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PRESCRIPTION

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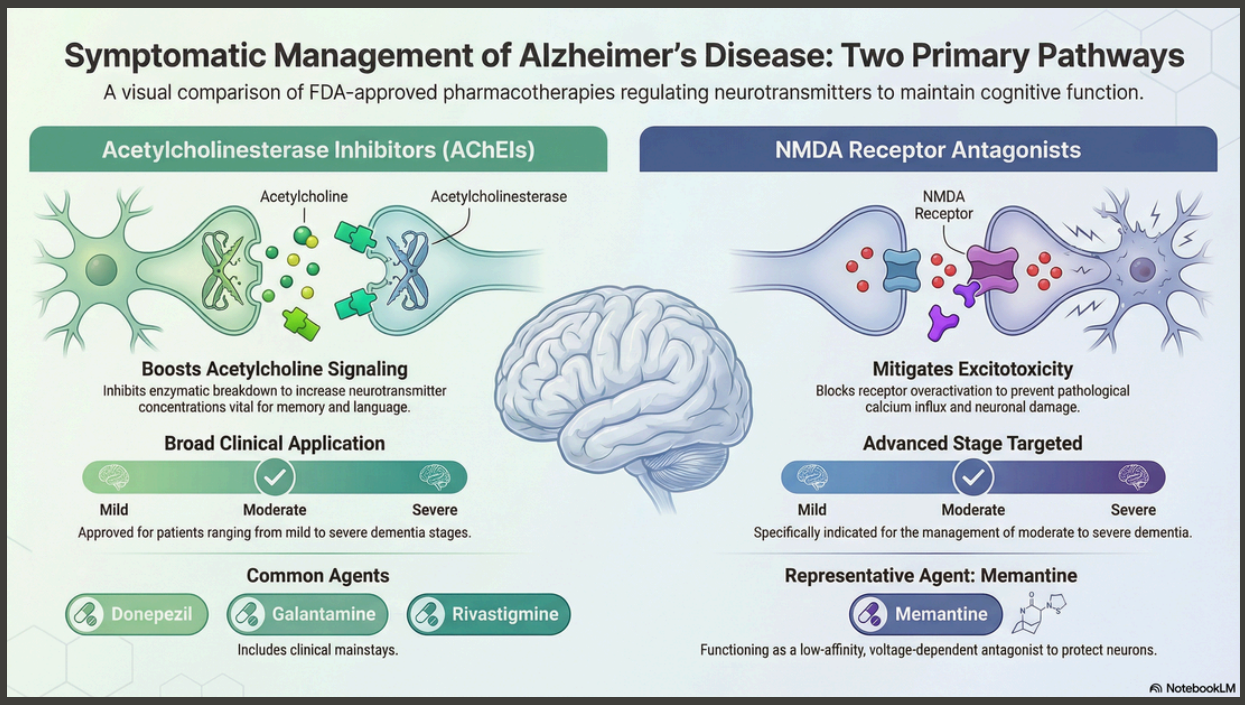
The Evolution of Modern Treatment Strategies in Alzheimer's Disease

By Associate Professor Dr. Gurmeet Kaur Surindar Singh

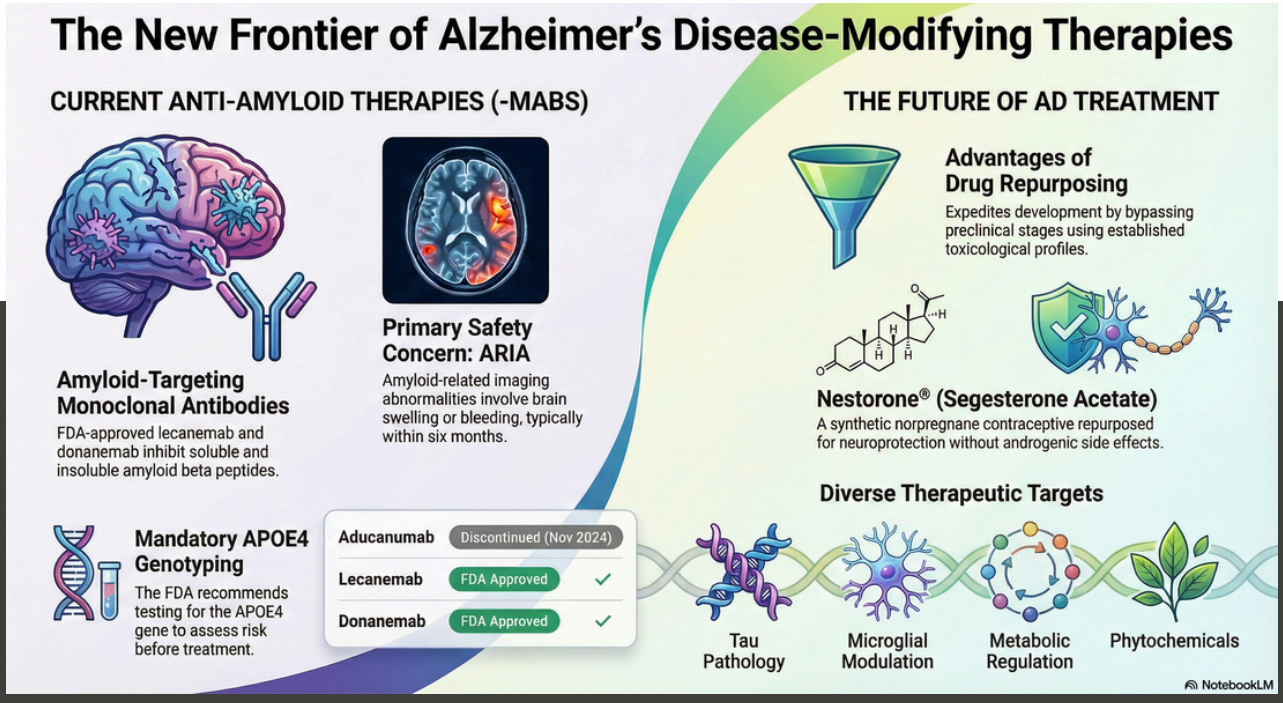
Alzheimer's disease (AD) is a neurodegenerative condition that affects individuals over the age of 65 years though early onset Alzheimer's is reported in people as young as 40 or 50. Despite accounting for roughly 70% of dementia cases, the disease's precise pathogenesis remains poorly understood and continues to elude definitive characterization. Among others, the cause of the disease involves a combination of factors that include the abnormal formation and aggregation of proteins, oxidative stress, neuroinflammation, mitochondrial dysfunction, and disruption in the cholinergic pathway. With the number of cases expected to increase to 139 million by 2050 (1), researchers are deciphering the disease causal factors and pathogenesis in order to lay the foundation for the potential treatment of AD.

