Cholinesterase inhibitors in mild cognitive impairment: a meta-analysis of randomized controlled trials
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CRD summary
The authors concluded that cholinesterase inhibitors modestly reduce the risk of conversion from mild cognitive impairment to dementia, but increase the risk of adverse effects and treatment withdrawal. The review appears to support the authors’ conclusions, but poor reporting of the review methods and limited information about the included studies make it difficult to assess the reliability of the conclusions.

Authors' objectives
To evaluate the long-term efficacy and safety of cholinesterase inhibitors (ChEIs) in patients with mild cognitive impairment (MCI).

Searching
MEDLINE (via PubMed), the Cochrane CENTRAL Register, EMBASE and PsycINFO were searched for studies published before April 2006; the search terms were reported. In addition, the manufacturers of marketed ChEIs were contacted for details of completed but unpublished trials. One study was presented as a poster at an international conference.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared ChEI with placebo were eligible for inclusion. The included studies evaluated donepezil (5 or 10 mg), galantamine (dose not reported) and rivastigmine (dose not reported). The duration of treatment, where reported, ranged from 24 weeks to 24 months.

Participants included in the review
Studies of patients that met clearly-defined and repeatable criteria for MCI were eligible for inclusion. The included studies enrolled patients with a Mini-Mental State Examination (MMSE) score of 24 or more, a Clinical Dementia Rating (CDR) score of 0.5, and a Hamilton Rating Scale for Depression (Ham-D) score of 13 or less. Patients were aged over 49 years in some studies and over 54 years in others.

Outcomes assessed in the review
The review assessed the long-term rate of progression to dementia (conversion), the number of patients with any adverse effect, the rate of discontinuation of treatment and mortality. The primary safety measure was the rate of discontinuation of treatment.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors stated that study quality was assessed using criteria suggested by the Centre for Reviews and Dissemination. The authors did not state how the validity assessment was performed.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the numbers of patients with each outcome of interest were presented, together with odds ratios (ORs) and 95% confidence intervals (CIs).

Methods of synthesis
How were the studies combined?
The pooled OR and 95% CI were calculated using the fixed-effect Mantel-Haenszel method. The weighted reduction (and 95% CI) in the risk of each outcome was also reported for each outcome. The number-needed-to-treat (NNT) to prevent one conversion to dementia was presented.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q statistic. Some differences between the studies were also discussed in the text.

Results of the review
Four RCTs (n=3,700) were included.

The authors stated that the quality of the included studies was satisfactory but reported no further details.

There was a statistically significant reduction in the risk of conversion to dementia for patients allocated to ChEI compared with placebo; the OR was 0.8 (95% CI: 0.6, 0.9), representing a modest weighted reduction of 23.9% (95% CI: 9.7, 35.8); the NNT was 24.

There was a significant increase in the risk of any adverse event for patients allocated to ChEI compared with placebo; the OR was 1.5 (95% CI: 1.3, 1.9), representing a weighted increase of 53.1% (95% CI: 26.2, 85.7).

There was a significant increase in the risk of discontinuing treatment for patients allocated to ChEI compared with placebo; the OR was 2.3 (95% CI: 1.9, 2.8), representing a weighted increase of 131% (95% CI: 92.8, 176.8). No significant heterogeneity was found for any of the meta-analyses (p=0.1 to p=0.9).

A pooled analysis of two studies of galantamine showed a significantly greater mortality in patients allocated to galantamine compared with placebo, 1.5% versus 0.5% (p=0.04). The mortality data for donepezil were incomplete.

Authors' conclusions
ChEIs were associated with a modest reduction in the risk of conversion from MCI to dementia but an increased risk of adverse effects and treatment withdrawal.

CRD commentary
The review addressed a question that was defined in terms of the participants, intervention, outcomes and study design. However, the eligibility criteria for long-term studies were not defined. Several relevant sources were searched and attempts were made to minimise publication bias. It was not clear whether any language restrictions were applied. The methods used to select the studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Validity was assessed but the results were not adequately reported. There was insufficient information regarding the characteristics of the included studies (e.g. drug dose, duration of the intervention and follow-up, and criteria used to determine progression to dementia). Statistical heterogeneity was assessed and the studies appear to have been appropriately pooled using a meta-analysis. The review appears to support the authors' conclusions, but the lack of reporting of review methods and the limited information about study outcomes make the reliability of the review conclusions uncertain.
Implications of the review for practice and research
Practice: The authors stated that it is too early to recommend treating patients with MCI with ChEIs.

Research: The authors stated the need for further studies to determine the clinical and neurobiological factors that predict conversion to dementia and response to ChEIs.

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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.