Authors' objectives
To assess and compare the evidence for the clinical efficacy of individual therapies for Alzheimer's disease (AD).

Searching
PERSUE-McGill University (a search engine providing access to several databases including Applied Science and Technology CINAHL, Core Biomedical Collection, Core Biomedical Collection III, HealthSTAR, MEDLINE and PsycINFO) and the Cochrane Library were searched for trials published after 1986 (search terms reported). In addition, review articles were handsearched and multi-media (newspapers, press clippings and popular magazines) were searched for additional references. Unpublished material and studies reported only as abstracts were excluded from the review. No language restrictions were reported.

Study selection
Study designs of evaluations included in the review
Clinical trials. The authors do not state any further criteria for study design a priori, however only data from randomised controlled trials (RCTs) were presented.

Specific interventions included in the review
Drug therapies for Alzheimer's disease that are on the market (i.e. available to consumers for purchase either by prescription or over the counter) or in Phase III pharmaceutical company clinical trials. Approval by Health Canada Drug Protection Branch or inclusion in a provincial government drug formulary were not considered prerequisites for inclusion. Fourteen therapies were therefore eligible for inclusion: donepezil, metrifonate, rivastigmine, galanthamine, lecithin, vitamin E, selegiline, ginkgo biloba, estrogen, aspirin, indomethacin, prednisone, linopirdine and propentofylline. Various regimens were used.

Participants included in the review
Individuals with Alzheimer's disease (AD). Only studies that used NINCDS/ADRDA diagnostic criteria were included in the review.

Outcomes assessed in the review
The authors do not state any a priori criteria for outcome measures. Outcome measures reported in the review included measures of cognitive performance and patient quality of life as assessed by rating scales (e.g. Alzheimer's Disease Assessment Scale (ADAS-cog), Clinical Global Impression of Change (CGIC) scale, Mini Mental State Examination (MMSE), Activities of Daily Living Checklist (ADLC), Neuropsychiatric Inventory (NPI), Clinical Global Improvement Scale (CGIS)). Adverse events and drop outs were also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection. However, one of the inclusion criteria stated that studies should have a quality score of at least 5 points and three reviewers assessed study quality independently.

Assessment of study quality
Criteria according to Jadad were used (see Other Publications of Related Interest no.1). These criteria were: was the study randomised; was the study described as double-blind; was there a description of withdrawals and drop-outs; was there a clear description of the inclusion/exclusion criteria; was the method used to assess adverse effects described; and were the methods of statistical analysis described? For each of the six Jadad criteria used, one point was awarded for an affirmative response and zero points for a negative response. The maximum possible total score was therefore 6 points. Three reviewers independently assessed blinded copies (i.e. with authors names, journal and study location...
details removed) of the studies. Discrepancies were resolved in a consensus meeting. Studies with a quality score of less than 5 points were excluded from the review.

Data extraction
The reviewers do not specifically state how the data were extracted from the studies. However, three blinded reviewers independently assessed data relating to the quality of the studies, the psychometric properties of the outcome measures used, and the appropriateness of the diagnostic criteria used to decide the eligibility of potential study participants. Data presented in the review tables and text included: bibliographic details, duration of study, quality and design of study, details about the intervention and control groups, participant numbers and entry criteria, outcome measures, results, drop outs, study funding and adverse events.

Methods of synthesis
How were the studies combined?
A narrative synthesis was used.

How were differences between studies investigated?
Some differences between the studies were discussed in the text of the review. Studies were subgrouped according to the treatment type.

Results of the review
26 RCTs (n=7409 participants) were included in the review.

Donepezil (n=4 studies, 1920 participants):
Jadad score ranged from 6-7 points. Overall, donepezil produced modest effects on both cognitive performance and global functioning. In addition, there was little evidence of any improvement in efficacy with the 10mg/day dose over the 5mg/day dose. However, some of the studies suffered from high drop out rates, which could compromise the validity of the findings.

