Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis

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CRD summary
The review assessed the efficacy of cholinesterase inhibitors (ChIs) for neuropsychiatric symptoms and functional impairment in Alzheimer disease. The authors concluded that ChIs have a modest beneficial impact on these outcomes. Their conclusions seem reliable. However, the clinical meaningfulness of the benefit observed is debatable, and some of the analyses upon which the conclusions were based were not statistically significant.

Authors' objectives
To assess the efficacy of cholinesterase inhibitors (ChIs) for neuropsychiatric and functional outcomes in individuals with mild to moderate Alzheimer disease (AD).

Searching
MEDLINE (from January 1966 to December 2001), Dissertation Abstracts Online, PsycINFO, BIOSIS Previews, PubMed and the Cochrane Controlled Trials Register were searched without language restrictions; the search terms were reported. The reference lists of relevant reviews and other publications were checked, and other researchers and pharmaceutical companies were contacted.

Study selection
Study designs of evaluations included in the review
Randomised, double-blinded placebo-controlled trials of a parallel or crossover design were eligible. The crossover trials were required to have a washout period of greater than one week.

Specific interventions included in the review
Studies evaluating named ChIs, where treatment was more than one month, were eligible for inclusion. The following ChIs were evaluated in the included studies: metrifonate, galanthamine, donepezil, tacrine, velnacrine, physostigmine, rivastigmine and epastigmine. Varying doses were used. The trial length ranged from 42 to 365 days.

Participants included in the review
Out-patients diagnosed as having mild to moderate 'probable' AD and a baseline Mini-Mental State Examination score of 10 to 26 were eligible for inclusion. Diagnosis was based on the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association's criteria. Some of the participants in the included studies did not have neuropsychiatric problems. The baseline scores ranged from 3.8 to 7.7 based on the non-cognitive portion of the Alzheimer Disease Assessment Scale (ADAS-noncog), and from 9.2 to 13.9 on the Neuropsychiatric Inventory (NPI).

Outcomes assessed in the review
Studies assessing neuropsychiatric outcomes using the ADAS-noncog (possible score of 0 to 50) or the NPI (possible score of 0 to 120), or assessing functional outcomes using a validated scale which separately measured activities of daily living (ADL) and instrumental ADL, were eligible. Studies were excluded if they used a combined measure of ADL and instrumental ADL. The functional outcome measures used in the included studies were the Physical Self-Maintenance Scale, Spontaneous Behaviour Interview, Nurses' Observation Scale for Geriatric Patients, Instrumental Activities of Daily Living Scale, and the Activities of Daily Living Scale.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion.
Assessment of study quality
Inclusion was restricted to studies that were randomised and double-blinded. The authors also reported whether the studies used an intention-to-treat (ITT) analysis. The reviewers independently assessed the studies.

Data extraction
Two reviewers independently extracted data blinded to the authors and journal where the article was published. Any discrepancies were resolved by consensus. The mean and variance for the change in scores from baseline were extracted for each study, using ITT data if available or otherwise completed participants data. Where necessary, the mean and variance were calculated from the data available in the paper. In individual studies where there were subgroups receiving different doses, the groups were combined and weighted by the subgroup sample size.

For neuropsychiatric outcomes, the weighted mean difference and 95% confidence interval (CI) were estimated for each trial and the data were presented as points of the scale. The NPI was used in preference to the ADAS-noncog if both measures were used in a single study. For functional outcomes, the standardised mean difference and 95% CI were estimated for each trial and the data were presented in standard deviations (SDs).

Methods of synthesis
How were the studies combined?
The trials were pooled using a random-effects model according to the outcome measure used: NPI, ADAS-noncog, instrumental ADL and ADL. The possibility of publication bias was assessed using funnel plots and Kendall's tau.

How were differences between studies investigated?
The Mantel-Haenszel test was used to investigate statistical heterogeneity between the studies (P<0.10). Sensitivity analyses were conducted: different Chls were pooled separately if there were more than three trials available for an individual drug; the effect of giving preference to NPI in studies using both the neuropsychiatric tests of interest was investigated; and separate analyses were conducted in which the results of the ITT analyses were compared with the completed participants analyses for each outcome.

Results of the review
Twenty-nine randomised controlled trials (RCT)s were included (n=13,443). Twenty-seven were of a parallel-group design and two were of a crossover design.

Neuropsychiatric outcomes.
The data from studies using the NPI and ADAS-noncog scales were pooled separately, owing to evidence of statistical heterogeneity when they were pooled together. In studies reporting the NPI (6 RCTs, n=2,927), there was a small improvement of 1.72 points (95% CI: 0.87, 2.57) in patients receiving Chls compared with placebo. In studies reporting the ADAS-noncog (10 RCTs, n=2,602), there was an improvement of 0.03 points (95% CI: 0.00, 0.05) in patients receiving Chls compared with placebo. The test for statistical heterogeneity was non significant for each group of studies.

Functional outcomes.
In studies using ADL measures (14 RCTs, n=3,738), patients receiving Chls improved by 0.10 SD (95% CI: 0.00, 0.19) compared with placebo. In studies using instrumental ADL measures (13 RCTs, n=4,176), patients receiving Chls improved by 0.09 SD (95% CI: 0.01, 0.17) compared with placebo. The test for statistical heterogeneity was non significant for each group of studies.

Similar effect sizes were found following most of the sensitivity analyses. For the NPI, the effect size was slightly greater for the completed participants analysis than for the ITT analysis.

There was no evidence of publication bias.
Authors' conclusions
In patients with AD living in the community, ChIs had a modest beneficial impact on neuropsychiatric and functional outcomes.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. A number of relevant electronic databases were searched with no language restrictions, and attempts were made to identify unpublished trials. The possibility of publication bias was assessed and no evidence of bias was found. The review methodology was well described and appropriate measures to avoid the introduction of bias were used. Study quality was taken into consideration by including only studies that met pre-specified criteria relating to quality.

There was very little information on the study participants: in particular, the baseline severity of AD and functional status were not reported, nor were the proportion of participants with neuropsychiatric problems and the other medications received. The statistical pooling of studies appeared appropriate and sensitivity analyses were conducted. The authors' conclusions were appropriate, although the clinical meaningfulness of what they described as a modest benefit is open to debate. In addition, only two of the four analyses on which they based their conclusions were statistically significant.

Implications of the review for practice and research
Practice: The authors stated that ChIs should be considered a therapeutic option for patients with mild to moderate AD who have neuropsychiatric symptoms.

Research: RCTs of ChIs in patients with AD and neuropsychiatric problems that consider long-term outcomes such as patient quality of life, institutionalisation and impact on carers, are required.

Bibliographic details

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Other publications of related interest
This additional published commentary may also be of interest. Cholinesterase inhibitors for Alzheimer disease [letters]. JAMA 2003;289:2359-61.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.