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Short Communication

Class-level aggregation obscures clinically relevant heterogeneity in anti-amyloid antibody trials: comments on a Cochrane review by individual members of the EADC

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The recent Cochrane metanalysis of anti-amyloid therapies for Alzheimer's disease represents an attempt to synthesize an evolving evidence base [1] The rigor of the Cochrane methodology, including systematic study identification, risk-of-bias assessment, and transparent

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statistical approaches, may provide a valuable foundation for evaluating therapeutics. However, the central issue is not methodological formality but whether the analytical framework is appropriate for a therapeutic field that has evolved substantially over time.

The central misconception of the review relates to the decision to include all amyloid-beta targeting monoclonal antibodies in one metanalysis. While such aggregation increases statistical power, it obscures the substantial drug-to-drug heterogeneity, and differences regarding trial designs and developmental eras. The trajectory from early agents such as bapineuzumab, solanezumab, and crenezumab to more recent antibodies like lecanemab and donanemab, reflect not only incremental optimization but also fundamental evidence-based shifts in target engagement, dosing strategies, patient selection, and biomarker integration [2]. These differences are highly relevant to clinical outcomes.

Early-generation antibodies were developed in a context where amyloid biology was less understood, amyloid positivity was not consistently confirmed before enrollment [3], and dosing was limited by concerns regarding amyloid-related imaging abnormalities [4]. These constraints contributed to modest or absent clinical effects, reflected in negative trial outcomes, which are now widely interpreted as reflecting suboptimal target engagement rather than definitive evidence against the therapeutic hypothesis. In contrast, later-generation antibodies, specifically lecanemab [5] and donanemab [6], were designed to preferentially bind aggregated forms of amyloid, deployed at higher doses, and tested in biomarker-confirmed populations at earlier disease stages. These advances are not merely incremental; they represent a qualitative shift in how the amyloid hypothesis has been operationalized in clinical trials.

By pooling results across this spectrum, the review implicitly assumes a degree of class homogeneity that does not align with the underlying biology or trial methodology. The review's subgroup analyses show that heterogeneity is not hypothetical. If treatment effects vary by antibody type, then a class-average estimate is not a neutral summary but a potentially misleading one. This approach dilutes signals from more recent agents with negative or inconclusive findings from earlier compounds. The review considers together 9 different drugs from 17 different studies, from which only 2 drugs were approved. Therefore, the aggregated estimates will underestimate the efficacy of currently approved therapies while overemphasizing the failures of prior generations. A stratified analysis, reflecting developmental stage or key pharmacodynamic characteristics (such as plaque clearance capacity), is needed to provide an informative synthesis.

This concern also affects external validity. Only a minority of the included studies correspond to therapies that are now relevant to practice (lecanemab and donanemab). Broad conclusions about "anti-amyloid therapies" derived predominantly from compounds that never entered clinical use should be interpreted cautiously when applied to currently available treatments. Aggregating across approved and non-approved therapies without differentiation conflate fundamentally different evidentiary standards. It also leads to conclusions about efficacy and safety that are disproportionately influenced by agents that failed to meet regulatory benchmarks. Therefore, the conclusions that removal of amyloid is not associated with clinically meaningful results and that "The findings of the review could therefore be an important support for decision-making in clinical practice" [1] cannot be made and are even clearly misleading.

A more informative approach would have been to present separate analyses for approved versus non-approved therapies. Such stratification allows readers to better interpret how the evidence base relates to current clinical decision-making. Without this distinction, there is a risk that the conclusions are perceived as applying uniformly across all agents, despite substantial differences in their evidentiary support.

Another major concern relates to the definition and application of clinical relevance. The review adopts thresholds for clinical meaningfulness that are derived from a limited number of anchoring studies defining the Minimal clinically important difference (MCID) [7]. Anchoring studies are inherently context-dependent, influenced by patient populations, disease stages, outcome measures, and methodological assumptions. These concerns are also reflected in a recent commentary in Lancet Regional Health [8] by authors from the European Medicines Agency involved in the evaluation of lecanemab and donanemab: "A decision on clinical relevance based solely on the MCID therefore did not appear adequate in this case, hence other lines of evidence were considered."

The strength of the Cochrane approach lies in its methodology, which facilitates reproducibility and comparability. However, when applied to a therapeutic area undergoing rapid scientific evolution and ignoring scientific insights, strict aggregation can inadvertently obscure clinically meaningful differences between interventions, and result in erroneous conclusions that could cause patient harm. As it stands, our view is that Cochrane should reconsider their report for withdrawal.

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Data availability

Not applicable.

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Declaration of competing interest

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