Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer’s disease
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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.

CRD summary
This study evaluated the cost-effectiveness of treatment with donepezil for patients with mild or moderate Alzheimer’s disease compared with no drug treatment. The authors concluded that donepezil was cost-effective for patients with mild Alzheimer’s disease in Spain. The methods and reporting of the study were adequate and the authors’ conclusions appear to be valid.

Type of economic evaluation
Cost-utility analysis

Study objective
This study evaluated the cost-effectiveness of treatment with donepezil for patients with mild or moderate Alzheimer’s disease compared with no drug treatment.

Interventions
Two doses of donepezil were available; 5mg and 10mg. This study used data from a randomised controlled trial (RCT), in which patients received either 5mg or 10mg per day, and the donepezil dosage was therefore assumed to be 7.5mg per day. This was compared with no drug treatment.

Location/setting
Spain/primary care.

Methods
Analytical approach:
A state-transition Markov model was developed to simulate the natural history of Alzheimer’s disease and to assess the impact that treatment with donepezil would have on the costs and health outcomes associated with an ongoing risk of disease over a six-, 12-, 18-, 24-, or 30-month time horizon. The authors stated that the analysis was conducted from a societal perspective and a health service perspective.

Effectiveness data:
The main treatment effectiveness parameter was from a single RCT that studied the dose impact of 5mg or 10mg per day of donepezil compared with placebo in patients with mild or moderate Alzheimer’s disease (Rogers, et al. 1998, see ‘Other Publications of Related Interest’ below for bibliographic details). The effects in patients receiving 5mg and those receiving 10mg were combined to increase the power of the study. The follow-up period was 24-weeks. A review of the literature was also undertaken and other clinical parameters included completion of treatment (compliance) and one-month transition probabilities between mild, moderate, severe, and death health states based on the natural history of the disease or adjusted for donepezil. These adjustments for donepezil were based on the relative risk of transitioning from mild to moderate and from moderate to mild for patients receiving donepezil compared with no treatment.

Monetary benefit and utility valuations:
The utility estimates for mild, moderate, and severe health states were calculated from a single study of 237 Alzheimer’s disease patients, in the Canary Islands, Spain, who completed the European Quality of life (EQ-5D) questionnaire (Lopez-Bastida, et al. 2006, see ‘Other Publications of Related Interest’ below for bibliographic details). The social values of health status in the EQ-5D were taken from interviews with 300 people in a health centre in Barcelona using the time trade-off approach. These were used to calculate the utilities for EQ-5D responses.
Measure of benefit:
The benefit measure was the number of quality-adjusted life-years (QALYs) and this was discounted at an annual rate of 3%.

Cost data:
The cost categories were direct medical costs and direct non-medical costs. Direct medical costs included the cost of donepezil, other drugs, medical visits, hospital admissions, emergency visits, orthopaedic devices, and others. Direct non-medical costs included the cost of carers. The cost data was reported in Euros (EUR) and was based on the single study of 237 Alzheimer's disease patients in the Canary Islands (Lopez-Bastida, et al. 2006). The cost of donepezil was based on the proportion of patients receiving 5mg and 10mg doses in the donepezil RCT. The price year was 2006 and an annual discount rate of 3% was applied.

Analysis of uncertainty:
One-way sensitivity analyses were performed on the time horizon, discount rates, initial number of patients in the mild, moderate, and severe states, and completion of treatment. A probabilistic sensitivity analysis, using 10,000 Monte Carlo simulations, was performed to assess the uncertainty in key parameters of the model. The results of this analysis were presented in a cost-effectiveness acceptability curve.

Results
In the base case, with a time horizon of 24 months and considering only the direct medical costs, the total cost of treatment with donepezil was EUR 4,543 and the total QALYs were 0.802 with all patients starting in the mild state. The total cost was EUR 5,955 and the QALY gain was 0.162 with all patients starting in the moderate state. In comparison, the total cost for no drug treatment was EUR 3,429 and the QALY gain was 0.705 with all patients starting in the mild state; and the total cost was EUR 3,912 and the QALY gain was 0.134 with all patients starting in the moderate state.

Compared with no drug treatment, donepezil was associated with an incremental cost-effectiveness ratio (ICER) of EUR 20,353 with all patients starting in the mild state; and EUR 71,037 with all patients starting in the moderate state. Other scenarios showed that extending the time horizon to 30 months and including the direct non-medical costs improved the ICER.

The univariate sensitivity analyses showed that these results were sensitive to the cost of donepezil and the initial distribution between mild and moderate health states. The results were robust to variations in the other parameters. The probabilistic sensitivity analysis showed that there was a 95% probability that donepezil was cost-effective at a willingness-to-pay threshold of EUR 25,000 per QALY.

Authors' conclusions
The authors concluded that donepezil was cost-effective for patients with mild Alzheimer's disease in Spain. They stated that budget decision makers should evaluate whether the benefits of donepezil were justified compared with other benefits that would be sacrificed from other health care areas.

CRD commentary
Interventions:
The interventions were well described. The no drug treatment comparator was justified due to the lack of evidence on the effectiveness of other relevant drugs. This justification was based on the results of a systematic review, which was conducted in 2001, and it is not clear whether any attempt was made to update it and confirm the results. Good modelling practice suggests that all viable treatment options should be considered in the model.

Effectiveness/benefits:
The main effectiveness estimate was taken from an appropriately selected single clinical trial. The authors implied that a systematic review of the literature on effectiveness was performed before building the model, which suggests that the study was chosen from this review, but no details of the review were reported and so it is not possible to determine if all relevant evidence was considered. The authors did not report the sample size of the study or whether an analysis to account for confounding was performed, but the study design was well described and the power of the study was...
increased by merging the two donepezil dose groups together. The follow-up period was 24-weeks, which was quite short compared with the model time horizons, but the results of an open study suggested a longer treatment effect and a number of different time horizons were considered. The utility derivation was well reported and appropriately considered the preferences of 237 Alzheimer's disease patients, who completed the EQ-5D. These were appropriately combined with social values from another Spanish study.

Costs:
The costs appear to have been consistent with the perspectives considered. The cost estimates were well reported and came from a study conducted in the Canary Islands, Spain and therefore relevant to the setting of the analysis. No resource data was presented. The price year was reported and discounting was appropriately applied.

Analysis and results:
The analytical approach was well reported and the state-transition Markov model was suitable for evaluating the treatment of the condition. The results of the model were reported clearly and fully. The issue of uncertainty was properly addressed through sensitivity analyses and the results were well presented. The derivation of the model inputs and the details of the probabilistic sensitivity analysis were not fully reported. The authors acknowledged and discussed some limitations of their analysis, such as that the effectiveness results were based on a single 24-week study outside of Spain, while the model extended this effectiveness up to 30 months. The validity of the results would be enhanced if it was possible to judge the quality of the review and be sure that all relevant evidence was considered. The authors compared their results with those of other studies and they were shown to be comparable.

Concluding remarks:
: The methods and reporting of the study were adequate and the authors’ conclusions appear to be valid.

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