Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis

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CRD summary
This review concluded that cholinesterase inhibitors (donepezil, galantamine and rivastigmine) were able to stabilise or slow decline in cognition, function, behaviour and global change when compared with placebo. There was no clear evidence to determine whether one of these drugs was more efficacious than another. The review was generally well conducted and the conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy and safety of cholinesterase inhibitors (donepezil, galantamine and rivastigmine) for the treatment of Alzheimer's disease.

Searching
MEDLINE, EMBASE, The Cochrane Library and IPA databases were searched from 1980 to July 2007. US Center for Drug Evaluation and Research and ClinicalTrials.gov were handsearched. Reference lists of relevant publications were screened.

Study selection
Randomised controlled trials (RCTs) that compared one cholinesterase inhibitor with another cholinesterase inhibitor or placebo in community dwelling and nursing home patient populations with Alzheimer's disease were eligible for inclusion. Studies were excluded if there were significant baseline differences between treatment groups. Eligible placebo-controlled trials had to be double-blinded. Eligible trials had to last at least 12 weeks and report at least one measure that evaluated cognition, function, behaviour or clinical global assessment of change. The safety outcome was incidence of adverse events.

The included studies administered donepezil in doses that ranged from 5mg to 10mg per day, galantamine in doses that ranged from 8mg to 32mg per day and rivastigmine in doses that ranged from 3mg to 12mg. Treatment durations of trials ranged from 12 to 104 weeks. Most of the included studies were of patients with mild to moderate dementia. Where reported, patient age ranged from 69 to 78 years. Most of the included patients were female.

The authors did not state how many reviewers assessed studies for inclusion.

Assessment of study quality
Study quality was assessed using criteria of randomisation, allocation concealment, baseline comparability, intention-to-treat analysis and loss to follow-up. Studies with a fatal flaw in one or more categories were rated as poor quality and excluded from the analysis.

Two independent reviewers performed validity assessment. Any disagreements were resolved by discussion or a third reviewer.

Data extraction
For continuous outcomes, mean and standard deviation were extracted to enable the calculation of mean difference (MD) and 95% confidence interval (CI). For dichotomous outcomes, event rate was extracted to enable the calculation of relative risk (RR) and 95% CI.

It appeared that data were extracted by two reviewers and checked by a third.
Methods of synthesis
Placebo-controlled trials were combined in meta-analyses using a random-effects model. Weighted mean differences (WMDs) with 95% CIs were calculated if outcomes were assessed using the same measurement scale. Standardised mean differences (SMDs) with 95% CIs were calculated if the outcomes were assessed using a number of different measurement scales. Pooled relative risks with 95% CIs were calculated for dichotomous outcomes. Statistical heterogeneity was assessed using $I^2$ statistic. Publication bias was assessed using funnel plots. Sensitivity analyses were performed on different doses. In the absence of head-to-head evidence for most of the drug comparisons, adjusted indirect comparison was employed to estimate the relative efficacy of the three drugs.

Results of the review
Twenty-six RCTs (22 placebo-controlled trials and four head-to-head trials) were included in the review. The total number of included patients was not reported. Where reported, 19 trials were judged as fair quality and four trials as good quality.

Compared with placebo, a significant improvement in cognition based on ADAS-cog scores was observed for donepezil (WMD -2.67, 95% CI -3.28 to -2.06; seven treatment comparisons), galantamine (WMD -2.76, 95% CI -3.17 to -2.34; 10 treatment comparisons) and rivastigmine (WMD -3.01, 95% CI -3.80 to -2.21; two RCTs). Significant heterogeneity was found only for the pooled outcome of rivastigmine ($I^2=70\%$).

Compared with placebo, a significant improvement in functional outcome change was observed for donepezil (SMD 0.31, 95% CI 0.21 to 0.40; eight treatment comparisons), galantamine (SMD 0.27, 95% CI 0.18 to 0.36; six treatment comparisons) and rivastigmine (0.26, 95% CI 0.11 to 0.40; three RCTs). No significant heterogeneity was found for these outcomes.

A significant improvement in behaviour based on the Neuropsychiatric Inventory was found for donepezil (WMD -4.3, 95% CI -5.95 to -2.65; four RCTs) and galantamine (WMD -1.44, 95% CI -2.39 to -0.48; five treatment comparisons) compared with placebo. No significant heterogeneity was found for all these outcomes.

A significant increase in responding to the treatment was observed for donepezil (RR 1.88, 95% CI 1.50 to 2.34; six treatment comparisons) and rivastigmine (RR 1.64, 95% CI 1.29 to 2.09; two RCTs) compared with placebo, but not for galantamine (RR 1.15, 95% CI 0.96 to 1.39; five treatment comparisons). No significant heterogeneity was found for these outcomes.

Potential publication bias was found only for the outcome of global assessment of change (funnel plots were not presented). Sensitivity analyses by dose did not significantly alter the results.

In head-to-head comparisons, one trial found donepezil to be more efficacious than galantamine and one study found rivastigmine to be more efficacious than donepezil. Two studies showed no significant difference in efficacy between these drugs.

Adjusted indirect comparisons did not show significant differences in cognition between drugs, but found global response to be better with donepezil and rivastigmine than with galantamine. The results favored donepezil over galantamine regarding the outcome of behaviour.

The most frequently reported adverse events were nausea, diarrhoea, dizziness and weight loss. Incidence of these adverse events between trials was consistently lowest for donepezil and highest for rivastigmine.

Authors' conclusions
Cholinesterase inhibitors (donepezil, galantamine and rivastigmine) were able to stabilise or slow decline in cognition, function, behaviour and global change when compared with placebo. There was no clear evidence to determine whether one of these drugs was more efficacious than another. Incidence of common adverse events appeared to be lowest with donepezil and highest with rivastigmine.

CRD commentary
This review's inclusion criteria were clear. Relevant databases were searched. Efforts were made to find both published
and unpublished studies, which reduced potential for publication bias. Publication bias was assessed and little evidence of it was found for most outcomes. It was unclear whether language restrictions were applied to the search, which made the risk of language bias difficult to assess. Steps were made to minimise reviewer errors and biases in the processes of data extraction and validity assessment; it was unclear whether study selection was performed in duplicate. Appropriate criteria were used to assess study quality. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The authors' conclusions reflected the evidence presented. There was limited reporting of some aspects, but this review was generally well conducted and the conclusions are likely to be reliable.

**Implications of the review for practice and research**

*Practice*: The authors did not state any implications for practice.

*Research*: The authors stated that further high-quality comparative evidence was required to confirm the conclusions from this review.

**Funding**

Partly funded by Cecil G Sheps Center for Health Services Research through the Center for Evidence-Based Policy; Oregon Health and Science University; one author was supported by grant K12RR023248.

**Bibliographic details**


**PubMedID**

18686744

**DOI**

10.2147/CIA.S

**Original Paper URL**

http://www.dovepress.com/articles.php?article_id=1747

**Other URL**

http://ukpmc.ac.uk/abstract/MED/18686744

**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Alzheimer Disease /drug therapy; Cholinesterase Inhibitors /therapeutic use; Galantamine /therapeutic use; Humans; Indans /therapeutic use; Phenylcarbamates /therapeutic use; Piperidines /therapeutic use; Rivastigmine; Treatment Outcome

**AccessionNumber**

12008106535

**Date bibliographic record published**

19/06/2008
03/02/2009

Date abstract record published
01/06/2011

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.