# *Failures in AD Clinical Trails: How will they change the future*

Aleeza Dhillon

*Abstract*

This paper investigates the reasons why clinical trials for treatments of Alzheimer's disease (AD) have failed and makes recommendations for improvement. The intricate AD pathophysiology, poor patient selection, inadequate dosage, and inappropriate trial design are a few of the factors contributing to clinical trials' low success rates. The research examines the use of imaging biomarkers, Aβ, and tau proteins, and other biomarkers in patient selection and diagnosis. It also talks about the ε4 allele and APP gene mutations as genetic risk factors for AD. The article highlights the requirement for a greater understanding of the underlying mechanisms causing AD and the creation of specialized treatment procedures that address various parts of the illness.

*Introduction*

Alzheimer's disease (AD) is a progressive neurological condition marked by memory loss and cognitive deterioration. Biological indicators for AD include accumulating amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) in the brain (DeTure, 2019). Despite substantial studies, clinical studies for potential AD therapies have routinely failed in recent years. We'll examine the factors that led to AD clinical trial failures and suggest potential improvements.

Multiple factors contribute to trial failures, including the complicated nature of AD pathogenesis, poor patient selection, insufficient dosage, and ineffective trial design (Yiannopoulou, 2019). The majority of current therapeutic trials use single-target strategies that do not address the complex pathology of AD. Therefore, clinical trials have had a low success rate (Cummings, 2020). An in-depth knowledge of AD pathogenesis and its heterogeneity is needed to improve the success of AD trials. This includes the discovery of biomarkers to improve patient selection, the creation of individualized therapy plans, and the addition of several therapeutic targets.

*Identifying AD*

Biomarkers have recently come to light as crucial tools for the identification and diagnosis of AD. The measurement of Aβ in the cerebrospinal fluid (CSF) is one of the most well-established biomarkers for AD (Nojima, 2022). According to studies, people with AD had reduced amounts of Aβ in their CSF. Additionally, it has been demonstrated that the ratio of Aβ42 to Aβ40 in the CSF is a good indicator of AD, with lower ratios indicating a higher chance of contracting the condition (Hansson, 2019). A*β* is an aggregation-prone and toxic polypeptide; the difference between Aβ42 and Aβ40 being two amino acid residues (Qiu, 2015). Another protein that is used as a biomarker would be tau, a protein found mainly in neurons, and is responsible for many healthy functions within the brain cells (Ellison, 2022). Measuring the amount of tau protein in the CSF is a crucial diagnostic for AD. A crucial part of the stability of microtubules in neurons is played by the protein tau. NFTs develop in the brain as a result of

hyperphosphorylation of tau protein in AD. According to studies, people with AD had greater tau levels in their CSF, which may be a result of the buildup of NFTs in their brains (Fagan, 2010). Imaging biomarkers for AD have also been developed as a result of recent developments in neuroimaging. Amyloid PET imaging is one such biomarker, which makes use of radiotracers to show the buildup of Aβ plaques in the brain. Amyloid PET imaging can identify Aβ accumulation in AD patients and distinguish AD from other types of dementia (Suppiah, 2019). Structural MRI is another imaging biomarker for AD and can recognize changes in brain size in areas where AD disease is present.

The likelihood of AD can be influenced by hereditary factors. The ε4 allele is one of the most well-known genetic risk factors for Alzheimer's disease. An important indicator of AD is the accumulation of beta amyloid protein in the brain, which is caused by the ε4 allele function in the transport and metabolism of lipids. A person is more likely to develop AD if they have one or two copies of the ε4 allele (Raulin, 2022). Another gene connected to Alzheimer's disease is the amyloid precursor protein (APP) gene, which codes for a protein implicated in the formation of beta-amyloid plaques (Chen, 2017). Mutations in the APP gene are responsible for both the overproduction of beta-amyloid protein and early-onset Alzheimer's disease.

*History of Clinical Trials*

Clinical trials have been overwhelmed by a high rate of failure, despite attempts to create effective treatments for AD. This highlights the complexity of the disease and the demand for a deeper comprehension of its underlying mechanisms. As a result, focusing on a single element of AD pathology might not be enough to have a significant therapeutic impact.

Another biological aspect that contributes to the failure of AD clinical trials is poor patient selection. While the degenerative changes in the brain may have already taken place decades before the onset of clinical symptoms, patients with mild to moderate AD disease were frequently enrolled in past clinical trials for the condition (Wenk, 2003). It is more difficult to appropriately assess the effectiveness of possible treatments in patients with late illness stages since they frequently have higher cognitive impairment. Determining the precise benefits of the trial is difficult since patients with numerous health disorders could not respond to treatment in the same manner as people without these conditions (Fogel, 2018). Additionally, it is difficult to design treatments that are efficient for all individuals due to the variability of AD, which has a variety of subtypes and underlying causes. Research demonstrates that those who have preclinical AD biomarkers are more likely to develop AD (Cummings, 2020). In order to stop or delay the advancement of the disease, it may be more effective to treat individuals when they are at an earlier stage of the condition.

