Donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease

The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease

E Loveman,* C Green, J Kirby, A Takeda, J Picot, E Payne and A Clegg

Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton, UK

* Corresponding author

Executive summary

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Executive summary

Epidemiology and background

Alzheimer's disease (AD) is the most common cause of dementia and is characterised by an insidious onset and slow deterioration in cognition, functional ability (e.g. activities of daily living) and behaviour and mood. AD prevalence rises with increasing age and the estimated prevalence of AD for a standard primary care trust with a population of 200,000 is approximately 1100. Current service involves a wide range of agencies. In 2001, the National Institute for Health and Clinical Excellence (NICE) recommended that cholinesterase inhibitors (donepezil, rivastigmine, galantamine) should be offered to patients with mild to moderate AD under a number of conditions. Patients with more severe AD may benefit from memantine but there is currently no guidance on its use.

Aim of the review

The aim of this review was to provide an update review of the best quality evidence for the clinical effectiveness and cost-effectiveness of donepezil, rivastigmine, and galantamine for mild to moderately severe AD. It also aimed to provide a review of the best quality evidence for the clinical effectiveness and cost-effectiveness of memantine for moderately severe to severe AD.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

Electronic databases were searched from inception to July 2004. Bibliographies of included studies and related papers were checked for relevant studies and experts were contacted for advice and peer review and to identify additional published and unpublished studies. Manufacturer submissions to NICE were reviewed.

Study selection

Studies were included if they met the following criteria.

- Interventions: donepezil, rivastigmine, galantamine or memantine.
- Participants: people diagnosed with Alzheimer's disease who met the criteria for treatment with donepezil, rivastigmine, galantamine or memantine.
- Design: systematic reviews of randomised controlled trials (RCTs) and RCTs comparing the different drugs with placebo or each other or non-drug comparators were included in the review of effectiveness. Economic evaluations including a comparator (or placebo) and both the costs and consequences (outcomes) of treatment were included.
- Primary outcomes: measures of global functioning, cognition, function, behaviour and mood, and health-related quality of life.

Studies in non-English languages were excluded. Studies published only as abstracts or conference presentations were included if sufficient detail was presented. Titles and abstracts were screened for eligibility by one reviewer and checked by a second reviewer. Inclusion criteria were applied to the full text of selected papers by two reviewers. Any differences in opinion were resolved though discussion or consultation with a third reviewer.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any differences in opinion resolved through discussion. The quality of included RCTs was assessed using criteria developed by the NHS Centre for Reviews and Dissemination. An outline assessment of economic evaluations was undertaken using a standard checklist.

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Data synthesis

The clinical and cost-effectiveness data were synthesised through a narrative review with full tabulation of the results of included studies. Where appropriate, meta-analysis of data was undertaken.

Results: clinical effectiveness

Donepezil

Thirteen published RCTs and one unpublished RCT were included. The results suggest that donepezil is beneficial when assessed using global and cognitive outcome measures. There appears to be a dose–response relationship with higher doses more likely to produce benefit. Mixed results were demonstrated on measures of function and behaviour and mood; over shorter durations of follow-up (up to 6 months) donepezil may be beneficial when assessed using these outcome measures.

Rivastigmine

Four published and two unpublished RCTs were included. The results suggest that rivastigmine is beneficial when assessed using global and cognitive outcome measures. The benefits demonstrated may be related to dose, with higher doses more likely to produce benefit. Results for measures of function were mixed: rivastigmine was beneficial at higher doses in some studies. There was no reported beneficial effect of rivastigmine on measures of behaviour and mood.

Galantamine

Six published RCTs and one unpublished RCT were included. The results suggest that galantamine is beneficial when assessed using cognitive and functional outcome measures. The benefits demonstrated may be related to dose, with higher doses more likely to produce benefit. Mixed results were demonstrated on global outcome measures and on measures of behaviour and mood.

Memantine

Two published RCTs were included; in one of these trials the participants were already being treated with donepezil. The results suggest that memantine is beneficial when assessed using functional and global measurements. The effect of memantine on cognitive and behaviour and mood outcomes is, however, less clear.

