A comparison of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease: a meta-analysis

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CRD summary
This review compared donepezil and galantamine separately with placebo. The authors concluded that the drugs have limited effects on measures of cognitive ability, and that galantamine is not superior to donepezil. The first conclusion should be treated with caution because of methodological limitations in the review, while the second could not be reliably obtained by considering only placebo-controlled trials.

Authors' objectives
To evaluate the efficacy of donepezil and galantamine in the treatment of cognitive symptoms of Alzheimer's disease (AD). A stated secondary objective was to determine whether galantamine is superior to donepezil.

Searching
The authors searched PsycINFO and PubMed for studies published after 1984 (the search terms were reported) and carried out manual searches (no details were reported).

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Placebo-controlled trials of donepezil and galantamine were eligible for inclusion. In the included studies, the doses used were 5 and 10 mg/day for donepezil and 8 to 36 mg/day for galantamine. The study duration ranged from 12 to 24 weeks for donepezil and from 3 to 6 months for galantamine.

Participants included in the review
The participants were patients with mild to moderate AD without any other psychiatric or neurological disorder. The mean age of the participants ranged from 69.8 to 73.7 years for donepezil studies and from 72.5 to 76.8 years for galantamine studies. The proportion of male participants ranged from 33 to 38% for donepezil and from 36 to 44% for galantamine.

Outcomes assessed in the review
The studies were required to report measures of cognitive ability and provide sufficient data to allow the calculation of an effect size. Donepezil studies reported the AD assessment scale-cognitive (ADAS-cog), the Japanese version of the ADAS-cog (ADAS-Jcog) and the mini-mental state examination (MMSE). All the galantamine studies used the ADAS-cog as a measure of cognitive ability.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

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

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
extraction. ADAS-cog and MMSE scores (mean and standard deviation (SD) or standard error) in each group were used to calculate the effect size (difference in means) for each study.

Methods of synthesis
How were the studies combined?
Studies of each drug were combined in separate meta-analyses using Cohen's d statistic (standardised mean difference) as a measure of effect. The fail-safe N statistic (number of negative studies that would be needed to overturn the observed treatment effect) was used to assess publication bias.

How were differences between studies investigated?
The authors did not state that they assessed heterogeneity between the studies.

Results of the review
Three RCTs (n=1,054) of donepezil and five RCTs (n=3,353) of galantamine were included.

The mean d for the donepezil studies was 0.48 (SD=2.25) for ADAS-cog/Jcog and -0.36 (SD=0.03) for MMSE scores; both represented a small to medium positive treatment effect compared with placebo.

For galantamine studies the mean d was 0.52 (SD=0.10), suggesting a medium positive effect of the drug on ADAS-cog scores compared with placebo.

The fail-safe N values were 7 for donepezil (ADAS-cog/Jcog), 4 for donepezil (MMSE) and 20 for galantamine. These suggested that the observed results could be overturned by a relatively small number of negative studies.

Authors' conclusions
Donepezil and galantamine are not greatly efficacious for treating the cognitive symptoms of AD. Galantamine is not superior to donepezil.

CRD commentary
The review question and inclusion criteria were clear, although the stated objective of comparing donepezil and galantamine could not be met by considering only placebo-controlled trials. The authors searched a limited range of sources and did not search for unpublished material, so it is possible that some relevant studies could have been missed. The validity of the included studies was not formally assessed, although the limitation to double-blind RCTs provides a basic level of validity assessment. Some details of the included studies were presented, although results of individual studies would have been helpful in interpreting the reported treatment effects. The methods used to select studies and extract the data were not reported, so it is difficult to comment on the risk of bias and errors being introduced during the review process. Publication bias was assessed, but the method used was not the best because it relies on assumptions about the treatment effect in hypothetical unpublished studies. Studies of each drug were combined by meta-analysis but, since potential sources of heterogeneity were not assessed, the results of the meta-analysis may not be reliable. In view of these limitations, the authors' conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that, despite their modest effects, donepezil and galantamine have practical value for the treatment of cognitive symptoms of AD.

Research: The authors stated that a meta-analysis of the effects of donepezil and galantamine on functional performance and quality of life may give a better idea of the efficacy and usefulness of these drugs.

Bibliographic details

PubMedID
15700322

DOI
10.1002/hup.676

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Alzheimer Disease /drug therapy /psychology; Cholinesterase Inhibitors /therapeutic use; Cognition Disorders /drug therapy /etiology /psychology; Galantamine /therapeutic use; Humans; Indans /therapeutic use; Male; Nootropic Agents /therapeutic use; Piperidines /therapeutic use; Treatment Outcome

AccessionNumber
12005000020

Date bibliographic record published
31/05/2006

Date abstract record published
31/05/2006

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.