

From Cholinesterase Inhibitors to Glutamate Receptors to Aducanumab: A Therapeutic Review of Alzheimer's Disease

Eyyel Karthikeyan

Bellarmino College Preparatory, 960 West Hedding Street, San Jose, CA, 95126, USA; eyyel.karthikeyan@gmail.com

Mentor: Polygence and Melvin King

ABSTRACT: Alzheimer's disease, a progressive, debilitating neurodegenerative disease, is the number one cause of dementia in older adults. Even with nearly forty years of research and advancements in AD, this disease remains without a cure. In 2021, the FDA (Food and Drug Administration) approved the use of aducanumab, a monoclonal anti-amyloid beta antibody, to treat symptomatic Alzheimer's disease. This drug targets the amyloid deposit that is thought to be the cause of the disease, unlike other drugs which focus on symptom management. However, this decision by FDA has become controversial. This has triggered a reevaluation of the science behind aducanumab. The inconsistencies between the FDA's stated lab research and the clinical outcome of the drug in practice are too profound. This review provides an essential scientific background for evaluating past and present AD treatments, which primarily targeted neuronal pathologies and novel advancements in targeting non-neuronal cells. This paper dwells on the trajectory of AD therapeutic research moving forward, with a simple understanding of the Amyloid Cascade Hypothesis.

KEYWORDS: Biomedical and Health Sciences, Alzheimer's disease; Aducanumab; Amyloid Cascade Hypothesis; amyloid beta (A β) plaques; Tau protein; cholinesterase inhibitors; glutamate regulator inhibitors; FDA.

■ Introduction

Alzheimer's disease:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that causes irreversible memory loss and other cognitive abilities over time. Alzheimer's disease generally affects the elderly, as patients exhibit the first clinical signs of AD at around 65 years old. Early-onset cases of AD are typically familial or gene-related. In contrast, the causes of late-onset cases, to this day, are unknown.¹ Common symptoms of AD are memory and cognitive deficits and psychotic symptoms. Under cognitive deficits, patients face progressive loss of cognitive abilities and struggle with problem-solving, language, calculation, and visual perception. Psychotic symptoms are a late development in AD; patients experience hallucinations and delusions, episodes of anger, and agitation that make management a challenge. AD affects approximately 6.2 million Americans and one-eighth of the population older than 65 years. Annual formal care for AD could cost a patient up to 27 thousand dollars.

Pathophysiological theories (Pt. 1) – Amyloid Cascade Hypothesis:

Alzheimer's disease can be characterized by two distinct abnormalities: the presence of amyloid plaques and the accumulation of neurofibrillary tangles, which lead to brain atrophy and neuronal loss. The amyloid cascade hypothesis postulates that neurodegeneration in AD is directly influenced by the abnormal accumulation or increase of amyloid beta (A β) plaques in various areas/regions of the human brain.²

The gyri (the ridges in the brain) are narrowed, the sulci (the grooves in the brain) are widened, the ventricles (the cavity containing CSF) enlarge in size, and ultimately, the brain

weight is reduced. AD patients' brains contain extracellular plaques of dense material called amyloids, which contain the neurotoxic peptide Amyloid β .³ Upon further study, scientists have figured out that the APP gene (amyloid precursor protein, a large molecule) is responsible for producing A β proteins in AD. Through proteolytic cleavage by α , β , and γ secretases, APP is cut into pieces, which generates smaller extracellular fragments (beta Amyloid-38, beta Amyloid-40, and beta Amyloid-42). These extracellular fragments precipitate into the interstitial fluids, A β 40 and A β 42, and bind to various proteins and neurotransmitter receptors, which causes an interference in the synaptic function. The elderly produce more neurotoxic protein A β 42 than A β 40.⁴ Therefore, APP instigates AD because, as stated above, APP, when broken down by α , β , and γ secretases through proteolytic cleavage, produces A β peptides which increase damage to neurons and neurotransmitters. Genetic mutations associated with early onset AD modify the secretase gamma function and increase the production of amyloid beta.

