Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis

CRD summary
This review assessed the effectiveness of antithrombotic agents in preventing central venous catheter-related thrombosis. The authors concluded that the limited evidence suggested that heparin did not significantly reduce thrombosis in patients receiviThis review assessed second-generation cholinesterase inhibitors for Alzheimer's disease. The authors concluded that, compared with placebo, cholinesterase inhibitors significantly improve the therapeutic effect and increase adverse events. The conclusions are likely to be reliable, but the variation in the studies must be borne in mind.

Authors' objectives
To assess the efficacy and safety of second-generation cholinesterase inhibitors (ChEIs) for the treatment of Alzheimer's disease (AD).

Searching
MEDLINE and EMBASE were searched from January 1980 to May 2002 for reports published in English; the keywords were listed. The Cochrane Library was searched from inception and reference lists in recent reviews, published reports of clinical trials, and identified studies were checked. The abstract reported that studies were also identified through pharmaceutical companies and journals, but no further details were given. Only original reports were included.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind, placebo-controlled, parallel-group trials were eligible for inclusion.

Specific interventions included in the review
Studies of currently available second-generation ChEIs given in therapeutic doses for at least 12 weeks were eligible for inclusion. The included studies used donepezil (1 to 10 mg/day), rivastigmine (1 to 12 mg/day) and galantamine (8 to 36 mg/day). The duration of treatment ranged from 12 to 54 weeks.

Participants included in the review
Studies of adults with AD were eligible if they were diagnosed using the standardised criteria of the Diagnostic and Statistical Manual of Mental Disorders (4th ed.), or the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association. [A:All but one of the studies were in patients with mild to moderate AD]

Outcomes assessed in the review
Studies that assessed cognitive outcomes using a validated scale were eligible for inclusion. The review assessed global response, cognitive response, any adverse event, drop-outs for any reason, and drop-out due to adverse events. Global response was defined as improvement (excluding 'unchanged' but including 'minimal improvement' or better) on a global assessment scale, either the Clinical Global Impression of Change (CGIC) or Clinician Interview-Based Impression of change plus caregiver input (CIBIC+). Cognitive response was defined as a 4-point or greater improvement on the Alzheimer's Disease Assessment Scale-cognitive portion (ADAS-cog). In the review, an adverse event was defined as any adverse event emerging during treatment as reported by the authors.

How were decisions on the relevance of primary studies made?
Two reviewers (blinded to the authors, location, date and journal of publication) selected the studies and reached consensus through discussion.
Assessment of study quality
Validity was assessed using the Jadad scale, which considers randomisation, blinding and withdrawals. Two reviewers (blinded to the authors, location, date and journal of publication) assessed validity and reached consensus through discussion.

Data extraction
Three reviewers extracted the data on an intention-to-treat basis and reached consensus through discussion (all three reviewers). The extracted data included treatment regimen, number randomised, number completing the study, outcome measures and results. Data were extracted using two different definitions for responders: global response and cognitive response (see Outcomes Assessed in the Review for definitions). The denominator used for calculating the number of patients with adverse events, dropping out for any reason and dropping out because of adverse events, were the intention-to-treat population. Manufacturers were contacted for missing data. For each study, the response rates were calculated for the treatment and placebo groups and the difference in response rates between the two groups was calculated.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis. The pooled difference and 95% confidence interval (CI) was calculated for each outcome using a random-effects model weighted by the sample size and between-study variance. The number-needed-to-treat (NNT), based on global response, and the number-needed-to-harm (NNH), based on the proportion of patients reporting an adverse event, were calculated along with their 95% CIs.

The possibility of publication bias was explored using a funnel plot and tested using the Begg and Mazumdar adjusted rank correlation test.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Subgroup analyses were conducted to assess the effect on the results of the following factors: ethnicity (Asian versus predominantly white patients); drug dose (low versus high; levels were defined for each individual drug in the paper); drug; duration of treatment (shorter term defined as 12 to 14 weeks, compared with longer term defined as 24 to 52 weeks); and CGIC definition (CGIC including the no change category compared with the stricter CGIC classification excluding the minor improvement and no change categories).

