Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial

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 donepezil (5 or 10 mg/day) for the treatment of patients with Alzheimer's disease.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of dementia of Alzheimer type, with or without a coexisting diagnosis of vascular dementia. The patients were also requested to have a regular carer, to be living in the community, and not to be already taking a cholinesterase inhibitor or to have a contraindication to donepezil. Finally, the doctor had to be uncertain on the clinical benefit of donepezil for these patients.

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

Dates to which data relate
The patients were recruited from October 1998 to September 2001, during which time the collection of effectiveness and resource use data began. The costs were estimated in 2000, which is presumed to have been the price year.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were carried out after the study sample had been identified. These showed that the study had 90% power to detect statistically significant differences in both the primary and secondary outcomes. The final study sample comprised 566 patients, who were allocated equally to the donepezil and placebo groups. All patients suffered from DSM-IV dementia of Alzheimer's type, while 93 (16%) had vascular dementia, 22 (4%) Parkinsonism, and 54 (10%) psychotic symptoms. In addition, 287 patients (51%) had co-morbidity (prior myocardial infarction, other
cardiovascular disease, stroke, hypertension, or requirement for aspirin), while 291 (51%) had mild and 275 (49%) had moderate dementia. The median age was 76 years (range: 54 - 93) in the donepezil group and 75 years (range: 46 - 90) in the placebo group. Forty-two per cent (donepezil) and 40% (placebo) of the men were allocated to the two groups, respectively. One patient withdrew consent before the beginning of treatment.

Study design
This was a prospective, double-blind, randomised, placebo-controlled, trial, which was carried out in 22 centres in the UK. The methods of randomisation and blinding were not described. Patients randomised to the donepezil group were further sub-randomised to 5 or 10 mg doses. After the first randomisation, eligible patients entered a 12-week run-in period, which was completed by 511 patients (246 in the donepezil group and 265 in the placebo group). A sample of 486 patients was further randomised (242 to donepezil and 244 to placebo) and entered phase 1 (48 weeks of treatment), which 293 patients completed. After a 6-week washout period, 105 donepezil patients and 89 placebo patients entered phase II (further 48 weeks of treatment), which was completed by 111 individuals. After a further 4-week washout period, 31 donepezil patients and 20 placebo patients entered phase III (48 weeks of treatment), which only 20 patients completed. After a further 4-week washout, 1 donepezil patient and 3 placebo patients entered phase IV (48 weeks of treatment).

The reasons for loss to follow-up were withdrawal, death, institutionalisation, National Health Service (NHS) prescribing, and cessation of treatment due to side effects. The authors stated that, initially, follow-up was planned to last 60 weeks, owing to budget limitations, but treatment was then extended indefinitely so as to achieve more statistical power.

Analysis of effectiveness
The analysis of the clinical study appears to have been conducted on the basis of treatment completers only. An intention to treat analysis was performed only for the primary outcomes and for the first 60 weeks. The primary outcome measures used in the analysis were the rate of institutionalisation (residential, nursing, or NHS continuing care) and the progression to disability. The progression to disability was defined as the loss of either two of 4 basic activities, or six of 11 instrumental activities on the Bristol activities of daily living scale (BADLS).

The secondary outcomes were:

- functional ability (BADLS; range: 0 - 60);
- the presence and severity of behavioural and psychological symptoms and signs of dementia, as measured by the neuropsychiatric inventory (NPI; range: 0 - 44);
- cognition, measured with the mini-mental state examination (MMSE, range: 0 - 30);
- progress to severe cognitive disability (MMSE < 10);
- psychological wellbeing of the principal caregiver, measured with the general health questionnaire (GHQ-30; range: 0 - 30);
- death from Alzheimer's disease (ignoring death from other causes);
- safety (serious adverse events); and
- compliance (numbers stopping treatment).

The authors stated that the two study groups were balanced at baseline in terms of demographics and disease characteristics. However, they noted that, owing to a higher percentage of side effects in the donepezil group, fewer donepezil patients who remained resident in the community completed the run-in treatment in comparison with patients receiving placebo. Multivariate models were used to identify potential independent predictors of the risk of institutionalisation. A sub-group analysis was also carried out using 22 sub-group investigations.
Effectiveness results
The rate of institutionalisation was 9% with donepezil and 14% with placebo at one year, (p=0.15), and 42% and 44% at 3 years, (p=0.4).

The relative risk of entering institutional care with donepezil relative to placebo was 0.97 (95% confidence interval, CI: 0.72 - 1.30; p=0.8).

Similarly, the proportions of patients who had progression of disability were 13% with donepezil and 19% with placebo at one year, (p=0.3), and 55% and 53% at 3 years, (p=0.9).

The relative risk of reaching the disability end point with donepezil relative to placebo was 1.02 (95% CI: 0.72 t- 1.45; p=0.9).

The relative risk of reaching this end point or entering institutional care with donepezil relative to placebo was 0.96 (95% CI: 0.74 - 1.24; p=0.7).

No difference was apparent between donepezil and placebo on the BADLS score at 12 weeks, but thereafter the donepezil group had better scores at all time-points.

During the 2-year study period, patients in the donepezil group averaged MMSE scores 0.8 points higher than patients in the placebo group (95% CI: 0.5 - 1.2, p<0.0001) and BADLS points 1.0 better than placebo (95% CI: 0.5 - 1.6; p<0.0001).

The groups were comparable in terms of cognition, behavioural and psychological symptoms and signs of dementia, psychological wellbeing of the principal caregiver, death from Alzheimer's disease, and safety.

More donepezil patients (36%) than placebo patients (20%) dropped out because of side effects and did not attend the 12-week assessment, (p=0.02).

