Methodology, results and quality of clinical trials of tacrine in the treatment of Alzheimer's disease: a systematic review of the literature

Arrieta J L, Artalejo F R

Authors' objectives
To systematically review the methodology, results and quality of clinical trials of tacrine in the treatment of Alzheimer's disease (AD).

Searching
The Cochrane Library and MEDLINE were searched from 1 January 1980 to 1 May 1997, using a search strategy proposed by Dickersin et al. (see Other Publications of Related Interest no.2).

Study selection
Study designs of evaluations included in the review
Clinical trials of tacrine in the treatment of AD. The follow-up ranged from 3 to 36 weeks in the randomised trials.

Specific interventions included in the review
Tacrine or placebo-based treatments. The tacrine dosage ranged from 25 to 200 mg/day in the randomised trials.

Participants included in the review
Patients with AD aged 40 years or older. The participants were selected on: (1) the basis of the degree of probability of the diagnosis of AD, as indicated by the National Institute of Neurological and Communicative Disorders, and the Stroke-Alzheimer's Disease and Related Disorders Association criteria; and (2) the degree of severity, as indicated by the Diagnostic and Statistical Manual of Mental Disorders (see Other Publications of Related Interest no.1).

Outcomes assessed in the review
The outcomes assessed were: adverse effects, cognitive function, behavioural, functional ability, global impression of clinical change and global scales of mental deterioration.

How were decisions on the relevance of primary studies made?
The trials were selected by two reviewers working independently, and any differences of opinion were resolved by discussion.

Assessment of study quality
The studies were assessed according to guidelines laid down by the Standards of Reporting Trials Group (see Other Publications of Related Interest no.3). The overall scores were obtained by totalling the points for 32 items, grouped within the following categories: description of the allocation of participants to each treatment; description of the blinding of the intervention and whether this proved successful; description of the patient follow-up and possible losses to follow-up; and description of the statistical analysis in the Methods and Results sections of the paper. The maximum possible score was 32. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The data were extracted by two reviewers working independently, and any differences of opinion were resolved by discussion.

Methods of synthesis
How were the studies combined?
The authors state that due to the heterogeneity between the studies, a statistical synthesis of the study results was not conducted. The studies were discussed in a narrative review, which reported the results according to each outcome measure.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Forty-three trials with 3,555 participants were included in the review. Twenty-one were randomised controlled trials (RCTs), of which 8 were of a parallel-group design and 13 were of a crossover trial design. Twenty-two were non-randomised and/or open trials.

The adverse events were more frequent at doses of at least 100 mg/day and disappeared on the discontinuation of tacrine. The adverse events affected an average (mean) of 59% of patients per trial (range: 34 to 90), mainly in the form of cholinergic manifestations (mean 30.2%, range 5: to 62) and transaminase elevations (mean 28.6%, range: 0 to 53). Over 80% of the patient withdrawals (1,149 of the 3,555 patients failed to complete) were tacrine-related.

Just over 20% of the patients given tacrine experienced improvements (p<0.05) in cognitive functions (3 to 4 points on the Alzheimer's Disease Assessment Scale cognitive subscale and 2 to 3 points on the Mini-Mental State Examination) and in functional ability at 3 to 6 months.

Cost information
The authors state that to be cost-effective, tacrine would have to delay institutionalisation by 9 months, on the basis of evidence drawn from a study by Knopman (see Other Publications of Related Interest no.4).

Authors' conclusions
Tacrine showed a modest dose-dependent degree of efficacy among a small proportion of patients with mild to moderate AD, yet it has important adverse effects which may limit its clinical usefulness. The greatest benefits were obtained at doses of 120 to 160 mg/day, although it was possible to obtain certain benefits at a dosage of 80 mg/day, thereby ameliorating the adverse effects of treatment. It is not known which AD patient subgroup could benefit from the treatment.

CRD commentary
The authors clearly stated their research question and the inclusion and exclusion criteria. There was also a quality scoring for the included trials. The literature search was limited to two databases of published literature and it was not reported whether there were any language restrictions. It is unclear whether additional unpublished or published, non-English studies may have been missed.

The review included non-randomised and randomised trials. It was not possible to combine the trials with a statistical analysis because of heterogeneity between the trials. The RCTs included trials of a crossover design which are not appropriate for the study of a progressive illness such as AD; this is confirmed in a Cochrane review (see Other Publications of Related Interest no.5). Thirteen of the twenty-one RCTs were therefore questionable inclusions in the narrative analysis. The authors stated that they did not combine the trials because of heterogeneity, but how that decision was made was not reported or discussed. There was also a very large number of drop-outs from the trials due to the adverse effects of tacrine. The authors' conclusions should be viewed with caution because of the poor methodological quality of the included trials.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.
Research: The authors state that information on the long-term effects (over 7 months) of tacrine and its effects on the quality of life, patient institutionalisation, mortality and patient burden on care-givers is inadequate. The authors further state that tacrine should be used as a benchmark for the evaluation of other aminoacridines such as donepezil, galantamine and metrifonate as antidementia drugs.

**Funding**
Fondo de Investigacion Sanitaria (Health Research Fund), grant number 96/0477.

**Bibliographic details**

**PubMedID**
16296676

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aged; Alzheimer Disease /drug therapy; Humans; Nootropic Agents /therapeutic use; Randomized Controlled Trials as Topic /methods /statistics & numerical data; Tacrine /therapeutic use

**AccessionNumber**
11998000944

**Date bibliographic record published**
31/12/1999

**Date abstract record published**
31/12/1999

**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.