



Alzheimer's disease immunotherapy and the amyloid hypothesis: when aggregation obscures interpretation

A widely publicised Cochrane review published on April 16, 2026, set out to synthesise evidence on the efficacy and safety of amyloid β -targeting monoclonal antibodies for Alzheimer's disease.¹ The authors aggregated data from 17 randomised trials of multiple amyloid immunotherapy agents involving more than 20 000 participants, concluding that these therapies probably result in little to no difference in cognitive function or dementia severity; small improvements in functional ability; and small increases in side-effects, notably amyloid-related imaging abnormalities indicating oedema or effusions (ARIA-E), with little or no difference in serious adverse events or death. These results and their overarching conclusion that "successful removal of amyloid from the brain does not seem to be associated with clinically meaningful effects in people with mild cognitive impairment or mild dementia due to Alzheimer's disease"¹ are, however, fundamentally undermined by pooling agents with markedly different, and in some cases negligible, target engagement.

The therapeutic premise—that removal of amyloid β will modify disease trajectory—has driven the development of successive generations of monoclonal antibody therapies over the last two decades. Although these treatments all target amyloid β , they have fundamental differences in their pharmacokinetics, dosing, and specific amyloid β target—which ranges from soluble monomeric forms through to fibrillar plaques. These distinctions are not only pharmacological but are also reflected by, and predictive of, the biological and clinical effect seen with individual drugs.^{2,3} Early agents such as bapineuzumab,⁴ solanezumab,⁵ and crenezumab⁶ neither achieved any meaningful amyloid removal nor resulted in clinical benefits. By contrast, in a 2023 pivotal phase 3 study, lecanemab, which preferentially targets amyloid protofibrils, reduced the mean amyloid burden in treated patients to below the threshold for being amyloid-positive on PET and slowed clinical decline by about 27% compared with placebo (adjusted mean change from baseline of 1.21 vs 1.66 on the Clinical Dementia Rating—Sum of Boxes scale) by 18 months.⁷ And donanemab, which targets fibrillar amyloid plaques, achieved similar or greater amyloid

clearance and a broadly similar slowing of clinical progression in its 2023 phase 3 randomised trial.⁸

Examination of side-effect rates, and ARIA-E in particular, provides further evidence for the flaws in the conclusions of the Cochrane review. Although the authors find overall that there was a small increase in the risk of ARIA-E rates, this concatenates the extremely low rates seen in drugs that had little or no impact on amyloid burden (eg, solanezumab and crenezumab had no more ARIA-E than placebo⁹) with the higher, albeit usually manageable and largely asymptomatic, rates (12.6% and 24%) seen in the phase 3 trials of lecanemab and donanemab.^{7,8} Interpreting these pooled estimates as representative of a uniform class effect risks obscuring important differences between individual therapies.

For drugs where statistically significant slowing of cognitive or functional decline is determined, it is, of course, important to consider whether any effects are clinically meaningful. Although methodologies can be applied to try to quantify clinical meaningfulness, none is perfect.^{10,11} Importantly, a sustained reduction in the rate of decline, even if moderate, could delay key clinical transitions: loss of independence, escalation of support, or need for institutional care. Some trials included in the Cochrane review¹ report small but consistent benefits in functional measures, particularly those reflecting more complex daily activities. The extent to which these

Published Online
April 23, 2026
[https://doi.org/10.1016/S0140-6736\(26\)00789-0](https://doi.org/10.1016/S0140-6736(26)00789-0)



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differences accumulate over time to produce ongoing benefit remains uncertain. But for patients and caregivers, disease slowing might be meaningful even if they fall short of predefined, and inevitably arbitrary, thresholds.

This leads to the central point. Patients and families are not interested in class effects. They are interested in the potential benefits, risks, burden, and, in some instances, costs of the specific therapies available. Patients, and the public, rate delaying progression and maintaining functional independence very highly and perceive drastic reductions in quality of life as Alzheimer's disease progresses from mild dementia to its most advanced stages.¹² Licensing authorities make judgements on the benefits and risks of a specific drug on the basis of available evidence for that drug: the fact that lecanemab and donanemab have gained approval in multiple countries and jurisdictions across the world^{10,13} reflects that these drugs are efficacious. The different views of payers point to different evaluations of value—clinical, economic, and societal—as well as different models of funding and systems readiness.⁹

Pooling the effects of agents with differing mechanisms or target engagement—many unsuccessful, some biologically inactive, and most abandoned—risks diluting both any clinical effects and any safety signals. The resulting summary¹ assumes a consistent class effect that is not borne out by the evidence, and in doing so risks obscuring real signals emerging from specific drugs. This Cochrane review negates neither the amyloid hypothesis nor amyloid-targeting therapy as a whole: the question is no longer whether drugs can remove amyloid and slow decline, but which individual drugs do so safely, cost-effectively, and in ways that are meaningful for patients.

NCF reports consulting and speaker fees paid to his institution from Eisai, F. Hoffmann-La Roche, and Eli Lilly; advisory board fees paid to his institution from Biogen and F. Hoffmann-La Roche and donated to charity from AbbVie; a speaker fee from Eisai donated to charity; and is a Member of the Research Strategy Council for Alzheimer's Society (UK). JMS is the Chief Medical Officer for

Alzheimer's Research UK, and reports institutional grants from LifeArc Foundation, British Heart Foundation, Alzheimer's Society, Alzheimer's Association, Alzheimer's Research UK, and Medical Research Council; royalties from Oxford University Press and Henry Stewart Talks; consulting, speaker, and advisory board fees from Eli Lilly, Roche Pharmaceuticals, Alamar Biosciences, and Receptive Bio; travel support from Alzheimer's Association, Alzheimer's Research UK, and Eli Lilly; and receives PET amyloid tracer from Alliance Medical for research. NCF and JMS acknowledge the support of the National Institute for Health and Care Research (NIHR) UCLH Biomedical Research Centre and the UK Dementia Research Institute; JMS is an NIHR Senior Investigator. These funders did not have any role in the writing of this Comment or the decision to submit it for publication. SK reports institutional funding from Alzheimer's Research UK and is a trustee of UK Dementia Research Institute and Worldwide Cancer Research, a scientific advisory board member of Dementia Discovery Fund, and an advisory board member of Alzheimer's Disease Data Initiative.

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