Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada


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 use of an anti-dementia drug, donepezil to slow the progression of dementia in patients with mild or moderate Alzheimer's Disease (AD).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Individuals with probable mild or moderate Alzheimer's Disease (Mini-Mental Health State Examination (MMSE) scores between 10 and 26).

Setting
Community and residential care. The economic analysis was conducted in Hamilton, Ontario, Canada.

Dates to which data relate
Effectiveness data were taken from a 30 week trial; the results of which were published in 1998. Resource data were collected from the Canadian Health Study of Ageing survey conducted between 1991 and 1992. The price year was 1997.

Source of effectiveness data
Effectiveness data were derived from a single study and the authors' opinion.

Link between effectiveness and cost data
Costing was undertaken using a different population sample to that used in the clinical trial. The costings were based on resource use in a 1991-1992 survey.

Study sample
In total 308 individuals were randomised to either the 5mg donepezil daily group or the placebo treatment group, with 154 subjects in each group. No information was provided regarding the method of randomisation or whether power calculations were used. (Note: There was also a 10mg donepezil daily treatment group, but these data were not used in this economic analysis, as there was no significant difference in efficacy between 5mg and 10mg dosages and the lower dose has fewer side effects).
Study design
The study was a double-blind randomised controlled trial. The duration of the trial was 24 weeks of active treatment, plus a further follow-up period of six weeks. The loss to follow up was 7% in the placebo group and 6% for patients receiving 5mg donepezil.

Analysis of effectiveness
The analysis of effectiveness was based on intention-to-treat. The primary health outcomes reported were changes in the Alzheimer's Disease Assessment Scale - Cognitive Sub-Scale and MMSE scores. At baseline analysis both groups were shown to have similar MMSE scores.

Effectiveness results
The effectiveness results were as follows:

After 24 weeks, 19 (12%) individuals in the donepezil group had MMSE scores greater than 26 compared with 11 (8%) in the placebo group.

59(38%) in the donepezil group had scores between 21-26 compared with 50(32%) in the placebo group;

39 (25%) in the donepezil group had scores between 15-20 compared with 51(33%) in the control group;

similarly the number of patients with MMSE scores between 10-14 in each group were 28(19%) and 25 (16%) respectively.

9 (6%) individuals in the donepezil group had scores under 10 compared with 17(11%) in the control group.

Clinical conclusions
Donepezil is a safe and efficacious treatment for individuals with mild to moderate AD and can significantly slow the onset of dementia over a 24 week treatment period.

Modelling
A 24 week decision analysis model was used to synthesise effectiveness data from clinical trials, with resource data to estimate the expected costs and outcomes after 24 weeks of treatment. A Markov model was then used to determine costs and outcomes over a further ten 24 week cycles, five years in total. There were six possible states in the Markov model: MMSE scores less than 10, 10-14, 15-20, 21-26, 27-30, and death. The probabilities of transition between these states were based on observations in the 24 week clinical trial for patients in the placebo group. The probability of mortality was based on that observed in a previous clinic-based AD cohort.

Methods used to derive estimates of effectiveness
Assumptions about effectiveness were derived from the authors opinion.

Estimates of effectiveness and key assumptions
As there is a lack of long-term outcome data, the authors assumed that treatment effects observed in the 24 week clinical trial, would be maintained, but not improved, in patients during the remainder of the five year model. The probability of cognitive decline would then be the same, both for patients who had received donepezil, and for those treated with placebo.

Measure of benefits used in the economic analysis
The benefit measure was the expected time spent in a state of non severe dementia (score greater than 10 on MMSE).
Direct costs
The economic analysis was conducted both from the perspective of health and social care services, and from a societal perspective. Data were taken from the 1991-1992 Canadian Survey on Ageing, which recorded the non acute health and social care resource use of people with probable AD, namely long term care, community services, medications and informal caregiver time. Acute healthcare costs were not included as studies in the literature suggest that there is no difference in use between people with or without AD. Using this survey data, and weighting results using data from an AD cohort in Alberta to take account of different MMSE groups, the probability of institutionalisation was calculated. A reimbursement case mix formula from Ontario was used to estimate the cost per day in residential care. Expert opinion and prices from the Ontario Drug Benefit Plan plus a 10% pharmacy mark-up and a dispensing fee of Can$ 6.11 were used in costing adjunctive medications such as antidepressants. Local data on prices of community services in the Hamilton area of Ontario were used. Caregiver time was valued using the minimum wage rate in Ontario of Can$ 6.85 per hour. Caregiver supervision time was excluded from the analysis, only active care time was costed. Costs and benefits were discounted at a rate of 5% per annum. 1997 price year was used.

Indirect Costs
Indirect costs were not included.

Currency
Canadian dollars (Can$).

