Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil

Stewart A, Phillips R, Dempsey G

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The health technology studied was donepezil, a piperidine-based derivative used for the treatment of patients suffering from Alzheimer disease (AD).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients suffering from AD.

Setting
The setting was community. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness evidence and resource use data were gathered from studies published between 1987 and 1998. The price year was 1997.

Source of effectiveness data
The effectiveness evidence was derived from published studies and authors' assumptions.

Modelling
A Markov model was used to simulate the progression of two groups of elderly patients: those with mild AD at the start of treatment and those with moderate AD at the start of treatment. Three main treatments were considered: donepezil 10 mg, donepezil 5 mg, and placebo. Within a series of 6-month cycles, patients could move from one state into a more severe state, based on a predetermined set of transitional probabilities, over a maximum period of 5 years. Movements to all states other than death were temporary, and in any direction except minimal to severe and severe to any stated. The definition of health states was based on different levels of severity of cognitive disability: minimal, mild, moderate, severe, and dead.

Outcomes assessed in the review
The health outcomes assessed in the review and which were used as parameters in the model were the transitional probabilities between different health states and the mortality rates associated with the three treatments (donepezil 10
mg, donepezil 5 mg, and placebo).

**Study designs and other criteria for inclusion in the review**
Different study designs were considered: cohort study for non-therapy progression, double-blinded randomised clinical trial for efficacy of donepezil, and other studies for mortality data.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Four primary studies were selected to assess the effectiveness outcomes associated with the treatment.

**Methods of combining primary studies**
Primary studies were not combined but, for mortality data, one study was used for the base case and another for a sensitivity analysis.

**Investigation of differences between primary studies**
The primary studies utilised different measures of severity of cognitive impairment, which were converted into a single measure (MMSE) by a referenced method.

**Results of the review**
Numerous transitional probabilities were estimated from the literature, but not all will be presented here. Those not presented are those which are 0, which are reported in the Modelling field, or those for which there is no change in state (the latter can be calculated by subtracting the others from 1).

In the case of a treatment based on donepezil 10 mg, when starting from the minimal state, the probability of moving to the mild state was 0.127.

From the mild state, the probability of moving to the minimal state was 0.233, and the probability of moving to the moderate state was 0.15.

From the moderate state, the probability of moving to the minimal state was 0.032, the probability of moving to the mild state was 0.226, and the probability of moving to the severe state was 0.226.

In the case of a treatment based on donepezil 5 mg, when starting from the minimal state, the probability of moving to the mild state was 0.108, and the probability of moving to the moderate state was 0.013.

From the mild state, the probability of moving to the minimal state was 0.245, the probability of moving to the moderate state was 0.225, and the probability of moving to the severe state was 0.04.

From the moderate state, the probability of moving to the minimal state was 0.032, the probability of moving to the mild state was 0.226, and the probability of moving to the severe state was 0.226.
The mortality rate was 53% over three years.

For placebo, the probabilities were:

minimal to mild: 0.222;
mild to minimal: 0.096;
mild to moderate: 0.058;
mild to severe: 0.019;
mild to severe: 0.533

For other movements between states, the values were 0.

In the severe and dead states, the probability of remaining in the same state was 1.

**Methods used to derive estimates of effectiveness**
The authors made a number of assumptions.

**Estimates of effectiveness and key assumptions**
As a simplifying assumption, the three-year survival rate was converted into a constant annual rate.

The first 6 months of drug therapy is at the drug efficacy rate, after which it is at the placebo rate.

Those in the severe state show no drug benefit.

**Measure of benefits used in the economic analysis**
The benefit measure used in the economic analysis was the number of years of life spent in a state less than severe dementia over a time horizon of 5 years.

**Direct costs**
A discount rate of 6% was used. Quantities and costs were not analysed separately and the cost/quantity boundary adopted was not reported. Drug acquisition costs and cost of care for older people with dementia, for a period of 5 years was considered. Care prices were updated from the Personal Social Services Price Index. The estimation of total acquisition costs of each treatment was derived using the Markov model and was based on several studies published in the literature. Resource use data were gathered from 1993 to 1995 and the price year was 1997.

**Statistical analysis of costs**
No statistical analysis of costs was reported.

**Indirect Costs**
Indirect costs were not included.

**Currency**
UK pounds sterling (£).
Sensitivity analysis
One-way sensitivity analyses were carried out to investigate the robustness of the model with respect to discount rate for costs and mortality rate. The values of the discount rate were 0%, 3%, and 10%. The mortality value was 30% and was derived from the literature.

Estimated benefits used in the economic analysis
For patients in the mild state, the years spent in a state less than severe were 1.82 for the therapy with donepezil 10 mg, 1.69 for donepezil 5 mg, and 1.57 for placebo. For patients in the moderate state, the years spent in a state less than severe were 0.87 for the therapy with donepezil 10 mg, 0.98 for donepezil 5 mg, and 0.59 for placebo.

