Cholinesterase inhibition for Alzheimer disease: a meta-analysis of the tacrine trials
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Authors' objectives
To determine the effects of cholinesterase inhibition with tacrine hydrochloride for the symptoms of Alzheimer's disease in terms of cognitive performance, clinical global impression, behaviour and functional autonomy.

Searching
The Cochrane Dementia and Cognitive Improvement Group's Specialized Register of trials was searched using the terms 'tacrine', 'tetrahydroaminoacridine' and 'THA'. The full search strategy is referenced (see Other Publications of Related Interest). Participating investigators of the included trials and the manufacturers of tacrine (Parke-Davis Pharmaceuticals, Morris Plains, NJ) were also contacted.

Study selection
Study designs of evaluations included in the review
Randomised double-blind placebo-controlled trials only, involving more than one day of treatment for Alzheimer disease. Only trials that had unconfounded treatment comparisons of tacrine versus placebo, or tacrine plus lecithin versus lecithin were considered. The trial had to be completed by January 1st 1996 to be included.

Specific interventions included in the review
Tacrine hydrochloride given for more than one day versus placebo, or tacrine hydrochloride plus lecithin versus lecithin. The duration of treatment in the included studies ranged from 3 to 36 weeks, and the dose of tacrine ranged from 20 to 160 mg/day.

Participants included in the review
People who were diagnosed as having 'probable' Alzheimer disease according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria. Age of participants ranged from 56 to 81 years.

Outcomes assessed in the review
Assessments of neuropsychological function, global clinical measures of change, behavioural disturbance, activities of daily living and quality of life. The scales most commonly used were the Mini-Mental State Examination (range: 0 - 30) as a measure of cognition; Clinical Global Impression of Change (range: 1 - 7) and Clinical Interview-Based Impression as overall measures of clinical usefulness; the neurocognitive scale of the Alzheimer Disease Assessment Scale (range: 0 - 50) as a measure of behavioural disturbance; and the Progressive Deterioration Scale to assess change in functional autonomy.

How were decisions on the relevance of primary studies made?
A single reviewer discarded irrelevant citations based on titles and abstracts of publications, although if it was suggested that an article could be of potential relevance it was retrieved for further assessment. Two reviewers independently selected trials for inclusion from the culled citation list. There were no disagreements about the selection of trials.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how many reviewers performed the data extraction.

Data on all individual patients were sought for the stated outcome measures, and for age, sex, severity of disease at
baseline, treatment assignment, dose, duration of treatment and withdrawal from the study. Only the first treatment period of crossover trials was considered. Data from any dose titration phase prior to the main efficacy phase were excluded.

Standardised differences at the 12-week end point were calculated for each study based on the intention to treat population. Odds ratios (ORs) for improvement with tacrine, compared with placebo, were calculated for each study.

**Methods of synthesis**

How were the studies combined?

Both the standardised differences and changes from baseline were analysed using meta-analysis techniques for data of a normal distribution. Random-effects pooled ORs, 95% confidence intervals (CIs) and number-needed-to-treat (NNT) were calculated.

The number needed for one withdrawal was also calculated, on the basis of drop-out rates.

How were differences between studies investigated?

Tests for heterogeneity between studies were performed. Regression analyses were performed to assess relationships between treatment effects and age, sex, severity of disease (based on Mini-Mental State Examination) at baseline, dose of tacrine, and exposure to tacrine prior to randomisation.

**Results of the review**

Twelve RCTs were included (n=1,984), of which 6 were crossover studies.

Cognition: Mini-Mental State Examination scores at 12 weeks were better in tacrine than placebo patients; intention-to-treat analysis showed a standardised difference of 0.62 (95% CI: 0.23, 1.00, p=0.002). There was no significant evidence of heterogeneity. The average final daily dose from each study showed no significant evidence of a greater treatment effect with increasing dose. Age and prior exposure to tacrine had little influence on the treatment effect. Men appeared to benefit more than women by an average of 0.44 points (95% CI: 0.02, 0.84, p=0.04); this differential effect was independent of age.

Clinical Global Impression of Change: the OR for improvement for tacrine, compared with placebo, was 1.58 (95% CI: 1.18, 2.11). There was no significant evidence of heterogeneity between the studies. Relating the treatment effect to average final daily doses provided some evidence for an increasing effect with increasing dose, although the effect was not significant (p=0.09). Age, sex, severity of dementia and prior exposure to tacrine had little influence on the treatment effect. The NNT was 42 (95% CI: 23, 125) when considering marked or moderate improvement and 11 (95% CI: 7, 31) when considering any level of improvement.

Behaviour: standardised difference on the noncognitive portion of the Alzheimer Disease Assessment Scale at 12 weeks showed a 0.58 (95% CI: 0.17, 1.00, p=0.006) difference in favour of tacrine. There was no significant evidence of heterogeneity among the studies. There were no significant effects of dose, age, gender, prior exposure to tacrine or disease severity on the treatment comparison.

Functional autonomy: the Progressive Deterioration Scale (4 studies) showed a standardised difference of 0.75 (95% CI: -0.43, 1.93, p=0.21) at 6 weeks.

Withdrawals: in studies with no dose titration phase (n=5), patients receiving tacrine were significantly more likely to withdraw (OR 3.63, 95% CI: 2.80, 4.71, p=0.001). In some studies, reason for withdrawal was given as elevated transaminase levels. The number of patients needed for one withdrawal was estimated to be 4 (95% CI: 3, 5).

**Authors’ conclusions**

Cholinesterase inhibition with tacrine appears to reduce deterioration in cognitive performance during the first 3 months and increase the odds of global clinical improvement. Effects observed on measures of behavioural disturbance were of questionable clinical significance, and functional autonomy was not significantly affected. The clinical
relevance of the benefits of cholinesterase inhibition remains controversial, and long-term trials with clinically-relevant end points are required.

**CRD commentary**
The inclusion criteria are stated clearly and the literature search seems to have been comprehensive. Some details of the review process (numbers of reviewers involved) are also stated. No validity assessment was undertaken, but this might not have been important given that inclusion was already restricted to double-blind placebo-controlled trials. Study details are not well presented but the method of pooling seems to have been appropriate.

The authors’ conclusions seem to follow from the results presented.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

Research: The authors state that efforts should be directed toward further defining the types of patients and the circumstances in which they may benefit from newer cholinesterase inhibitors, prospectively defining subgroups to assess response and using better measures of important functional and behavioural outcomes. Addressing these issues reliably requires much larger trials, ideally all using a common core set of assessments of behaviour and function, as well as cognition and Clinical Global Impression of Change. None of the cholinesterase inhibitors have reliable controlled data on meaningful outcomes such as dependency and institutionalisation, or other aspects of long-term efficacy; such trials are urgently needed.

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**Other publications of related interest**

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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.