Inadequate dosage of supposed therapies is another biological aspect that has contributed to the failure of clinical studies for AD. Numerous prior AD clinical trials employed doses that may not have been adequate to produce therapeutic results, according to studies. An anti- Aβ antibody clinical trial, for instance, used doses that were lower than those necessary to produce efficient Aβ clearance in preclinical models (Lemere, 2010).

In addition, given the complexity of AD pathophysiology, current trial designs might not be ideal. Traditional randomized controlled trial designs, which were frequently employed in earlier AD clinical studies, might not be the most effective way to assess AD therapies. For instance, RCTs frequently have predetermined study lengths that might not be sufficient to assess the long-term effects of AD therapies. Furthermore, RCTs frequently rely on goals related to

cognition and functionality, which cannot fully reflect the molecular changes causing AD (DeTure, 2019).

*Expedition 3: A Failure*

The Expedition 3 experiment, a phase III clinical trial of solanezumab, a monoclonal antibody that targets brain amyloid plaques, is one instance of a particular AD clinical trial that has failed in recent years (Doody, 2014). The Alzheimer's Disease Assessment ScaleCognitive Subscale (ADAS-Cog) score change from baseline at 80 weeks was the trial's primary outcome, which included 2,129 patients with moderate AD dementia (Doody, 2014). The ADAS-Cog score difference between the solanezumab and placebo groups was not statistically significant (p=0.095), so the experiment did not achieve its primary aim. The Expedition 3 trial may have failed for a number of reasons (Doody, 2014). Solanezumab's failure to effectively target brain-amyloid plaques is one possibility that could apply, given that the treatment's impact size was less distinct than anticipated. Another reason is that the experiment may have been underpowered, ,meaning the sample size was not big enough to successfully determine the effectives of the drug. Additionally, because patients with moderate AD dementia may have had less severe -amyloid pathology than those with more advanced stages of the illness, the inclusion of these patients may have lessened the impact of the treatment. The Expedition 3 trial's findings are in line with other recent clinical trials of -amyloid-targeted treatments, which have likewise been unable to show any discernible cognitive advantages in patients with AD dementia
(Honig, 2018).

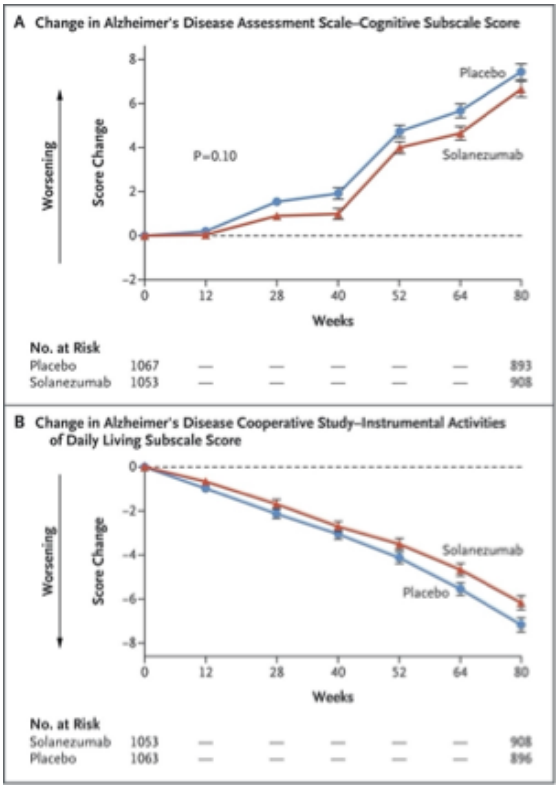


Figure 1. Panel A displays the findings of the main outcome, which is the average change from baseline (represented by a dashed line) in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale. Higher scores indicating more significant cognitive impairment Meanwhile, Panel B shows the outcomes of the secondary functional outcome of the average change from baseline (represented by a dashed line) in the instrumental subscale of the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory. Lower scores indicate greater functional loss. There was no notable discrepancy observed between the groups at week 80 regarding the alteration in their score compared to their baseline (Honig, 2018).

