

# Review: cholinesterase inhibitors have a modest effect on neuropsychiatric and functional outcomes in Alzheimer's disease

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Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA* 2003 Jan;280:210–6.

**QUESTION:** How effective are cholinesterase inhibitors for neuropsychiatric and functional outcomes in people with mild to moderate Alzheimer's disease?

## Design

Systematic review with meta-analysis.

## Data sources

The authors searched Medline, Dissertations Abstracts, PsychInfo, Biosis, Pubmed, and the Cochrane Controlled Trials Register through December 2001; examined bibliographies of reviews, original research articles, and other articles of interest; and contacted researchers and pharmaceutical companies for additional studies.

## Study selection

Published and unpublished double blind randomised trials in any language were eligible if they focused on outpatients diagnosed with mild to moderate probable Alzheimer's disease who were treated for at least one month with a cholinesterase inhibitor. 29 parallel group placebo controlled trials were included.

## Data extraction

Two reviewers extracted data independently about study methods, sources of bias, and outcomes. Sixteen trials included neuropsychiatric outcomes and 18 included functional measures. Neuropsychiatric outcomes were measured with the Neuropsychiatric Inventory (NPI) and the Alzheimer Disease Assessment Scale, non-cognitive (ADAS-noncog). Data were combined using weighted mean differences. Functional outcomes were measured with activities of daily living and instrumental activities of daily living scales. Data were analysed using standardised mean differences.

## Main results

People treated with cholinesterase inhibitors were more likely to show improved functional and neuropsychiatric outcomes than controls (improvement of 1.72 points on the NPI over controls, 95% CI 0.87 to 2.57 points; and 0.03 points on the ADAS-noncog; 95% CI 0 to 0.05 points). There was no difference in efficacy between various cholinesterase inhibitors.

## Conclusions

Cholinesterase inhibitors appear to have a modest effect on neuropsychiatric and functional outcomes in Alzheimer's disease. It is uncertain whether these benefits affect long term outcomes such as quality of life, institutionalisation, and caregiver burden.

## COMMENTARY

Controversy remains about the drug of choice for treating Alzheimer's disease. This review by Trinh *et al* is therefore timely and appropriate. It complements another recent review by Cummings on the use of cholinesterase inhibitors.<sup>1</sup> Cholinesterase inhibitors are the most widely used treatment for Alzheimer's disease. Four cholinesterase inhibitors were approved by the United States Food and Drug Administration after several large double blind randomised trials, but only donepezil, rivastigmine and galantamine are in common use. These drugs only appear to improve symptoms in people with mild to moderate Alzheimer's disease.

Trinh *et al* focused studies of neuropsychiatric symptoms, functional outcomes, or both. The selection of these outcome measures is justifiable since they reflect clinical domains of practical significance to patients and their caregivers. Even small differences on activities of daily living (ADL) scales may be of great importance to families and caregivers. The findings suggest that cholinesterase inhibitors have significant effects in people with mild to moderate Alzheimer's disease who have neuropsychiatric disturbances, and should be considered as a treatment option in psychiatric and behavioural disturbances.

The review focuses on a limited number of outcome measures, however. It is important to measure the effects of these drugs in multiple domains, including cognitive and global functioning. The review also provided limited explanations about differences in the results of various clinical trials. For example, the authors did not highlight the impact of differences in inclusion criteria. Some studies included relatively more severely affected or less affected participants, or patients with more or less comorbidities. Both of these factors may influence the magnitude of treatment effect. Moreover, the authors did not acknowledge the possibility that cholinesterase inhibitors may affect other currently developing targets for Alzheimer's disease therapy, such as ApoE, amyloid peptides and tau proteins.<sup>2</sup>

Other unanswered questions include: (1) are there differences within types of cholinesterase inhibitors?; (2) what effects do gender and ERT have on outcomes?; (3) what are the effects of ApoE and other genotypes of patients?; and (4) what are the pharmacokinetic and pharmacodynamic differences of various cholinesterase inhibitors? It is reasonable to select studies for analysis as these reviewers have done, but it should be with full understanding of the similarities and differences of these drugs and how these characteristics limit comparisons of clinical significance and utility.

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- 1 Cummings JL. Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. *Am J Geriatr Psychiatry* 2003; **11**: 131–145.
- 2 Lahiri DK, Farlow MR, Greig NH *et al*. A critical analysis of new molecular targets and strategies for drug developments in Alzheimer's disease. *Curr Drug Targets* 2003; **4**: 97–112.
- 3 Farlow MR, Lahiri DK, Poirier J *et al*. Treatment outcome of tacrine therapy depends on Apolipoprotein genotype and gender of the subjects with Alzheimer's disease. *Neurology* 1998; **50**: 669–77.