychiatry. 2003;64:7-10.
26. Citron M. Alzheimer's disease: strategies for disease modification. Nature Reviews Drug Discovery. 2010;9(5):387-98. https://doi.org/10.1038/nrd2896.
27. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's disease: past, present, and future. Journal of the International Neuropsychological Society. 2017;23(9-10):818-31. https://doi.org/10.1017/S135561771700100X.
28. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet. 2006;368(9533):387-403. https://doi.org/10.1016/S0140-6736(06)69113-7.
29. Barten DM, Albright CF. Therapeutic strategies for Alzheimer's disease. Molecular Neurobiology. 2008;37:171-86. https://doi.org/10.1007/s12035-008-8031-2.
30. 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(3):263-9. https://doi.org/10.1016/j.jalz.2011.03.005.
31. Apostolova LG. Alzheimer disease. Continuum: Lifelong Learning in Neurology. 2016;22(2):419-34. https://doi.org/10.1212/CON.0000000000000307.
32. Mayo Clinic. Diagnosing Alzheimer's: How Alzheimer's is diagnosed. Mayo Foundation for Medical Education and Research (MFMER). 2024. Available from: https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048075. Accessed April 2024.
33. Alzheimer's Association. Earlier Diagnosis. 2024. Available from: https://www.alz.org/alzheimers-dementia/research_progress/earlier-diagnosis#csf. Accessed April 2024.
34. Vinters HV. Emerging concepts in Alzheimer's disease. Annual Review of Pathology: Mechanisms of Disease. 2015;10:291-319. https://doi.org/10.1146/annurev-pathol-020712-163927.
35. Grossberg GT, Desai AK. Management of Alzheimer's disease. Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2003;58(4):M331-53.
36. https://doi.org/10.1093/gerona/58.4.M331.
37. Desai AK, Grossberg GT. Diagnosis and treatment of Alzheimer's disease. Neurology. 2005;64(12_suppl_3):S34-9. https://doi.org/10.1212/WNL.64.12_suppl_3.S34.
38. Shah RS, Lee HG, Xiongwei Z, et al. Current approaches in the treatment of Alzheimer's disease. Biomedicine & Pharmacotherapy. 2008;62(4):199-207. https://doi.org/10.1016/j.biopha.2008.02.005.
39. Vaz M, Silvestre S. Alzheimer's disease: Recent treatment strategies. European Journal of Pharmacology. 2020;887:173554. https://doi.org/10.1016/j.ejphar.2020.173554.
40. Cummings J. New approaches to symptomatic treatments for Alzheimer's disease. Molecular Neurodegeneration. 2021;16:1-3. https://doi.org/10.1186/s13024-021-00424-9.
41. Corbett A, Smith J, Ballard C. New and emerging treatments for Alzheimer's disease. Expert Review of Neurotherapeutics. 2012;12(5):535-43. https://doi.org/10.1586/ern.12.43.
42. Delagarza VW. Pharmacologic treatment of Alzheimer's disease: an update. American Family Physician. 2003;68(7):1365-73.
43. Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. Therapeutic Advances in Neurological Disorders. 2013;6(1):19-33. https://doi.org/10.1177/1756285612461679.
44. Chu LW. Alzheimer's disease: early diagnosis and treatment. Hong Kong Medical Journal. 2012;18(3):228.
45. Lakhan SE. Alzheimer Disease Treatment & Management. Medscape. 2024. Available from: https://emedicine.medscape.com/article/1134817-treatment?form=fpf#d10. Accessed April 2024.
46. Briggs R, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease. Clinical Medicine. 2016;16(3):247-53. https://doi.org/10.7861/clinmedicine.16-3-247.
47. Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer's disease. Current Neuropharmacology. 2010;8(1):69-80. https://doi.org/10.2174/157015910790909520.
48. Scarpini E. Scheltens P, Feldman H. Treatment of Alzheimer's disease: current status and new perspectives. Lancet Neurol. 2003;2:539-47. https://doi.org/10.1016/S1474-4422(03)00502-7.
49. Alzheimer's Association. Lecanemab Approved for Treatment of Early Alzheimer's Disease. 2024. Available from: https://www.alz.org/alzheimers-dementia/treatments/lecanemab-leqembi. Accessed April 2024.
50. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: appropriate use recommendations. Journal of Prevention of Alzheimer's Disease. 2023;10(3):362-77.
51. https://doi.org/10.14283/jpad.2023.30.
52. Lakhan SE. Lecanemab (Rx). Medscape. 2024. Available from: https://reference.medscape.com/drug/leqembi-lecanemab-4000310. Accessed April 2024.