*Future Implications*

Future clinical studies of -amyloid-targeted treatments, like the Expedition 3 study, could be enhanced in a number of ways. In order to ensure that the patient group has a more uniform amount of -amyloid pathology, the inclusion criteria could first be improved (Srivastava, 2021). Since these individuals may have had less severe -amyloid pathology than patients with more advanced stages of the disease, adding patients with moderate AD dementia in Expedition 3 may have lessened the treatment's impact. Future studies might select patients with higher levels of amyloid pathology using biomarkers, which can improve the chance of therapeutic benefit.

Second, the trial's duration could be lengthened for patient follow-up over a longer period of time. The experiment in Expedition 3 lasted 80 weeks, which might not have been long enough to notice a therapeutic impact (Cummings, 2020). Longer treatment periods may be considered in subsequent trials in order to delay or stop the disease's progression.

Thirdly, it may be possible to investigate combination therapy that takes aim at various pathways involved in the etiology of AD. Medicines that target other components of the disease, like neuroinflammation or tau pathology, may be more effective when combined with medicines that target -amyloid. Overall, the Expedition 3 trial's failure serves as a reminder of the difficulties in creating AD treatments and the pressing need for more investigation into the disease's fundamental causes. Future studies might examine the use of combination medicines to boost healing effectiveness.

*Aducanumab: The Future*

Aducanumab, another monoclonal antibody that targets -amyloid plaques, was being tested in the ENGAGE and EMERGE trials (Cambridge, 2019). It has been approved by the Food and Drug Administration (FDA) as acceptable treatment for AD. The medication specifically targets beta-amyloid protein, which is thought to cause plaques in the brain and contribute to the onset of Alzheimer's disease (Beshir, 2022). In clinical studies, the anti-beta-amyloid drug aducanumab was found to halt cognitive loss in people with early-stage Alzheimer's disease. It has been demonstrated to decrease the brain's beta-amyloid levels (Beshir, 2022).

| | Study 302 Final Data | | |
|---|---|---|---|
| | Week 78 Placebo decline (N=548) | Week 78 Difference vs. placebo (%) p-value | |
| | | Low Dose (N=543) | High Dose (N=547) |
| **CDR-SB** | n=288<br>1.74 | n=290<br>**-0.26 (-15%)**<br>0.0901 | n=299<br>**-0.39 (-22%)**<br>0.0120 |
| **MMSE** | n=288<br>-3.3 | n=293<br>**-0.1 (3%)**<br>0.7578 | n=299<br>**0.6 (-18%)**<br>0.0493 |
| **ADAS-Cog 13** | n=287<br>5.162 | n=289<br>**-0.701 (-14%)**<br>0.1962 | n=293<br>**-1.400 (-27%)**<br>0.0097 |
| **ADCS-ADL-MCI** | n=283<br>-4.3 | n=286<br>**0.7 (-16%)**<br>0.1515 | n=295<br>**1.7 (-40%)**<br>0.0006 |

Table 1. Met the primary and secondary objectives. Positive result on tertiary endpoint- 87% less decline v. Placebo. Low does for primary endpoint and two secondary endpoints display numerically favorable results (FDA, 2019).

However, due to inconsistent findings from clinical trials, Aducanumab's effectiveness has been a subject of discussion, and further study is required to properly comprehend its long-term consequences and advantages (Vaz, 2022). In addition to being costly and requiring monthly infusions, the medication might be extremely burdensome for both patients and the healthcare system. Therefore, it is important that researchers continue to change clinical trials designs in order to find more effective treatments regarding AD. In the future, clinical trials should reflect the effective strategies observed in previous trials, but change those aspects that have been proven to lead to a growing failure rate.

Bibliography

"Aducanumab (marketed as Aduhelm) Information." *FDA*, 2021, www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information.

Beshir, Semira Abdi. "Aducanumab Therapy to Treat Alzheimer's Disease: A Narrative Review." *International Journal of Alzheimer's Disease*, 2022, https://doi.org/10.1155/2022/9343514. Accessed 23 Apr. 2023.

Cambridge. "Biogen and Eisai to Discontinue Phase 3 ENGAGE and EMERGE Trials of Aducanumab in Alzheimer's Disease." *Eisai*, 2019, www.eisai.com/news/2019/news201917.html. Accessed 23 Apr. 2023.

Chen, Guo-fang. "Amyloid Beta: Structure, Biology and Structure-Based Therapeutic Development." *APS*, 2017, www.nature.com/articles/aps201728. Accessed 23 Apr. 2023.

Cummings, Jeffrey. "Alzheimer's Disease Drug Development Pipeline: 2020." *Wiley Online Library*, 11 July 2020, pp. 1-29, www.ncbi.nlm.nih.gov/pmc/articles/PMC7364858/pdf/TRC2-6-e12050.pdf. Accessed 23 Apr. 2023.