Pathophysiological theories (Pt. 2) – Tau pathology:

Tau protein, a microtubule-associated protein, helps with the structural stability of microtubules. Misfolding of tau protein causes neurofibrillary tangles and is also thought to be responsible for the cause of AD.⁵ At first, scientists questioned whether tau proteins impacted AD. Firstly, no tau gene mutations were found in any form of familial AD. Secondly, filamentous deposits of hyperphosphorylated tau correlated with other forms of dementia, such as Parkinson's Disease, but not so much with AD.

Along with Amyloid β , tau protein aggregates arranged as sheets in the brain cause the axons and the dendrites to swell.

An accumulation of both neurofibrillary and intercellular tangles causes cytoskeletal abnormalities in the entorhinal area, hippocampus, neocortex, and nucleus basalis, resulting in problems with declarative memory (memory associated with names, dates, and facts) as an initial symptom of AD.

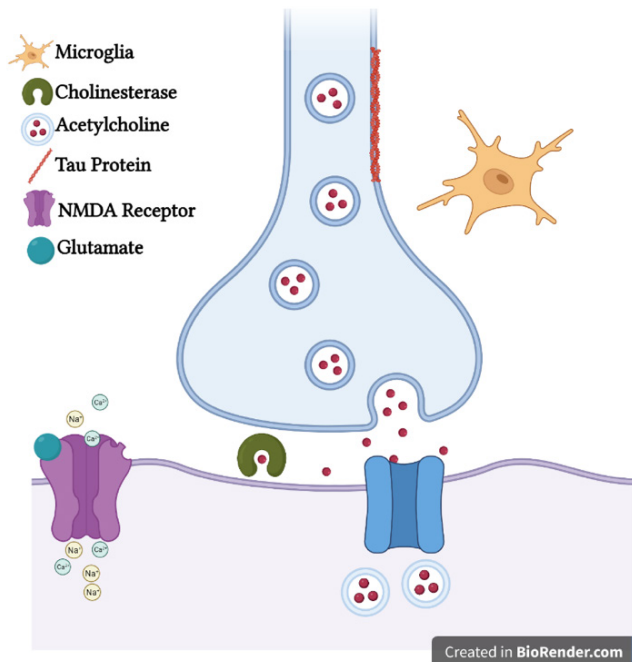


Figure 1: Normal Neuronal Synapse.

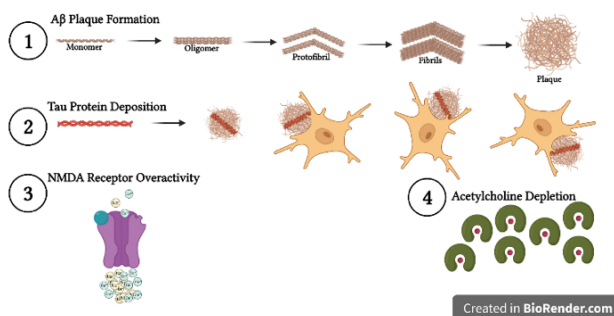


Figure 2: Pathophysiology of Alzheimer's Disease.

History of Traditional (Neuronal) Treatments:

During the past few years, testing, technology, and protocol advancements have made it easier to spot AD. First, protocols such as physical, neurological, or neuropsychological examinations have become more sophisticated and standardized. Second, through magnetic resonance imaging (MRI) of the brain, scientists can identify, diagnose, and rule out other possible causes of dementia. Third, as stated previously, amyloid plaques, a prime AD cause, can now be visualized by positron emission tomography (PET). Even with such positive news, scientists still have found no cure for AD. Earlier treatment focus was centralized around symptom management by regulating neurotransmitters.