The multivariate models showed that BADLS, NPI, and age were strong independent predictors of institutionalisation, while MMSE was only weakly predictive. In particular, the model predicted that a 2 to 3 point improvement in BADLS with donepezil would reduce the rate of admission to institutional care by between 5 and 15%. This corresponds to an average of 2 to 5 days less institutional care per donepezil patient per year.

The sub-group analysis (the results of which were less reliable due to the small numbers of patients) showed that a lesser cognitive response was noted with higher baseline NPI score, greater cognitive response in Alzheimer’s disease with a vascular component than without, and lesser functional response in the presence of Parkinsonism.

Clinical conclusions
The effectiveness analysis showed that donepezil did not lead to significant improvements in clinical end points in comparison with placebo. Small advantages in cognition and both behavioural and psychological symptoms were observed.

Measure of benefits used in the economic analysis
The authors stated that the summary benefit measure used in the economic analysis was the number of ”days in a high level of disability” avoided. However, such a measure, derived from the effectiveness analysis, was not explicitly calculated. In addition, it was not combined with the costs because of the lack of statistically significant differences between donepezil and placebo. Thus, in effect, a cost-consequences analysis was finally performed.

Direct costs
Discounting was not relevant as the costs were evaluated during a 12-week period. The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were visiting
nurse, social worker, domestic help, meals on wheels, day care centre, day hospital, visits to family doctor, hospital doctor, hospital stay, nursing home stay, residential home stay, and unknown overnight stay. The costs of donepezil and institutionalisation were not considered. Informal care (i.e. active and passive caregiver time) was not costed because the differences between the groups did not reach statistical significance. The cost/resource boundary of the NHS appears to have been adopted. Resource use was derived from assumptions and data estimated from the clinical trial. The costs were derived from Personal Social Services Research Units in 2000. The price year might also have been 2000.

**Statistical analysis of costs**
The t-test and bootstrapping models were used to test the statistical significance of differences in the estimated costs.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
UK pounds sterling (.).

**Sensitivity analysis**
Sensitivity analyses were not carried out. The authors frequently referred to the results of the sensitivity analysis (reported already) as multivariate statistical models.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The total annual costs per patient were 2,842 in the donepezil group and 2,344 in the placebo group.

The difference in costs was 498 (+/- 352). Although this favoured the placebo group, it did not reach statistical significance, (p=0.16).

The extra-cost with donepezil was mainly attributable to the hospitalisation costs (825 versus 439 per year; p=0.09).

**Synthesis of costs and benefits**
The costs and benefits were not combined because there was no statistically significant difference between the groups in either the costs or benefits.

**Authors' conclusions**
Donepezil was not a cost-effective strategy for the treatment of patients with Alzheimer's disease. Only limited improvements in clinical outcomes were observed and these did not reach clinical significance. Further, the extra costs associated with donepezil were not offset by delayed institutionalisation.

**CRD COMMENTARY - Selection of comparators**
The selection of placebo as the comparator was appropriate, not only because it reflected the current practice in several settings but also because it allowed the active value of donepezil to be determined. The authors stated that other drugs were available for Alzheimer's disease, namely rivastigmine and galantamine, but that these had an efficacy and safety profile comparable to donepezil. You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
The analysis of effectiveness relied on a well-conducted clinical trial, which was based on two randomisation steps and sub-randomisation. The authors highlighted the advantages of using such a design. First, patients who defaulted from treatment in the first 12 weeks could be omitted from the long-term comparison without introducing bias. Second, patients effectively contributed twice to the 12-week efficacy comparison. The use of randomisation and blinding limited the potential impact of confounding and bias. The study groups were comparable at baseline, as a result of the good randomisation procedure. Power calculations were carried out to determine the appropriateness of the sample size. The patients were recruited from several centres, and the study sample appears to have been representative of the patient population. The loss to follow-up and the reasons for withdrawal were clearly reported. These issues tend to enhance the internal validity of the analysis. However, it seems that some clinical outcomes have been analysed on the basis of treatment completers only. The authors noted the difficulties in recruiting participants, but stated that the study group was representative of the patient population.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because there was no statistically significant difference in terms of the main benefit measure. In effect, a cost-consequences analysis was conducted.

Validity of estimate of costs
The economic analysis focused on the direct costs and the perspective of the NHS appears to have been adopted. The authors stated that a societal perspective was used because informal care was initially estimated. However, it was not costed, owing to the lack of statistically significant differences between the groups. Also, the indirect costs were not included. In general, almost all categories of costs were comparable. The authors' hypothesis of cost-neutrality was not demonstrated since the inclusion of donepezil and institutionalisation costs would have resulted in substantial extra costs. The unit costs were presented separately from the quantities of resources used, which would facilitate the replication of the cost analysis. The estimation of resource use reflected real-life consumption because of the pragmatic design of the trial. The source of the costs was provided. The costs were estimated in 2000 values and 2000 is presumed to have been the price year. This will simplify any reflation exercises in other settings.

Other issues
The authors stated that their results confirmed those from published studies. The issue of the generalisability of the study results to other settings was not addressed and all estimates were specific to the study setting. This affected the external validity of the analysis. The study referred to patients suffering from Alzheimer's disease and this was reflected in the authors' conclusions.

Implications of the study
The authors suggested that no clear implications for the use of donepezil could be drawn from the results of the analysis. A rational strategy might be that those who believe that donepezil (or other cholinesterase inhibitors) produce worthwhile benefits may treat all patients, while those who believe that the effects are not clinically relevant should treat none. Future studies should further investigate the cost-effectiveness of donepezil, whilst attempting to achieve higher compliance and follow-up. The identification of those patients who could achieve the greatest benefits would be helpful.

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