Navigating the Next Wave of Clinical Trials for Alzheimer's Disease Research

Rachel Sudhakar[1]

[1] Faculty of Science, University of Ottawa, Ottawa, ON, Canada

Correspondence: sudhakar.rachel@gmail.com

Date Published: April 30, 2026
DOI: https://doi.org/10.18192/UOJM.V16iS1.7815

As the most prevalent cause of dementia globally, Alzheimer's disease continues to be a major contributor to institutionalization, disability, and caregiver burden.[1] For many years, the only available treatments were symptomatic ones that provided a slight, transient improvement in cognitive function without changing the course of the disease. Consequently, a growing skepticism regarding disease-modifying strategies and a string of failed trials characterized Alzheimer's clinical research. However, expectations have changed recently due to developments in therapeutic design, biomarker science, and trial methodology. These developments have brought renewed momentum to the field while also raising important questions about how progress should be interpreted.

A major turning point has been the re-emergence of amyloid-targeting therapies. In Alzheimer's disease, a protein called amyloid beta builds up in the wrong way to create plaques outside of cells, which are thought to trigger other problems like tau pathology, neuroinflammation, and synaptic dysfunction.[2] Previous anti-amyloid medications often failed due to their late administration or insufficient plaque removal. Newer monoclonal antibodies have been designed to overcome these limitations.[3] Lecanemab was tested in individuals with early symptomatic Alzheimer's disease and confirmed amyloid pathology.[4] Participants who received lecanemab had significant decreases in amyloid levels on PET scans and experienced a meaningful slowdown in mental and daily functioning decline over 18 months compared to those who received a placebo.[5] While the absolute clinical effect size was modest, the trial provided the first consistent evidence that reducing amyloid could alter disease trajectory.

Also, studies showed similar results for donanemab, an antibody that targets a modified form of amyloid beta mostly found in existing plaques.[6] Donanemab treatment led to a noticeable reduction in plaques and a slower decrease in overall thinking and daily living skills in people with early symptoms of the disease. The trial was notable for using a "treat-to-clear" strategy, which halted dosage as soon as amyloid levels dropped below a predetermined threshold. This approach decreased total drug exposure and provides a possible means of striking a balance between cost, safety, and benefit.[7] However, both lecanemab and donanemab were linked to brain imaging issues, such as swelling and small bleeding in the brain, especially in people who carry the *APOE* ε4 allele.[8] These findings show how mechanism-driven success intensifies risk stratification and monitoring

In addition to amyloid-directed treatments, tau pathology has drawn more attention because it is more closely associated with neuronal loss and cognitive decline than amyloid burden alone.[9] Tau-targeting strategies focus on stopping the clumping or spread of abnormal tau proteins in neurons, which could help address issues later in the disease process. A growing understanding that Alzheimer's disease is biologically diverse and unlikely to respond to single-target approaches is reflected in the inclusion of tau-directed agents in combination trials, although they are still in the early stages of clinical development.[9] This shift toward multi-mechanism strategies marks a conceptual evolution in how Alzheimer's trials are designed, even as they complicate interpretation of outcomes.

Drug delivery advancements have also started to change the therapeutic environment. Using "brain shuttle" technology, trontinemab is a new type of anti-amyloid antibody designed to improve its movement across the blood–brain barrier by using a special process called receptor-mediated transcytosis.[10] In early studies, trontinemab showed a much faster and greater decrease

in plaque at lower doses than older antibodies, suggesting it reaches the central nervous system more effectively.[11] Although these results are biologically remarkable, they also highlight a persistent problem in Alzheimer's research: higher target engagement does not always equate to higher clinical benefit. As trontinemab moves closer to late-stage trials, its final worth will be determined by whether improved delivery results in outcomes that patients and caregivers can understand.[11]

Alongside advances in drug delivery, rapid progress in biomarker science has changed how Alzheimer's disease trials are designed. Blood tests for phosphorylated tau, combined with tau and amyloid positron emission tomography, now allow researchers to detect disease earlier and enroll participants at very early stages.[12] While this process has improved trial efficiency and biological precision, it has also raised concerns about relying too heavily on biomarkers as stand-ins for meaningful clinical outcomes. Many studies report clear biomarker changes without matching improvements in cognition, daily functioning, or quality of life.[13] Alzheimer's disease affects more than just memory; cognitive test scores alone often fail to capture outcomes that matter most to patients and caregivers, such as independence and behavioural symptoms.[13,14] Aligning trial endpoints with these patient-centered outcomes, therefore, remains a key challenge in the field.

The transition to clinical practice becomes even more challenging due to the selection of trial participants. Although multimorbidity, frailty, and advanced age are common characteristics of Alzheimer's patients, many studies on the disease do not include these individuals.[15] Mechanism-driven treatments may behave differently in these groups, particularly if vascular disease or polypharmacy alters their risk profiles. The disparity between trial populations and actual patients will increasingly influence clinical decision-making as disease-modifying treatments gain widespread use.

Alzheimer's disease research is at a pivotal stage. Emerging evidence indicates that early intervention can meaningfully alter disease biology and slow progression. However, translating these advances into meaningful clinical benefit will require a shift in how trials are designed and evaluated. Future studies should prioritize patient-centered endpoints, including functional independence and quality of life, alongside traditional biomarkers, rather than relying on biomarker change as primary indicators of success. Trial populations should also be expanded to better reflect real-world patients, particularly those with multimorbidity and frailty who are frequently excluded from clinical trials. In addition, incorporating real-world outcome measures, such as functional status and caregiver burden, into trial frameworks may help bridge the gap between mechanistic success and everyday impact. Aligning biological precision with real-world relevance will ultimately determine whether these innovations represent true therapeutic progress in a field marked by both urgency and uncertainty.