Pharmacological management (Pt. 1) – Cholinesterase Inhibitors:

FDA approved the first of three cholinesterase inhibitors primarily for mild to moderate AD dementia in 1997. AD

patients have reduced levels of acetylcholine because of low levels of choline acetyltransferase, the enzyme that helps with its production in the brain. Another enzyme, cholinesterase, breaks down acetylcholine. Because AD patients have limited amounts of acetylcholine, patients are treated with cholinesterase inhibitors to block the breakdown of acetylcholine. The cholinergic hypothesis links cholinesterase inhibitors as a potential cure for AD. Acetylcholinesterase activity primarily observed in post and antemortem studies suggest that cholinergic abnormalities contribute to AD. Acetylcholine is associated with memory. Acetylcholine receptors are situated on neurons. A loss of acetylcholine receptors can increase the likelihood of AD.

The effect of cholinesterase inhibitors results in improved cognition, neuropsychiatric symptoms, and activities of daily living of patients with mild to moderate dementia. A clinical trial in London conducted in 2005, comparing the effect of cholinesterase inhibitors versus a placebo on a sample size of 3000 patients, proved the success of the drug. The 70-point Alzheimer's disease Assessment Scale and the Cognitive Subscale demonstrated the drug's potency. However, other evidence declares that 30 to 50 percent of patients with AD showed no observable benefit, and only 20 percent faced positive outcomes. Therefore, cholinesterase inhibitors' viability is questioned as they may work only for certain AD patients with specific backgrounds and symptoms. Nevertheless, despite its ineffectiveness, cholinesterase inhibitors have scored higher than any form of placebo in testing and have shown improvement for some.⁶

Pharmacological management (Pt. 2) – Glutamate Regulator Inhibitors:

FDA approved glutamate regulator inhibitors for moderate to severe AD in 2003. Glutamate is an excitatory amino acid that acts on NMDA (N-methyl-D-aspartate) receptor in cortical and hippocampal neurons. This helps with learning and memory. However, excessive NMDA stimulation causes excitotoxicity. Hence, NMDA receptor antagonists are given because of their neuroprotective capabilities. Glutamate production then influences amyloid β production, which is believed to be connected to AD according to the amyloid cascade hypothesis.⁷

Mini-Mental State Examination (MMSE) and CDR determine the severity of dementia. Cholinesterase inhibitors are typically used in AD patients expressing mild to moderate dementia. Glutamate receptor inhibitors have been shown to improve cognition in dementia patients. Similarly, with AD, glutamate receptor inhibitors had positive effects in a 24-week trial among 322 patients.⁸ Furthermore, scientists have analyzed that combining glutamate receptor and cholinesterase inhibitors leads to the best improvements and most effective results in symptom management. However, this combination still does not impact the pathogenesis and progression of the disease itself; hence scientists have focused on other methods to study.

Pharmacological management (Pt. 3) – Aducanumab:

Recent attention has been given to the Amyloid Cascade Hypothesis by looking for treatment options for decreasing

A β levels. For example, one theory is to develop drugs that inhibit or remove secretase formation. As stated earlier, β and γ secretases cleave APP, which produces A β and ultimately causes AD. On the other hand, A secretase prevents A β accumulation, unlike its counterparts β and γ . Therefore conversely, researchers seek ways to increase α -secretase levels/activity in patients with AD. Another approach to decreasing A β is through immunological methods. Researchers have found that A β immunotherapy in mice appears to reduce A β levels. Aducanumab is a form of immunotherapy approved by the FDA.

Aducanumab is a monoclonal antibody. Monoclonal antibodies can be manufactured by cloning individual antibody-producing white blood cells. Specific monoclonal antibodies are artificial proteins that target other natural proteins to support the body's immune system. For example, Aducanumab, a monoclonal antibody, targets and eradicates amyloid beta natural proteins.¹⁰ Amyloid beta in the brain comes in one of several "types" or "variations." For example, DEA is a soluble chemical reagent used to isolate soluble amyloid beta (soluble amyloid oligomers); Guanidine is a chemical reagent used to isolate insoluble amyloid beta (amyloid plaques). Aducanumab bound more quickly to the A β plaques in the parenchymal region than in the vascular region. Approaching this drug from a scientific perspective, researchers have identified two possible theories to prove aducanumab's efficacy in reducing plaques. First, when aducanumab binds to amyloid beta, it blocks the activation of receptors on the plaques, protecting the body from the negative impact of membrane depolarization. Secondly, Amyloid beta causes calcium dyshomeostasis in neurons and microglia by binding to metabotropic receptors. Therefore, aducanumab can recruit microglia.