Sensitivity analysis
A series of sensitivity analyses was undertaken in order to account for uncertainty, although the precise type of sensitivity analysis undertaken does not appear to have been stated. Parameters varied included discount rate (varied between 0% and 10%), 5 year life expectancy rates (100% to 0%), extending treatment coverage to patients with MMSE scores less than 10, varying the monthly dispensing fee, increasing caregiver time to Can$15 per hour and using MMSE aggregation weights based on the Ageing Survey rather than the Alberta study.

Estimated benefits used in the economic analysis
The incremental time gained in a non severe state of dementia over the five year period for the donepezil group was 0.2 years (2.41 years compared with 2.20 years) using a 5% discount rate.

Cost results
Overall expected five year costs per patient in the donepezil group were lower by Can$ 882, (Can$ 80,305 compared with Can$ 81,187 for the placebo group) (5% discount rate).

Healthcare costs were lower in the donepezil group by Can$ 929 per patient (Can$ 62,551 versus Can$ 63,480).

Informal caregiver costs were slightly higher, Can$ 48 per patient (Can$ 17,755 versus Can$ 17,707).

The intervention remained the dominant strategy in sensitivity analysis, except if treatment were extended to those with an MMSE score less than 10, when incremental costs per patient would be Can$ 1,554.

The incremental effect per patient ranged from 0.18 to 0.24 years of severe dementia free life gained.

Synthesis of costs and benefits
Costs and benefits were not combined since the intervention was the dominant strategy.
Authors' conclusions
The use of donepezil by people with mild or moderate Alzheimer's Disease over a five year period will lead to improved outcomes at a lower cost than providing standard care alone. The data on which the analysis is based is limited and further economic analyses will be required as more data become available.

CRD COMMENTARY - Selection of comparators
The choice of comparator, standard care without an anti dementia drug was justified by the authors, on the grounds that donepezil is the first anti dementia drug to be licensed in Canada. You the user, should consider whether this is applies to your own setting.

Validity of estimate of measure of benefit
The analysis was based on a double-blind randomised controlled trial of donepezil versus placebo, which was appropriate for the study question. The study sample was representative of the study population. Sample groups were shown to be clinically comparable at analysis. In addition the authors assumed that donepezil would maintain its treatment effect after 24 weeks, although no long-term studies had been conducted at the time of publication to justify this assumption which does not appear to have been tested in sensitivity analysis. The authors acknowledged the lack of long-term outcome data. Estimation of benefits in the 24 week period was obtained directly from the effectiveness analysis. This choice of estimate was justified.

Validity of estimate of costs
Although the authors reported that costs were estimated from the societal perspective, indirect costs associated with people with AD were not included in the analysis. Even though the majority of these individuals will be retired at onset of illness, they will still make a contribution to household production and other activities such as volunteering. Such costs, although difficult to value, should not be omitted from a full societal analysis; a delay in onset may ensure that individuals continue to contribute. The authors stated that only active informal caregiving time was included in the economic analysis, this approach may undervalue the contribution of caregivers significantly, since, in the mild to moderate stage of dementia, the need for supervision is important in order to prevent individuals harming themselves or others, or becoming lost. Costing such supervision time is difficult, however, due to issues of joint production. This omission is likely to underestimate the overall costs of caregiving and therefore may bias the results of the analysis in favour of the intervention. However the economic study understandably does not provide detail on how the survey estimated time spent caring: this is difficult to do, with caregivers tending to overestimate the actual incremental time spent caring compared to their contribution to household activities prior to the onset of dementia. Additional costs to caregivers due to the detrimental impact of caregiving upon their physical and mental health have not been included in the analysis. For instance the use of antidepressants by caregivers is widely reported in the literature. Costs were reported separately from quantities, and were obtained from a single study. Survival data and transition probabilities based on the clinical trial were used to extrapolate resource use and costs over a five year treatment period. Unit costs were taken from a mixture of published sources as well as from expert opinion where required. A sensitivity analysis of unit costs and resources used was conducted. Discounting was applied to the model, which was appropriate, and the date to which prices related was reported.

Other issues
This is an interesting and well conducted study. However the authors did not make comparisons of their findings with those from other studies, although one very similar study using a 5 year Markov model for donepezil had been published in the UK. The issue of generalisability to other settings was not addressed, although it was acknowledged that the results of the study applied to the study setting only. The authors do not appear to have presented their results selectively. Another issue that this study does not consider is the effect of extending time spent in informal care. The psychological impact on caregivers of potential short term gains in cognitive function, may lead to additional distress as carers will have to go through the process of loss of cognitive function again. The incremental psychological burden of caring is not inconsiderable, particularly as caring can be more intensive in the mild and moderate stages of dementia where people with AD can be a danger to themselves and others, requiring a higher degree of supervision than in patients with more severe levels of dementia.
Implications of the study
Well designed economic evaluations alongside clinical studies are required to examine the impact of anti dementia drugs on long term outcomes. Such evaluations should seek to measure the impact on caregiver burden, by using well validated instruments such as the Zarit Caregiver Burden Scale, and all costs associated with informal caregiving should be included in such an analysis. Furthermore the lost productivity of people with AD themselves, also needs to be quantified.

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