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Comparative Assessment: Effectiveness and Safety of Anti-amyloid Antibodies, Neuropsychiatric Drugs and Placebo in Dementia and Cognitive Impairment: A Systematic Review, Frequentist and Bayesian Network Meta-Analyses

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Disclaimer

This study is a meta-analysis based on data from previously registered randomized controlled trials so no new clinical trial was conducted or registered for this work. All authors declare that they have no conflicts of interest.



Abstract

The antiamyloid antibodies (AABs) have redefined Alzheimer's disease (AD) treatment, but their comparative value against symptomatic neuropsychiatric drugs (NPDs) is unclear, due to fragmented evidence and heterogeneous population and outcomes. To address this, we developed AlzMeta.app 2.1, a web application that allows comparing effectiveness and safety of NPDs, AABs and placebo through pairwise and frequentist and Bayesian network meta-analyses of randomized trials in AD and related dementias (18/08/2025). According to PRISMA-NMA and GRADE guidelines, we compared: (1) NPDs against placebo across multiple dementia syndromes (181 studies, 41,930 participants), and (2) AABs, NPDs, and placebo in mild cognitive impairment and mild-to-moderate AD (104 studies, 42,980 participants).

Guidelines

This study was done in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for Network-Meta-Analyses (NMA). The certainty (confidence) of underlying evidence was assessed with the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation).

2.3. Data analysis and reporting

- 1 Relative measures have been converted to absolute risks (ARs) and benefits, expressed as AR per 1000 people and Numbers-Needed-to-Treat (NNT) for additional harmful (NNT_H, higher is better) and beneficial outcomes (NNT_B, lower is better). In AlzMeta.app 2.1, NNT_B/NNT_H calculations can be calculated for each particular case by incorporating different baseline risk estimates.
- 2 Outlier detection was first performed using dmetar package in R. Then, we investigated the validity and robustness of the results with Baujat plots and graphic display of heterogeneity (GOSH) plot analysis. Finally, we did sensitivity analysis after removing influential cases and studies with high risk of bias, including the publication bias. Further sensitivity analyses were done for different dementia diagnoses and stages of dementia, dosage regimes and treatment duration (shorter and longer than 1 year), as well as by omitting studies with participants younger than 65 years on average.
- 3 Correlation coefficients were calculated between the cognitive, functional, behavioural and psychological outcomes (the Pearson product moment correlation coefficient), as well as between the safety outcomes (the Spearman rank correlation coefficient). In order to test whether the risk of bias and baseline participant characteristics (age, sex, baseline scores on MMSE and ADAS-Cog) impact the results in our NMAs, we performed Bayesian network meta-regression with the gemtc package in R.

2.4. The Risk of Bias and Certainty of Evidence

- 4 The Revised Cochrane risk-of-bias tool (RoB-2) was used to evaluate potential bias, classified as “low risk”, “some concerns”, or “high risk”. This included assessment of the bias occurring due to the randomization process, deviations of intended interventions, missing outcome data, outcome measurements, and selection of reported results. Risk of bias plots were generated by robvis web app. Publication bias was statistically evaluated for continuous outcomes with ≥10 studies by funnel plots and Egger’s regression test. The certainty of underlying evidence at comparison-level was rated by GRADE assessment, focusing on: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.5. Role of funding source

- 5 The funders of the study had no role in study design, data collection, analysis, interpretation or writing of the report.

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