Previously tried medications that targeted amyloid beta in humans were unsuccessful because they could not penetrate the blood-brain barrier. Researchers use PET scanning to image amyloid plaques in people treated with aducanumab or a placebo for around 54 weeks.¹¹ Based on positive clinical results in the lab, the FDA approved aducanumab in 2021 as it had unforeseen success in reducing A β plaques in the human brain, seen through SUVR (Standardized Uptake Value Ratio). However, its success in the chemical lab did not guarantee success in clinical trials. For example, there is currently uncertainty of clinical benefit for patients with AD who took aducanumab. When aducanumab was tested in the lab, scientists observed that it successfully removed A β but did not ensure AD reversal. The damage done by the increase in A β might be irreversible, and aducanumab could be ineffective in decreasing A β levels; it is also incapable of removing the symptoms of AD itself. Aducanumab also has harmful side effects. Over one-third of the patients have ARIA (Amyloid-related imaging abnormalities). ARIA-E is edema and brain swelling; ARIA-H is hemorrhage and bleeding in the brain. Patients with ARIA, shown in MRI, can still express no symptoms. This provides a fundamental reason to perform MRIs before and after treatment. Further, patients with one APOE4 gene allele are at increased risk for Alzheimer's dis-

ease, whereas those with two alleles have an even higher risk. Patients with the APOE4 gene allele also have a higher risk of having ARIA. Therefore, prior to treatment, genotyping should be considered to determine whether the patient carries the gene, and if so, genetic counseling may be recommended.¹² The other two common adverse effects are Headache and UTI (urinary tract infection).¹³ Scientists are unsure of the risks of treatment with aducanumab and suggest that testing such as MRIs should be taken to ensure patient safety.

There are numerous ethical dilemmas with aducanumab. For one, aducanumab was not treated to marginalized populations, reinforcing this idea of systemic racism in scientific studies. In addition to limiting participants, aducanumab treatment is expensive, totaling 50,000 dollars.¹⁴ In addition to the cost of treatment, patients must spend money on MRI scans and infusions, negatively impacting Medicare premiums.¹⁵ Therefore, aducanumab is not only unsuccessful in clinical trials but is also unethical and costly.

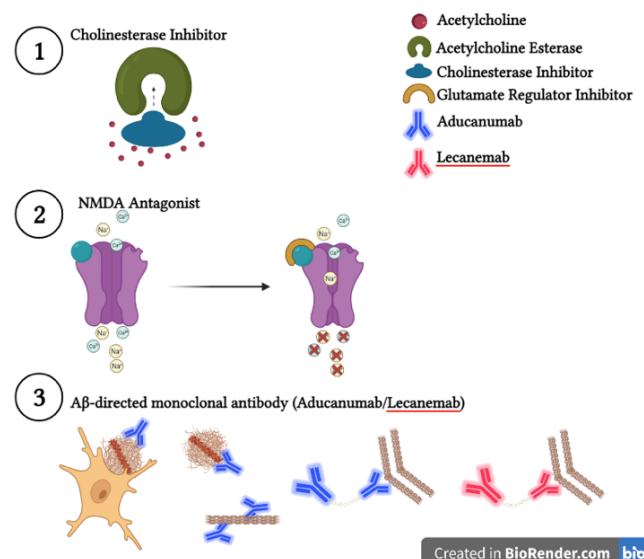


Figure 3: Pharmacological management for Alzheimer's Disease

■ Discussion

FDA Approval: EMERGE and ENGAGE Trials:

Both trials, EMERGE and ENGAGE, were stopped early after a planned futility analysis. EMERGE trial had a positive outcome, but ENGAGE did not. Following the termination of both trials, additional data was collected, and *Post Hoc* analysis was done. Both clinical trials observed a substantial reduction in brain amyloid levels as assessed by amyloid PET imaging; however, there were no clinical benefits for patients, regardless of a reduction in brain amyloid levels. EMERGE had a smaller clinical decline (22 percent relative reduction and a 0.39 absolute reduction for the CDR Sum of Boxes score). For high-dose aducanumab, Biogen, the biotechnological company that conducted the study EMERGE and ENGAGE, accounted for the difference between the outcomes of the two trials because of a difference in the duration of high-dose aducanumab received.¹⁶ Also, AD phenotypes may have heterogenous expression contributing to the difference between the outcomes of the two

trials.¹⁷ A tiny fraction of patients had antibodies against aducanumab that may stop it from working.¹⁸

Recent/Current Therapies: Lecanemab, Aducanumab's Successor:

In January 2023, Lecanemab, a second-line monoclonal antibody, received accelerated approval from FDA. Unlike Aducanumab, which binds more to fibrils, Lecanemab binds tenfold more to toxic protofibrils. A randomized, double-blind, phase 2b experiment was conducted with Lecanemab with a 10-mg/kg biweekly schedule. Like Aducanumab, this also had a similar effect in reducing amyloid beta.¹⁹

Also, like aducanumab pretreatment, CSF or PET scans are needed to confirm the presence of amyloid protein deposition in the brain. At 18 months, CDR-SB was -0.45 lower in patients who received Lecanemab than in patients who received a placebo (95% CI -0.67 to -0.23, $P < 0.001$). The plasma biomarker amyloid beta 42/40 ratio, p-tau181, was significantly lower. One-fourth of the patients had infusion reactions like fever, chills, and changes in blood pressure. Headaches were the other common adverse effect. Lecanemab also causes ARIA-E and ARIA-H. For example, twenty patients without APOE4 genes benefited more in a test. However, Lecanemab treatment costs at least twenty-five thousand dollars annually. Yet, compared to aducanumab, the side effects are fewer. Lecanemab's difference in the binding site, which is more on toxic protofibrils, may contribute to better adverse effects than aducanumab. This study did not test if there is any clinically meaningful benefit. A phase III study is still at work right now.²¹

Future (Non-Neuronal) Therapies: Microglia:

Scientists studying microglia pathology propose that the amyloid cascade hypothesis is only partially responsible for the initiation of AD. This prevalent theory states that an increase in amyloid- β deposition leads to the formation of AD. However, the amyloid cascade hypothesis is insufficient to explain the full aspect of AD, as AD is a prevalent disease with different etiologies. Therefore, researchers have investigated the effect of neuroinflammation on the trajectory of AD. Under neuroinflammation, scientists observe microglial activation as a potential treatment for AD. In the early stages, microglia phagocytose clears A β aggregates. Microglia form a protective barrier around amyloid deposits. In the later stage, too much accumulation of A β leads to the formation of dense core plaques and shields them from neurons. After toxic A β accumulation, tau pathology causes neurons to become damaged and stressed. Tau pathology also leads to an inflammatory state of microglia that further secretes cytokines. Cytokines activate astrocytes that further damage the synapse. This damaged synapse, a negative outcome, is commonly seen in the later stage in AD patients.

Microglial cells are the innate immune cells of the central nervous system. In the central nervous system, microglia are resident phagocytes that maintain homeostasis, such as injury response and pathogen defense. Studying the physiology of microglial cells, researchers noticed that microglia often clean up dying cells' debris to promote a healthy brain environment.

Likewise, in the presence of pathogens or plaques, microglia produce cytokines to recruit more immune cells. This mechanism is called immune surveillance. Microglia's cytokines maintain homeostasis between pro/anti-inflammatory states. In AD, patients have dysregulated crosstalk (communication), tilting the balance towards inflammation.