DeTure, Michael A. "The Neuropathological Diagnosis of Alzheimer's Disease." *National Library of Medicine*, 2 Aug. 2019, pp. 1-18, https://doi.org/10.1186/s13024-019-0333-5. Accessed 23 Apr. 2023.

Doody, Rachelle. "Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease." *New England Journal of Medicine*, 2014, www.nejm.org/doi/full/10.1056/nejmoa1312889.

Ellison, Tim S. "Outcome Measures for Alzheimer's Disease: A Global Inter-Societal Delphi Consensus." *The Journal of Alzheimer's Association*, 20 Dec. 2022, alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1002/alz.12945. Accessed 23 Apr. 2023.

Fagan, Anne M. "Cerebrospinal Fluid Biomarkers of Alzheimer's Disease." *NIH*, 2010, pp. 1-19, www.ncbi.nlm.nih.gov/pmc/articles/PMC2846664/pdf/nihms180632.pdf. Accessed 23 Apr. 2023.

Fogel, David B. "Factors Associated with Clinical Trials That Fail and Opportunities for Improving the Likelihood of Success: A Review." *Elsevier*, 2018, www.ncbi.nlm.nih.gov/pmc/articles/PMC6092479/pdf/main.pdf. Accessed 23 Apr. 2023.

Hansson, Oskar. "Advantages and Disadvantages of the Use of the CSF Amyloid β (Aβ) 42/40 Ratio in the Diagnosis of Alzheimer's Disease." *Alzheimer's Research and Therapy*, 2019, pp. 1-15, https://doi.org/10.1186/s13195-019-0485-0.

Honig, Lawrence S. "Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease." *New England Journal of Medicine*, 2018, www.nejm.org/doi/10.1056/NEJMoa1705971?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200www.ncbi.nlm.nih.gov.

Lemere, Cynthia A. "Can Alzheimer Disease Be Prevented by Amyloid-β Immunotherapy?" *NIH*, 2010, www.ncbi.nlm.nih.gov/pmc/articles/PMC2864089/pdf/nihms-194354.pdf.

Nojima, Hisashi. "Clinical Utility of Cerebrospinal Fluid Biomarkers Measured by LUMIPULSE System." *ANNALS*, 2022, pp. 1-12,

www.ncbi.nlm.nih.gov/pmc/articles/PMC9735374/pdf/ACN3-9-1898.pdf. Accessed 23 Apr. 2023.

Qiu, Tian. "Aβ42 and Aβ40: Similarities and Differences." *Peptide Science*, 28 May 2015, pp. 522-29, onlinelibrary.wiley.com/doi/abs/10.1002/psc.2789. Accessed 23 Apr. 2023.

Raulin, Ana-Caroline. "ApoE in Alzheimer's Disease: Pathophysiology and Therapeutic Strategies." *BMC*, 2022, pp. 1-26, https://doi.org/10.1186/s13024-022-00574-4. Accessed 23 Apr. 2023.

Srivastava, Sukriti. "Alzheimer's Disease and Its Treatment by Different Approaches: A Review." *European Journal of Medicinal Chemistry*, 2021, www.sciencedirect.com/science/article/abs/pii/S0223523421001690?via%3Dihub. Accessed 23 Apr. 2023.

Suppiah, Subapriya. "The Who, When, Why, and How of PET Amyloid Imaging in Management of Alzheimer's Disease—Review of Literature and Interesting Images." *MDPI*, 2019, www.ncbi.nlm.nih.gov/pmc/articles/PMC6627350/pdf/diagnostics-09-00065.pdf. Accessed 23 Apr. 2023.

Vaz, Miguel. "Role of Aducanumab in the Treatment of Alzheimer's Disease: Challenges and Opportunities." *NCBI*, 2022, www.ncbi.nlm.nih.gov/pmc/articles/PMC9124475/pdf/cia-17-797.pdf. Accessed 23 Apr. 2023.

Wenk, Gary L. "Neuropathologic Changes in Alzheimer's Disease." *National Library of Medicine*, 2003, www.psychiatrist.com/read-pdf/12701/. Accessed 23 Apr. 2023.

Yiannopoulou, Konstantina G. "Reasons for Failed Trials of Disease-Modifying Treatments for Alzheimer Disease and Their Contribution in Recent Research." *Biomedicines*, 2019, pp. 1-16, www.ncbi.nlm.nih.gov/pmc/articles/PMC6966425/pdf/biomedicines-07-00097.pdf. Accessed 23 Apr. 2023.