Age effects on clinical trial results in Alzheimer dementia

Therapeutic trials in Alzheimer disease (AD) are notoriously difficult and have produced no new approved treatments in the past decade. Trial success often depends on decline in a placebo arm, and population characteristics that diminish placebo decline reduce the chance of detecting positive therapeutic effects of a drug. This study of data from multiple trials of AD dementia demonstrates that age can have such an effect: older participants showed less decline than younger participants by differences that were both meaningful and greater than expected.

Age effects were limited to cognitive test results. Baseline imbalances likely accounted for some of the effect on decline since older patients had better initial cognitive scores, a predictor of slower progression. Differences in baseline scores would have been even more pronounced if age-adjusted. Such considerations are worth exploring, but this hardly blunts the key point that ignoring age effects on progression in study populations can negatively influence trial results.

These effects may be mitigated by several strategies, including stratification, lowering an age threshold, and more rigorous exclusion of comorbid conditions, each with some tradeoff in increased trial burden or consequences. Another mitigation is improvement of diagnostic accuracy. The recent negative bapineuzumab and solanezumab studies enrolled an unexpectedly high percentage of patients with dementia who did not have increased cerebral amyloid and were unlikely to have had AD. Amyloid-negative subjects had higher baseline cognitive scores and slower decline similar to older individuals in this study.

The useful findings described here serve a cautionary note not to take age effects for granted in designing clinical trials. It will be important to confirm reproducibility of the results and at the same time to explore the effects of mitigations, including use of diagnostic biomarkers, to improve trial success.


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