Further, microglia are responsible for synaptic pruning, removing unwanted or unused synapses or connections between neurons. Microglia and neurons communicate with each other. The regulatory mechanisms include direct contact with neighboring neurons by immune checkpoint signals. CX-3CL1-CX3CR1 and CD200-CD200R1 pathways are the main inhibitory pathways leading to microglia inactivation. In AD, there is a deficiency in CD200, CD200R, and CX3CR1, leading to the absence of constraints for microglial behavior.²²

TREM2 (Triggering Receptor Expression on Myeloid cells 2) and TYROBP (TYRO protein tyrosine kinase-binding protein) are receptors on microglia that enable phagocytosis of viable neurons, a process termed phagoptosis. TREM2 and TYROBP are considered genetic risk factors for AD. Microglia signals a TREM2-TYROBP pathway that interacts with A β and tau. Scientists have found this pathway in *Drosophila* (fruit fly).²³ In the case of A β , microglia suppress neurodegeneration through TREM pathways; in the case of tau, microglia speed up neurodegeneration through TREM pathways. In a 2017 study in mice, increasing TREM led to increased amyloid plaques.²⁴

The human brain has billions of neurons and a microtubule scaffolding system. Tau protein is a microtubule-binding protein. In Alzheimer's disease, abnormal tau protein causes intracellular neuron damage. Antibodies can modify disease progression when they block the spread of tau pathology. Antibodies can target tau both internally and externally. Scientists have also tried to target tau in AD through immunotherapy, targeting tau protein. Similarly, aducanumab is a monoclonal antibody that targets the amyloid beta in AD rather than the tau protein. Tau is produced by non-neuronal cells, which include glia, ependymal and epithelial cells, and pericytes. On the contrary, amyloid beta is produced by neuronal cells. TREM2 is a genetic risk factor associated with non-neuronal cells that expedite neurodegeneration, as seen in Alzheimer's disease. APOE (Apolipoprotein E) is expressed primarily by microglial cells. The APOE gene mutation is the leading cause of late-onset AD. Having at least one APOE e4 gene increases your risk of AD two to threefold, and two APOE e4 genes by eight to twelvefold.²⁵ This mutation causes lipid accumulation in microglial cells and affects their function. Currently, only therapeutic strategies are pursued as a viable treatment for AD by targeting APOE.²⁶ TREM2 is a microglia receptor that recognizes, internalizes, and clears amyloid beta. The goal of targeting TREM2 is to clear the amyloid beta plaques to cure AD, claimed by the Amyloid Cascade Hypothesis. This identifies the similarity between the TREM2 receptor of microglia and aducanumab, which both remove plaques. One model of how non-neuronal factors contribute to AD can be seen through a mouse model. For example, the results of a mouse model suggested that TREM2 therapies that target amyloid

beta are quite effective in reducing AD pathology. Further, neuronal mitochondrial dysfunction has led to cases of sporadic Alzheimer's disease rather than cases of genetic variation. Targeting these neuronal mitochondria is another potential treatment option. This is also because TREM2 represents how non-neuronal factors can contribute to AD reduction. Future research should target tau protein and APOE by decreasing plaque accumulation, using knowledge of how non-neuronal and neuronal factors contribute to AD.

■ Conclusion

Alzheimer's disease is a neurodegenerative disorder causing cognitive impairment in the elderly. Traditional treatment options help with symptom management, not altering the underlying pathology. For instance, cholinesterase inhibitors are used for mild to moderate AD symptoms. In addition, glutamate regulators are used for moderate to severe AD symptoms. Recently, aducanumab was given expedited approval by FDA when it helped reduce plaques. However, aducanumab has not been clinically shown to impact the symptoms of AD significantly. Aducanumab also comes with side effects requiring monitoring. The FDA's approval of aducanumab has stirred much controversy. In the future, microglia therapies will be studied. Because microglial cells are the innate immune cells of the central nervous system, future treatments revolve around targeting microglial-mediated APOE, TREM2 pathway, and immune checkpoint signaling.

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■ Author

Eyyel Karthikeyan is a high school junior at Bellarmine College Preparatory. He has always had a passion for the field of Neuroscience. As the president of the Neuroscience Club at Bellarmine, he is passionate about teaching Neuroscience topics to avid students. In the future, he plans to combine his love for neuroscience and his interests in medicine to pursue a career as a neurosurgeon.