Metrifonate (n=6 studies, 1779 participants):
Jadad score ranged from 5-8 points.
Metrifonate given once daily was quite well tolerated with only a small proportion of participants withdrawing due to adverse effects. All of the trials reported a statistically significant effect of treatment on ADAS-cog scores. However, the magnitude of the effect varied across trials. In general, the placebo groups deteriorated over time whilst the treatment groups did not change or improved slightly. The efficacy of metrifonate appeared to be similar to that of donepezil.

Rivastigmine (n=2 studies, 1424 participants):
Jadad score ranged from 5-8 points. The disparate method of reporting made it difficult to compare the magnitude of the results. The two studies also suffered from a heterogeneous mix of participants, high drop out rates and differences in their statistical analyses. However, both studies reported an improvement on the Progressive Deterioration Scale for those assigned to the high dose treatment group as compared to placebo with no apparent benefit from low dose rivastigmine.

Lecithin (n=1 study, 440 participants):
Jadad score = 5 points. The efficacy of lecithin is unclear from this one study. The selection procedure used (based on a good response to tacrine) may have prejudiced the results and the four week duration of the study was probably too short to demonstrate any beneficial effects considering the slow steady progression of the disease. In addition, not all of the data were presented for the study and there was no clear placebo comparison.
Selegiline (including vitamin E) (n=7 studies, 635 participants):

Jadad score ranged from 5-8 points. Selegiline, although promising with its antioxidant activity, was not convincingly shown to be efficacious in any of the trials. Some improvement was found on a few items of the cognitive scales used but these changes did not correlate with changes in patient behaviour. Despite the lack of efficacy, it is notable that this drug exhibited a low incidence of adverse effects, none of which were serious enough to interrupt treatment.

Ginkgo Biloba (n=3 studies, 493 participants):

Jadad score = 7 points. The trials differed in duration, treatment regimens, outcome measures and sample size. In addition, only one of the trials was restricted to participants with AD and presented data on adverse effects and dropouts. Overall, there was little or no impact of treatment on global impairment.

Linopirdine (n=1 study, 375 participants):

Jadad score = 6 points. Based on only the one trial, linopirdine doses do not appear to have beneficial effects. This, along with the associated risk of liver compromise, casts doubt on the drugs clinical usefulness.

Propentofylline (n=2 studies, 343 participants):

Jadad score = 5 points. Propentofylline appears to have small beneficial global and cognitive effects with long-term administration, although the clinical relevance of these effects is uncertain. The drug also appears to have a safe profile even after one year of continuous use.

There were no RCTs involving galanthamine, estrogen, aspirin, indomethacin, or prednisone.

Authors' conclusions

Donepezil, metrifonate and rivastigmine all provide statistically significant modest benefit on cognitive performance and global functioning to the elderly with probable AD whom are eligible for inclusion in clinical trials. In the absence of trials of longer duration, there is little evidence that these agents are more than symptomatic treatments. The efficacy of ginkgo biloba as a treatment for AD appears to be less than that of any of the above AChE inhibitors. Although all of these medications appear to be well tolerated, in terms of the occurrence of adverse events, drop-out rates are sometimes high and may have resulted in an overestimation of apparent treatment effects.

CRD commentary

This review was based on a reasonable search of the literature for published data, though details of the search strategy were not presented. In addition, unpublished data were not included in the review therefore increasing the risk of publication bias. The a priori criteria for inclusion especially with regards to outcomes and study design were also not clearly presented. The methods used for selecting the studies and for assessing their quality were clearly stated, but it was not clear how data were extracted for the review and how many reviewers were involved.

The studies were summarised using a narrative synthesis, which given the differences between the studies appears to be appropriate. Details of the studies were summarised both within data tables and within the text of the review. Overall, the findings of the review appeared to be supported by the data presented.

Implications of the review for practice and research

Practice: The authors do not state any implications for practice.

Research: The authors highlight a number of deficiencies in the trials which should be considered in future research. Methods of trial reporting should be consistent (i.e. in terms of duration, study design, outcome measures etc.) since at present a wide variety of outcome scales are used which often do not have adequate psychometric assessment.
Bibliographic details

Original Paper URL

Other publications of related interest

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Subject indexing assigned by CRD

MeSH
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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.