Results: cost-effectiveness

Donepezil

Nine published economic evaluations of donepezil and the industry submission were included, together with two published abstracts. The literature is dominated by industry-sponsored cost-effectiveness studies and the studies identified report varied methodology and results. There are concerns over the dominant use of mini-mental state examination (MMSE) to consider disease progression, costs and outcomes in the published cost-effectiveness studies, as it has limitations for defining disease severity and also in the modelling of disease progression in AD. From a UK perspective, of three UK studies, two report donepezil as not cost-effective, whereas a third study reports an additional cost (£1996) of between £1200 and £7000 per year in a non-severe AD health state (concerns over these estimates are raised, suggesting that they may underestimate the true cost-effectiveness of donepezil). Cost-effectiveness analysis undertaken in the present review suggests that donepezil treatment has a cost per quality-adjusted life-year (QALY) in excess of £80,000, with donepezil treatment reducing the mean time spent in full-time care (delays progression of AD) by 1.42–1.59 months (over a 5-year period); cost savings associated with this reduction do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels generally considered acceptable by NHS policy makers.

Rivastigmine

Four published economic evaluations of rivastigmine and the industry submission were included, plus one published abstract. The literature is dominated by industry-sponsored cost-effectiveness studies. Cost-effectiveness studies for rivastigmine are based almost solely on methods involving MMSE as a measure of cognitive function, with rivastigmine treatment related to delays in cognitive function and patient benefits over time. As noted above, there are concerns over the use of cognitive function (e.g. MMSE) alone to consider progression of AD. From a UK perspective, two UK cost-effectiveness studies report additional costs associated with rivastigmine treatment. Cost-effectiveness analysis undertaken in the current review suggests that rivastigmine treatment has a cost per QALY in excess of £57,000, with rivastigmine treatment reducing the mean time spent in full-time care (delays progression) by 1.43–1.63 months (over a 5-year period); cost savings associated with this reduction do not offset the cost of treatment sufficiently to make it appear a cost-effective intervention. ►

Galantamine

Five published economic evaluations of galantamine (industry sponsored) plus the industry submission were included. Cost-effectiveness studies for galantamine have all used the same methodology to model disease progression over time, with country-specific cost-effectiveness studies published. From a UK perspective, one UK study reports a cost per QALY of £8693 for 16-mg galantamine treatment and £10,051 for 24-mg galantamine treatment (concerns over these estimates are raised, suggesting that they may underestimate the true cost-effectiveness of galantamine). Cost-effectiveness analysis undertaken in the present review suggests that galantamine treatment has a cost per QALY in excess of £68,000, with galantamine reducing the time spent in full-time care (delays progression) by 1.42–1.73 months (over a 5-year period); cost savings associated with this reduction do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels generally considered acceptable by NHS policy makers.

Memantine

Two published (in press at the time of the study) economic evaluations and the industry submission were included, plus three published abstracts. Published studies (industry sponsored) have used a similar methodology to consider disease progression for AD. One cost-effectiveness study reports analysis for the UK, finding that memantine treatment results in cost savings and benefits in terms of delaying disease progression (concerns over these estimates are raised, suggesting that they may underestimate the true cost-effectiveness of memantine). In the current review, the cost-effectiveness of memantine has not been modelled separately, but where alternative parameter inputs on the cost structure and utility values have been used in a reanalysis using the industry model, the cost-effectiveness is reported at between £37,000 and £52,000 per QALY, with this alternative analysis still based on what is regarded as an optimistic or favourable effectiveness profile for memantine.

Generalisability of the findings

A number of issues need to be considered when assessing the results of the present review. These include the characteristics of the participants included in the individual trials, the outcome measures used, the length of study duration, the effects of attrition and the relationship between statistical significance and clinical significance. Many included trials were sponsored by industry.

Need for further research

Future research should include: information on the quality of the outcome measures used; development of quality of life instruments for patients and carers; studies assessing the effects of these interventions of durations longer than 12 months; comparisons of benefits between interventions; and research on the prediction of disease progression.

Publication

Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. *Health Technol Assess* 2006;**10**(1).

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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