Clinical and cost-effectiveness of donepezil rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review

Authors' objectives
To provide a rapid and systematic review of the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine and galantamine in the symptomatic treatment of people suffering from Alzheimer's disease (AD).

Searching
The following databases were searched from their inception to March to July, 2000: MEDLINE, EMBASE, the Cochrane Library, DARE, NHS EED, the National Research Register, the Science Citation Index, BIOSIS Previews, EconLit, the MRC Clinical Trials Directory, an Early Warning System database, Current Controlled Trials Register, TOXLINE, Index to Scientific and Technical Proceedings, and GEARs. The search dates for each database and the search terms used were provided in an appendix. The bibliographies of related papers were examined and experts were contacted for additional published or unpublished studies. The manufacturers of the drugs also provided information for the review.

The authors did not report any contact with the authors of the included studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and systematic reviews of RCTs were eligible for inclusion. Studies published in languages other than English were excluded. Systematic reviews published as abstracts or conference presentations were also excluded.

Specific interventions included in the review
Studies assessing donepezil, rivastigmine or galantamine were eligible for inclusion. The review included studies that compared the drugs with each other or with another form of treatment, such as rehabilitation or specialist clinics. The included studies investigated donepezil, rivastigmine or galantamine at various doses and durations in comparison with placebo.

Participants included in the review
AD. Studies investigating the drugs in persons with AD were eligible for inclusion.

Outcomes assessed in the review
Studies reporting the effect of the drugs on changes in cognition, function, behaviour, mood, quality of life or time to institutionalisation, were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The titles and abstracts of the studies identified were screened independently by two reviewers, and the full-text copies of studies appearing to pass the inclusion and exclusion criteria were retrieved. Two reviewers then independently assessed the full-text of these studies against the full inclusion and exclusion criteria, and resolved any discrepancies by discussion.

Assessment of study quality
The quality of the included systematic reviews was assessed using a checklist NHS Centre for Reviews and Dissemination (CRD; see Other Publications of Related Interest no.1), while the quality of the included RCTs was assessed using the method described by Jadad et al. (see Other Publications of Related Interest no.2). Both of these quality assessment tools have been validated and are widely used. The validity of the included studies was assessed by one reviewer and checked by a second. Any discrepancies were resolved by discussion between the reviewers.
Data extraction
The data were extracted from the included studies by one reviewer and checked by a second. Any discrepancies were resolved by discussion between the reviewers.

The data extracted from the systematic reviews included: study authorship; publication year; country; study design; research question; search strategy details; inclusion and exclusion criteria; interventions; patient characteristics; results, i.e. global, cognitive, and functional and quality of life outcome measures, and information on adverse effects; methodology used; general comments; and the overall CRD quality score and the criteria assessed.

The data extracted from the RCTs included: study authorship; publication year; study design; intervention details including drug, dose and duration, and details of cointerventions; the total number of patients in each arm; characteristics of the target population; exclusion criteria; details of the participants; study setting; results, i.e. global, cognitive, and functional and quality of life outcome measures, and information on adverse effects; methodology used; general comments; and the overall Jadad quality score and the criteria assessed.

The extracted data were presented in tabular format: a summary of the data was tabulated in the main body of the report, while more comprehensive tables of data were provided in the appendices.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the agent being investigated, i.e. studies which investigated donepezil, rivastigmine or galantamine were grouped with other studies assessing the same drug.

A narrative overview was presented. This commented on the quantity and quality of the research evidence base for the use of each drug in the treatment of AD, and on the clinical effectiveness (including adverse effects) of the drug.

The authors did not pool the studies in a meta-analysis.

How were differences between studies investigated?
The authors do not report a formal assessment of the heterogeneity of the studies. However, they did discuss some elements that may have led to differences between the studies. This included the quality of the studies, variability of the inclusion and exclusion criteria, variations in the doses of individual drugs, and differences in the follow-up procedures.

Results of the review
A total of 26 studies were included. Twelve studies investigated donepezil: 3 systematic reviews, 5 RCTs (n=1,980) and 4 studies submitted by the drug manufacturers as 'Commercial in Confidence' (CIC; n=1,133). Ten studies investigated rivastigmine: 3 systematic reviews, 5 RCTs (n=1,990) and 2 studies submitted as CIC (n=1,380). Six studies investigated galantamine: no systematic reviews, 3 RCTs (n=1,614) and 3 studies submitted as CIC (n=1,324).