REFERENCES

1. 2025 Alzheimer's disease facts and figures. Alzheimers Dement. 2025 Apr 29;21(4):e70235. doi: 10.1002/alz.70235. PMCID: PMC12040760.
2. Murphy MP, LeVine H 3rd. Alzheimer's disease and the amyloid-beta peptide. J Alzheimers Dis. 2010;19(1):311-23. doi: 10.3233/JAD-2010-1221. PMID: 20061647; PMCID: PMC2813509.
3. Alkhalifa AE, Al Mokhlf A, Ali H, Al-Ghraiybah NF, Syropoulou V. Anti-Amyloid Monoclonal Antibodies for Alzheimer's Disease: Evidence, ARIA Risk, and Precision Patient Selection. J Pers Med. 2025 Sep 15;15(9):437. doi: 10.3390/jpm15090437. PMID: 41003140; PMCID: PMC12470750.
4. Knopman DS. Lecanemab reduces brain amyloid-β and delays cognitive worsening. Cell Rep Med. 2023 Mar 21;4(3):100982. doi: 10.1016/j.xcrm.2023.100982. PMID: 36948153; PMCID: PMC10040446.
5. 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 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948. Epub 2022 Nov 29. PMID: 36449413.
6. Jayaprakash N, Elumalai K. Translational Medicine in Alzheimer's Disease: The Journey of Donanemab From Discovery to Clinical Application. Chronic Dis Transl Med. 2024 Dec 16;11(2):105-116. doi: 10.1002/cdt3.155. PMID: 40486952; PMCID: PMC12142702.
7. Shcherbinin S, Evans CD, Lu M, Andersen SW, Pontecorvo MJ, Willis BA, et al. Association of Amyloid Reduction After Donanemab Treatment With Tau Pathology and Clinical Outcomes: The TRAILBLAZER-ALZ Randomized Clinical Trial. JAMA Neurol. 2022 Oct 1;79(10):1015-1024. doi: 10.1001/jamaneurol.2022.2793. PMID: 36094645; PMCID: PMC9468959.
8. Smith EE, Phillips NA, Feldman HH, Borrie M, Ganesh A, Henri-Bhargava A, et al. Canadian Consortium on Neurodegeneration in Aging Investigators. Use of lecanemab and donanemab in the Canadian healthcare system: Evidence, challenges, and areas for future research. J Prev Alzheimers Dis. 2025 Mar;12(3):100068. doi: 10.1016/j.tjpad.2025.100068. Epub 2025 Jan 31. PMID: 39893139; PMCID: PMC12184013.
9. Congdon EE, Ji C, Tetlow AM, Jiang Y, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease: current status and future directions. Nat Rev Neurol. 2023 Dec;19(12):715-736. doi: 10.1038/s41582-023-00883-2. Epub 2023 Oct 24. PMID: 37875627; PMCID: PMC10965012.
10. Klein G, Rabinovici GD, Zetterberg H, Tonietto M, Bittner T, Rukina D, et al. Interim biomarker results for trontinemab, a novel Brainshuttle™ antibody in development for the treatment

of Alzheimer's disease. Alzheimers Dement. 2025 Dec 25;21(Suppl 5):e104288. doi: 10.1002/alz70859_104288. PMCID: PMC12740797.
11. Smith J, Mummery CJ, Cummings JL, Rabinovici GD, Salloway S, Sperling RA, et al. TRONTIER 1 and TRONTIER 2: Pivotal trials of trontinemab in early symptomatic Alzheimer's disease. Alzheimers Dement. 2025 Dec 26;21(Suppl 5):e104294. doi: 10.1002/alz70859_104294. PMCID: PMC12741723.
12. Zhang Y, Bi K, Zhou L, Wang J, Huang L, Sun Y, et al. Advances in Blood Biomarkers for Alzheimer's Disease: Ultra-Sensitive Detection Technologies and Impact on Clinical Diagnosis. Degener Neurol Neuromuscul Dis. 2024 Jul 30;14:85-102. doi: 10.2147/DNND.S471174. PMID: 39100640; PMCID: PMC11297492.
13. Pascoal TA, Aguzzoli CS, Lussier FZ, Crivelli L, Suemoto CK, Fortea J, et al. Insights into the use of biomarkers in clinical trials in Alzheimer's disease. EBioMedicine. 2024 Oct;108:105322. doi: 10.1016/j.ebiom.2024.105322. Epub 2024 Oct 3. PMID: 39366844; PMCID: PMC11663755.
14. Stoeckel LE, Fazio EM, Hardy KK, Kidwiler N, McLinden KA, Williams B. Clinically meaningful outcomes in Alzheimer's disease and Alzheimer's disease related dementias trials. Alzheimers Dement (N Y). 2025 Feb 19;11(1):e70058. doi: 10.1002/trc2.70058. PMID: 39975465; PMCID: PMC11837731.
15. Stirland LE, Choate R, Zanwar PP, Zhang P, Watermeyer TJ, Valletta M, et al. Multimorbidity in dementia: Current perspectives and future challenges. Alzheimers Dement. 2025 Aug;21(8):e70546. doi: 10.1002/alz.70546. PMID: 40755143; PMCID: PMC12319240.

Conflicts of Interest Disclosure
There are no conflicts of interest to declare.