In this issue

Preclinical studies play an important role in understanding the disease and offer invaluable insights for translation to human AD. Thus, there is a continuous battle to identify animal models that accurately mirror the multifaceted human AD pathogenesis. Although there is no cure for AD, current interventions can be divided into pharmacological and non-pharmacological approaches that address different aspects of the disease, where the former manage the symptoms and the latter the quality of life.



Therapeutic strategies for AD are categorized into symptomatic and disease-modifying interventions. The symptomatic agents approved by the United States (US) Food and Drug Administration (FDA) during the late 1990s and early 2000s are traditionally classified as acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. AChEIs, such as donepezil, galantamine, and rivastigmine, function by inhibiting the enzymatic breakdown of acetylcholine into choline and acetic acid. This inhibition increases the concentration and signalling duration of acetylcholine, a neurotransmitter fundamental to memory, language, and other higher-order cognitive functions (2). Meanwhile, memantine, a low-affinity, voltage-dependent NMDA receptor antagonist, mitigates glutamate-induced excitotoxicity by blocking the overactivation of the receptor. This mechanism inhibits the pathological influx of calcium ions, thereby preventing neuronal damage (3). AChEIs are currently used for mild to severe dementia, whereas NMDA receptor antagonist is for moderate to severe dementia (4, 5). To date, the FDA has approved only a small selection of drugs for symptomatic management, however they offer vital support for cognitive function. The potential for side effects necessitates careful clinical monitoring; however, these agents provide an essential basis for treatment in the absence of a definitive cure.



Therapeutic approaches that involve disease-modifying therapy for the treatment of AD targeting amyloid plaques are known as anti-amyloid antibodies, namely aducanumab, lecanemab, and donanemab, approved by the FDA for mild dementia or early AD. The "-mab" suffix in the generic name indicates that the drug is a monoclonal antibody. Aducanumab is an IgG1 antibody that targets the amyloid protein, which received accelerated approval by the FDA in 2021 and has been discontinued as an AD treatment in November 2024, leaving only two amyloid-targeting drugs, lecanemab and donanemab, that inhibit aggregated soluble and insoluble forms of amyloid beta peptide. Early findings indicate side effects in certain individuals that lead to swelling and bleeding in the brain, known as amyloid-related imaging abnormalities (ARIA), that are mild to moderate in severity with symptoms including confusion, headache, and dizziness. ARIA is seen in the first 6 months of treatment in patients with two copies of apolipoprotein E (APOE4), a risk factor gene of AD, or those with previous microbleeds or superficial siderosis (6, 7). The FDA currently recommends APOE genotyping before starting these treatments. Immunotherapies are also expensive and may trigger autoimmune responses in the AD brain. Although the risk of ARIA remains a primary safety concern for current anti-amyloid therapies, the approval of drugs like lecanemab and donanemab has revitalized the AD drug pipeline after two decades since the last approvals of AChEIs and NMDA receptor antagonists. This progress has catalyzed the exploration of diverse therapeutic targets beyond the amyloid cascade, including phosphorylated tau pathology, microglial modulation, metabolic regulation, and small-molecule drug repurposing (8). Consequently, researchers are investigating phytochemicals derived from medicinal plants alongside drug repurposing strategies. The latter expedites the development timeline by bypassing specific preclinical stages, as the toxicological profiles of these agents are already established. In our laboratory, we are currently exploring the repurposing of segesterone acetate (Nestorone®; NES), a synthetic norpregnane already FDA-approved as a contraceptive. Due to its high specificity for progesterone receptors and lack of cross-reactivity with androgenic or glucocorticoid receptors, NES represents a potent neuroprotective candidate capable of long-term administration with a favorable safety profile.