Results of the review
Sixteen randomised controlled trials (RCTs; 7,954 patients) were included: 8 RCTs of donepezil, 2 RCTs of rivastigmine and 6 RCTs of galantamine.
All of the included studies scored 4 or 5 points on the Jadad scale.

Global response (9 RCTs, 4,468 patients): statistically significant heterogeneity was detected in the meta-analysis (P=0.002). After excluding the one study of exclusively Japanese patients, heterogeneity was no longer statistically significant (P=0.10). ChEI treatment in predominantly Caucasian populations significantly increased global response rates compared with placebo (8 RCTs, 4,205 patients); the difference was 9% (95% CI: 6, 12). The NNT for non-Asian studies was 12 (95% CI: 9, 16).

Cognitive response (5 RCTs, 2,419 patients): ChEI treatment significantly increased cognitive response rates compared with placebo; the difference was 10% (95% CI: 4, 17). Statistically significant heterogeneity was detected (P=0.01). One study appeared to be responsible for the heterogeneity, but the authors were unable to account for its contribution to the heterogeneity.

Safety (14 RCTs): compared with placebo, ChEI treatment significantly increased adverse events (by 8%, 95% CI: 5, 12), drop-outs (by 8%, 95% CI: 5, 11) and drop-out due to adverse events (by 7%, 95% CI: 3, 10). Statistically
significant heterogeneity was detected for all three meta-analyses. The NNH for adverse events was 12 (95% CI: 10, 18). [A:Donepezil and rivastigmine increased adverse effects compared to placebo. No significant statistical heterogeneity was found for either meta-analysis].

The funnel plots showed no evidence of publication bias.

The results of subgroup analyses according to specific drug, drug dose, duration of treatment and CGIC definition, were also reported.

**Authors' conclusions**
Compared with placebo, ChEIs modestly but significantly improve the therapeutic effect and increase adverse events in patients with AD. The NNT for one patient to benefit was small.

**CRD commentary**
The review question was clear in terms of the study design, intervention, participants and outcomes. A number of relevant sources were searched and the search terms were stated. Full details of the journals searched or the pharmaceutical companies contacted were not given. No attempts were made to minimise language bias. Two or more reviewers selected the studies, assessed validity and extracted the data, which reduces the potential for bias and errors. Validity was assessed using specified established criteria and only double-blind RCTs were included. No information on the characteristics of the participants (e.g. severity of AD) was given.

The data were combined in a meta-analysis and statistical heterogeneity was assessed. Where significant heterogeneity was found for efficacy outcomes, potential causes were explored or considered. The authors pointed out that the heterogeneity of studies assessing cognitive response was unexplained. The authors' conclusions are likely to be reliable, but the heterogeneity of the studies included in the safety analysis must be borne in mind.

Several of the authors have received funding from pharmaceutical companies such as Pfizer, Janssen-Ortho and Neurotherapeutics, Novartis, AstraZeneca, and Merck Sharp Dohme.

**Implications of the review for practice and research**
Practice: The authors stated that the results support current guidelines advocating treatment of AD with ChEIs.

Research: The authors stated that future studies should assess clinically important outcomes such as delay to institutionalisation, maintenance of activities of daily living, and reduced caregiver burden.

**Bibliographic details**

**PubMedID**
12975222

**Original Paper URL**
http://www.cmaj.ca

**Other publications of related interest**
This additional published commentary may also be of interest. Drug therapy for Alzheimer's disease [letters]. CMAJ 2004;170:1371-4.
Indexing Status
Subject indexing assigned by NLM

MeSH
Alzheimer Disease /drug therapy; Cholinesterase Inhibitors /administration & dosage /therapeutic use; Dose-Response Relationship, Drug; Double-Blind Method; Humans; Time Factors; Treatment Outcome

AccessionNumber
12003008601

Date bibliographic record published
30/04/2005

Date abstract record published
30/04/2005

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.