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Letter

Interpreting evolving evidence in Alzheimer's disease: implications for dementia clinicians

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The recent Cochrane systematic review of amyloid-targeting therapies for early-stage Alzheimer's disease[1] has understandably received a great deal of public interest. Unfortunately, its interpretation risks misrepresenting the current state of therapeutic development in this field. The central concern is the aggregation of data from very different agents. The meta-analysis pools early, largely negative trials with studies of later agents with different targets. The later agents have demonstrated efficacy in larger phase 3 trials and have received regulatory approval from bodies including the Medicines and Healthcare products Regulatory Agency, the US Food and Drug Administration, and the European Medicines Agency. Although systematic reviews are inclusive by definition, the absence of meaningful stratification by developmental phase, mechanism or trial design introduces a substantial interpretive limitation. In addition, the conclusion of the review that 'amyloid removal' does not produce clinical benefits does not fit with the stated aim of the review, which was to test whether monoclonals produced clinical benefit, with some of the monoclonals assessed having absolutely no effect on amyloid.

Alzheimer's disease trials have also evolved in terms of design. Early trials were often conducted without biomarker confirmation, with suboptimal dosing or with incomplete understanding of target engagement. Later-phase trials of currently approved therapies have differed with respect to patient selection, methodological rigour and biological precision. Treating these distinct trials as directly comparable conflates early exploratory failure with later positive phase 3 outcomes. Although the review also examined the subgroup of agents that subsequently received regulatory approval, pooled estimates alone may not fully capture differences in biological target engagement, trial methodology and duration of follow-up that are relevant to interpretation of treatment effects. For clinicians working with people with or at risk of dementia, this distinction is critical. Decision-making increasingly depends on nuanced interpretation of evolving evidence, particularly where disease-modifying therapies are concerned. Analyses that do not adequately distinguish between different generations of trials and therapeutic approaches risk obscuring clinically relevant effects that have met contemporary regulatory standards.

The Cochrane review also discusses the meaningfulness of the drugs' benefits. Assessment of meaningfulness should incorporate the perspectives of people living with Alzheimer's disease and their families, while remaining grounded in outcomes directly supported by randomised trial evidence. The broader implications are also significant. Cochrane reviews carry considerable weight in shaping public discourse and policy. It is therefore unsurprising that patient organisations and charities have responded with caution. There is a risk that such analyses may be used by payers or decision makers as justification to restrict access to approved treatments, particularly if the conclusions do not sufficiently distinguish between exploratory and confirmatory phases of drug development.

The review provides a valuable synthesis of available evidence, but its interpretation may understate important differences between therapeutic generations and patterns of target engagement. Critical evaluation of amyloid-targeting therapies is essential and entirely appropriate. However, analyses should distinguish between agents that failed to engage their biological target and those that have demonstrated substantial amyloid removal and subsequently received regulatory approval. Greater attention to biological target engagement, trial design and therapeutic generation would provide a more clinically informative synthesis of the available evidence. The field would also benefit from full publication of long-term extension analyses, including comparisons between early- and delayed-treatment groups, to clarify the durability and cumulative clinical impact of treatment effects.

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Author contributions

I.K. drafted the letter. J.B.R., J.A., D.A., H.A., R.B., A.B., E.C., C.D., R.D., N.F., S.H.H., J.J., D.J., S.K., F.K., M.S.P.K., P.M., B. McFarlane, B. McGuinness, C.M., C.P., J.R.P., G.R., J. Rasmussen, C.R., J.-P.T., B.R.U., A.V.V. and V.R. reviewed or edited it and approved the final version.

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Reference

1 Nonino F, Minozzi S, Sambati L, Del Giovane C, Baldin E, Bassi MC, et al. Amyloid-beta-targeting monoclonal antibodies for people with mild cognitive impairment or mild dementia due to Alzheimer's disease. *Cochrane Database Syst Rev* 2026; **4**: CD016297.

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