Executive summary

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

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Executive summary

Background
Alzheimer’s disease is the most common cause of dementia and is characterised by an insidious onset and slow deterioration. The estimated prevalence of Alzheimer’s disease for a standard health authority (500,000 people) is about 3330. Current service involves a wide range of agencies, and drug therapy for some patients.

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.

Methods
A systematic review of the literature was undertaken.

Data sources
Searches were made of electronic databases, including MEDLINE, EMBASE, The Cochrane Library, Database of Abstracts of Reviews of Effectiveness, NHS Economic Evaluation Database, National Research Register, Science Citation Index, BIOSIS, EconLit, MRC Trials database, Early Warning System, Current Controlled Trials, TOXLINE, Index of Scientific and Technical Proceedings, and Getting Easier Access to Reviews. All sources were searched over the period covered by the databases up to March/July 2000. Bibliographies of related papers were assessed for relevant studies and experts were contacted for advice and peer review, and to identify additional published and unpublished references. Manufacturer submissions to the National Institute for Clinical Excellence (NICE) were reviewed.

Study selection
Studies were included if they fulfilled the following criteria.

- Intervention: donepezil, rivastigmine or galantamine used to treat Alzheimer’s disease.
- Participants: people diagnosed with Alzheimer’s disease who meet the criteria for treatment with donepezil, rivastigmine and galantamine.
- Outcomes: measures assessing changes in cognition, function, behaviour and mood, quality of life (including studies assessing carer well-being and carer-input), and time to institutionalisation.
- Design: systematic reviews of randomised controlled trials (RCTs) and RCTs comparing donepezil, rivastigmine or galantamine with placebo or each other or non-drug comparators were included in the review of effectiveness. Economic studies of donepezil, rivastigmine or galantamine used to treat Alzheimer’s disease that included a comparator (or placebo) and both the costs and consequence (outcomes) of treatment were included in the review of cost-effectiveness.

Data extraction and quality assessment
Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. The quality of RCTs was assessed using the Jadad scale and the quality of systematic reviews was assessed using criteria developed by the NHS Centre for Reviews and Dissemination. The quality of economic evaluation studies was assessed by their internal validity (i.e. the methods used) using a standard checklist, and external validity (i.e. the generalisability of the economic study to the population of interest) using a series of relevant questions.

Data synthesis
The clinical effectiveness and cost-effectiveness of donepezil, rivastigmine and galantamine were synthesised through a narrative review with full tabulation of results of all included studies. In the
economic evaluation, the reviewers assessed whether adjustments could be made to existing models to reflect the current situation in England and Wales.

Results

Clinical effectiveness
- Donepezil – three systematic reviews and five RCTs (plus four studies from industry*) were found. Results suggest that donepezil is beneficial when assessed using global and cognitive outcome measures.
- Rivastigmine – three systematic reviews and five RCTs (plus two studies from industry*) were found. Results suggest that rivastigmine is beneficial in terms of global outcome measures.
- Galantamine – one systematic review and three RCTs (plus three studies from industry*) were found. Results suggest that galantamine is beneficial in terms of global, cognitive and functional scales.

Summary of benefits
It is difficult to quantify benefits from the evidence available in the literature. Statistically significant improvements in tests such as ADAS-cog (Alzheimer’s Disease Assessment Scale cognitive subscale) may not be reflected in changes in daily life.

Costs/cost-effectiveness
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 are taken into consideration, estimates fluctuated more widely and there were, in some cases, conflicting results for sub-group 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. Cost-effectiveness ratios in two studies could not be extracted as the associated overall effectiveness was not reported and interpretation of the costs results alone is difficult due to the exclusion of drug therapy costs. The fourth study found average net costs within the first year, but a cost saving at 2 years, but it was not clear whether the data presented could be translated into incremental cost-effectiveness ratios.
- Galantamine – no published economic evaluations of galantamine were found.

For each drug there was a further economic analysis performed by industry*.

Economic implications of prescribing these drugs are uncertain. The main issue is not drug costs per se, but the impact across different sectors. Currently, this remains unclear since the financing and provision of care for patients with Alzheimer’s disease in England and Wales is complex and difficult to unravel. Any cost savings would depend mainly on release of funds from residential care.

Conclusions
Implications
On the basis of the current evidence, the implications of the use of donepezil, rivastigmine or galantamine to treat patients with Alzheimer’s disease are unclear. The main issue is whether the modest benefits seen in the outcome measures used in the trials would translate into benefits significant to patients.

Future research
Future research should include: development of quality-of-life instruments for patients and their carers; comparisons of benefits from drugs with those from other interventions; identification of those patients likely to benefit from drug treatment; development of protocols of treatment withdrawal if not beneficial; economic evaluations. Ongoing research should provide valuable evidence.

Publication

* Unpublished data, submitted as commercial in confidence
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