Non-pharmacological interventions in patients with AD have gained recognition with growing research highlighting their benefits to quality of life. Quality of life interventions may include cognitive stimulation therapy, physical exercise, and social engagement activities, all of which aim to enhance well-being and maintain independence for as long as possible. By combining these approaches, caregivers and healthcare professionals can provide comprehensive support tailored to the individual needs of those affected by AD. In preclinical research, rodent environmental enrichment (EE) has been used as a translational model for potential therapy in human AD. Based on this model, the principle of the possibility of manipulating environmental factors may influence cognitive health and neuroprotection. Building upon this framework, our laboratory is currently investigating the therapeutic potential of EE both as a standalone intervention and in combination with Persicaria minor. This medicinal plant is of particular interest due to its established neuroprotective properties, attributed to its high concentration of bioactive phytochemicals. By evaluating the synergistic effects of EE and Persicaria minor supplementation, we aim to determine whether this dual-paradigm approach can further attenuate neurodegeneration and enhance cognitive resilience in AD models.

References

1. Dementia statistics: Alzheimer's Disease International; 2021 [Available from: https://www.alzint.org/about/dementia-facts-figures/dementia-statistics/.
2. Knight R, Khondoker M, Magill N, Stewart R, Landau S. A Systematic Review and Meta-Analysis of the Effectiveness of Acetylcholinesterase Inhibitors and Memantine in Treating the Cognitive Symptoms of Dementia. Dementia and Geriatric Cognitive Disorders. 2018;45(3-4):131-51.
3. Agatonovic-Kustrin S, Kettle C, Morton DW. A molecular approach in drug development for Alzheimer's disease. Biomedicine & Pharmacotherapy. 2018;106:553-65.
4. Zuliani G, Zuin M, Romagnoli T, Polastri M, Cervellati C, Brombo G. Acetyl-cholinesterase-inhibitors reconsidered. A narrative review of post-marketing studies on Alzheimer's disease. Aging clinical and experimental research. 2024;36(1):23.
5. McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, et al. Memantine for dementia. Cochrane Database Syst Rev. 2019;3(3):Cd003154.
6. Van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. New England Journal of Medicine. 2023;388(1):9-21.
7. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. Jama. 2023;330(6):512-27.
8. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2024. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2024;10(2):e12465.

QUESTION 01

What is the primary mechanism by which AChEIs alleviate symptoms in patients with AD?

A. Reduction of tau protein phosphorylation.
B. Promotion of amyloid-beta clearance from the brain.
C. Blockade of glutamate receptors to prevent excitotoxic neuronal damage.
D. Inhibition of acetylcholine breakdown, resulting in enhanced cholinergic neurotransmission.

Answer: D. AChEIs increase acetylcholine levels to improve communication between nerve cells.

QUESTION 02

In the clinical management of patients receiving anti-amyloid monoclonal antibodies, why is APOE4 genotyping currently recommended?

A. To identify individuals at a higher risk of developing ARIA.
B. To predict the likelihood of rapid cognitive improvement following anti-amyloid therapy.
C. To guide the frequency and type of neuroimaging required during treatment monitoring.
D. To determine which patients may benefit from adjunctive therapies targeting tau pathology.

Answer: A. APOE4 genotyping is recommended not to determine if a patient is eligible for therapy, but for risk assessment and monitoring strategies.

QUESTION 03

What is the conceptual basis for using environmental enrichment in preclinical models of Alzheimer's therapy?

A. To simulate the effects of physical exercise on cardiac function.
B. To identify patients at risk for ARIA after monoclonal antibody treatment.
C. To investigate the role of dietary supplements in amyloid plaque formation.
D. To potentially modulate neuroprotection and improve cognitive function by modifying environmental factors.

Answer: D. EE serves as a model to show how sensory, cognitive, and social stimuli can biologically influence the brain's resilience against degeneration.

About the author

Dr. Gurmeet Kaur Surindar Singh is an Associate Professor at the Department of Pharmacology and Life Sciences, Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Malaysia. She earned her PhD in Medicine from the University of Sydney, Australia, in 2015. Her current research interests predominantly center on neuroscience, with a specific focus on neurosteroid metabolism in Alzheimer's disease, the use of nutraceuticals and synthetic steroids in dementia treatment, and the application of environmental enrichment strategies in dementia care. Dr. Gurmeet has made significant contributions to the field, publishing in reputable endocrinology and neuroscience journals, authoring book chapters, and securing numerous research grants from the Ministry of Higher Education (MoHE), Malaysia. She currently holds the esteemed position of Editor-in-Chief of the International Journal of Pharmaceuticals, Nutraceuticals, and Cosmetic Science (IJPNaCS), published by Penerbit UiTM. Additionally, she heads the Brain Degeneration and Therapeutics Research Group and contributes her expertise to the university's ethics committee.

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