Cost results
Drug acquisition costs for a treatment of 5 years were 3,866.77 with donepezil 5 mg and 5,378.61 for donepezil 10 mg. The results of the Markov model indicated that there was little difference in the expected costs of the three treatments. For patients in the mild state, the total costs were 45,694.43 for the therapy with donepezil 10 mg, 45,119.18 for donepezil 5 mg, and 44,277.72 for placebo. For patients in the moderate state, the total costs were 46,716.27 for the therapy with donepezil 10 mg, 46,193.20 for donepezil 5 mg, and 45,719.45 for placebo.

Synthesis of costs and benefits
Costs and benefits were combined by performing average and incremental cost-effectiveness analyses.

For patients in the mild state, the average cost-effectiveness ratio was always lower for donepezil 10 mg (25,121.25) than donepezil 5 mg (26,702.40) and placebo (28,196.80). For the same patient group, the incremental analysis showed that the therapy based on donepezil 10 mg was most cost-effective: the incremental cost required to achieve an extra year in a state less than severe dementia was 4,450.68 with donepezil 10 mg versus 5 mg, and 7,047.648 with donepezil 5 mg compared to placebo.

For patients in the moderate state, results were different. The average cost-effectiveness ratio was lower for donepezil 5 mg (47,100.35) than donepezil 10 mg (53,777.53) and placebo (77,607). For the same patient group, the incremental analysis showed that donepezil 5 mg was the most cost-effective therapy: the incremental cost was 3,565.44 with reduced benefit with donepezil 10 mg versus 5 mg and only 1,209.71 with donepezil 5 mg compared to placebo.

The sensitivity analyses indicated that results were affected by discount rate and mortality rates, but that the ranking of alternative treatments did not change.

Authors' conclusions
The authors concluded that donepezil (10 mg or 5 mg) was a cost-effective strategy for the treatment of patients suffering from AD. High drug acquisition costs were largely balanced by a longer time spent in less severe states of dementia compared to patients in the placebo group, making the therapy 'approximately cost-neutral'.

CRD COMMENTARY - Selection of comparators
The reason for the selection of the comparator was clear. Donepezil (in different doses) was compared with a placebo, given the lack of other technologies stated by the authors.

Validity of estimate of measure of effectiveness
The effectiveness measures (model parameters) were not derived from a review of the literature, but based on estimations obtained from studies, which were not combined. Search methods and criteria to ensure the validity of primary studies were not reported. However, the authors did not consider the impact of differences between the primary studies when estimating effectiveness measures in terms of mortality in the sensitivity analysis. It would have
been useful had the sensitivity analysis been extended to account for uncertainty in the other estimates, for example by using 95% confidence intervals for transition probabilities.

**Validity of estimate of measure of benefit**
The estimation of benefit was modelled through a Markov model, which appeared appropriate to simulate the natural history of the disease, although one needs to consider the authors’ assumptions, particularly in extrapolating from the primary source estimates. Years spent in states better than severe cognitive impairment seems appropriate for similar technologies. However, in order to estimate cost-effectiveness, comparison should be made with all possible technologies to which resources could be allocated from a single budget. Benefit would therefore need to be measured in terms that allow relative valuation, for example by reference to individual preference or quality of life.

**Validity of estimate of costs**
The estimation of costs accounted only for direct costs (drug acquisition expenditures). A limitation of the analysis, however, could have been the exclusion of indirect costs, which appeared to be relevant due to the high expenditures borne by people caring for subjects suffering from AD (the authors acknowledged this). In addition, costs and quantities were not reported separately and no sensitivity analysis was performed varying them, thus limiting the external validity of the study.

**Other issues**
The generalisability of the results to other settings was partially addressed by performing sensitivity analyses. The authors made few comparisons of their findings with those of other studies. The authors also recognised some limitations of the study arising from the different sources of cost and effectiveness data.

**Implications of the study**
The main implication of the model was that "donepezil must be viewed as an economically desirable innovation", given that it increases the time that AD patients spend in lower levels of disability. How cost-effective it is remains to be estimated, as discussed in the commentary.

**Source of funding**
None stated.

**Bibliographic details**

**PubMedID**
9695032

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aged; Alzheimer Disease /drug therapy /economics; Cognition Disorders /drug therapy /economics; Cost-Benefit Analysis /statistics & numerical data; Disease Progression; Dose-Response Relationship, Drug; Great Britain /epidemiology; Humans; Indans /economics /therapeutic use; Markov Chains; Models, Economic; Models, Neurological; Models, Psychological; Nootropic Agents /economics /therapeutic use; Piperidines /economics /therapeutic use; Severity of Illness Index; Treatment Outcome

**AccessionNumber**
21999006166

Date bibliographic record published
31/03/2002

Date abstract record published
31/03/2002