Donepezil.
The information found suggested that donepezil is beneficial for the treatment of patients with mild to moderate AD when assessed using both global and cognitive outcome measures. However, the effects were small and may not translate into a clinical benefit. The side-effects included nausea, vomiting and diarrhoea but these were usually mild and transient. The generalisability of these findings may be limited to those patients with mild to moderate AD, and to those with limited co-morbidity or concomitant interventions.

Rivastigmine.
The information found suggested that rivastigmine is beneficial for the treatment of patients with AD when assessed using both global and cognitive outcome measures. Statistically-significant cognitive and functional outcomes were not reported in all studies. Improvements on these scales may not lead to clinical improvement. The adverse events included nausea, vomiting diarrhoea, headaches, dizziness, abdominal pain, fatigue, malaise, anxiety and agitation. The
generalisability of these findings may be limited to those patients with mild to moderate AD.

Galantamine.

The information found suggested that galantamine is beneficial for the treatment of patients with AD when assessed using global, cognitive and functional scales. Statistically-significant improvements were reported in the two better quality studies investigating galantamine. The common adverse events were mostly gastrointestinal and most events were mild. The generalisability may be limited to patients with mild AD.

The results of the individual studies were presented in tabular format in the main report and in extensive appendices. However, no pooled estimate of the overall effect of any of the drugs was calculated.

Cost information
Nine economic studies were found, which could not be closely compared.

Donepezil.

The five studies of donepezil produced a variety of cost-effectiveness estimates. While the base-cases showed increased effectiveness and were cost-saving in two studies, they were more costly in the other three. When sensitivity analyses were taken into consideration, the estimates showed wider fluctuations and there were, in some cases, conflicting results for the subgroup analyses, thus casting doubt on the robustness of the estimates.

Rivastigmine.

Of the four rivastigmine studies, the oldest has been surpassed by more recent evaluations. The cost-effectiveness ratios in two studies could not be extracted, as the associated overall effectiveness was not reported; in addition, it was difficult to interpret the cost results alone since the costs of drug therapy were excluded. The fourth study found average net costs within the first year, but a cost-saving at 2 years, but it was unclear whether the data presented could be translated into incremental cost-effectiveness ratios.

Galantamine.

No published economic evaluations of galantamine were found.

There was a further economic analysis for each drug; this was conducted by the drug manufacturer and submitted as CIC.

Authors' conclusions
On the basis of the current evidence, the implications of the use of donepezil, rivastigmine or galantamine to treat patients with AD are unclear.

CRD commentary
The review question was well presented in terms of the interventions, participants, outcomes and study designs that were eligible for inclusion in the review. The review benefited from the fact that the review processes (i.e. study identification, study selection, data extraction, quality assessment and data synthesis) were explained in a clear and concise fashion. Inclusion of the original protocol was also informative. In particular, the transparency of the report benefited from details of the number of studies excluded at each stage of the identification process, and the reasons why these studies were not included in the review.

One serious limitation was restricting the included studies to those published in full and in the English language. These exclusion criteria may very well have caused pertinent studies to be missed.

The studies were presented in a very detailed manner. The conclusions drawn, and the subsequent recommendations,
appear to follow from the information given. However, there was some duplication in the presentation of the results, which could lead to confusion for the reader: a summary table was presented in the body of the report, while more comprehensive tables were provided in the appendices.

Overall, the methodological rigour of both the review and of the included studies (RCTs and systematic reviews) would suggest that the conclusions of the review are accurate.

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

Practice: The authors state that, currently, there is uncertainty as to whether the modest benefits seen in the outcome measures used in the trials would translate into significant benefits to the patients. The practical economic implications of prescribing these drugs are also uncertain. The main economic issue is not the drug costs per se, but the impact across different sectors. Currently, this remains unclear since the financing and provision of care for patients with AD in England and Wales is complex and difficult to unravel. Any cost-savings would depend mainly on the release of funds from residential care.

Research: The authors state that future research is needed. This should address the following: the development of quality-of-life instruments for patients and their carers; comparisons of benefits from drugs with those from other interventions; the identification of those patients likely to benefit from drug treatment; the development of protocols for withdrawal if the treatment is not beneficial; and economic evaluations of the interventions.

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