Propentofylline treatment for Alzheimer disease and vascular dementia: an economic evaluation based on functional abilities

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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.

Health technology
Propentofylline drug treatment (300mg three times daily one hour before meals) for the treatment of patients with mild to moderate Alzheimer disease and/or vascular dementia.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Male and female patients with mild to moderate Alzheimer disease and/or vascular dementia who had been diagnosed for at least six months, were aged between 50 and 85 years, and who lived in the community. Mild to moderate Alzheimer disease and/or vascular dementia was defined as having a score of 15 to 25 on the Mini-Mental State Examination (MMSE), a score of three, four or five on the Global Deterioration Scale (GDS), and a score of 5 to 23 on the Syndrome Short Test.

Setting
The setting was the community, including patients living at home or in residential or nursing homes. The economic study was performed in Canada.

Dates to which data relate
Effectiveness data were taken from a 48-week randomised controlled trial (RCT) published in 1998. The dates of the trial were not given. Cost data were from a variety of sources. Home care costing and costs of informal care was derived from the Capital Health Authority (Edmonton) Home Care Information System (April 1994 to December 1995). Drug prices were from the Alberta Drug Benefit Program, published in 1996 by the Canadian Pharmaceutical Association. The date and source of the costs of adverse events were not stated. The price year was 1994/95.

Source of effectiveness data
The effectiveness data were taken from a single study.

Link between effectiveness and cost data
Retrospective Canadian costing was performed on the group of patients who had taken part in a published European RCT study.
Study sample
550 patients were recruited into the clinical trial, and 11 were withdrawn after their baseline visit and were not included in the study or the consequent intention to treat analysis. This left 539 trial participants, 257 in the propentofylline group, and 282 in the placebo group. 106 of the 539 had diagnosed vascular dementia. This group was too small for subgroup analysis to be conducted. Power calculations used to establish sample size were not reported in the paper.

The trial compared propentofylline to placebo. Readers are referred to the original published paper by Rother et al (1998) for more detail.

Study design
The study was a randomised, double-blind, parallel group, multicentre (30 centres) European clinical trial. Subject allocation, the length of follow-up and loss to follow-up were not reported in the economic paper. Drop out rates were 27% for the propentofylline group and 22% for the placebo group, and these were not statistically significant different, (p=0.19 using a Chi square test). The placebo dropouts were not statistically different from the placebo completers. The treatment group dropouts had inferior health status compared to the treatment group completers.

Analysis of effectiveness
Intention to treat analysis was used. Treatment effects, in this paper, were measured using two global dementia staging scales, which measured the progression of dementia. The first was the Clinical Global Impressions (CGI) Item II, which is a measurement of change. The second measure was the Global Deterioration Scale (GDS) that measures cognitive decline. In the original clinical trial, a third measure, the Gottfries-Brane-Steen (GBS) scale, was also used.

The groups were comparable at baseline in terms of major demographic characteristics.

Effectiveness results
Using the CGI outcome, the propentofylline group improved by an average 0.17 of a step in the scale compared to the placebo group who worsened by 0.05 of a step. The difference between the two groups was 0.22 and was statistically significant, (p=0.03).

Using the GDS outcome, the propentofylline group improved by an average 0.13 of a stage compared to the placebo group who worsened by 0.06 stages. The difference between the two groups was 0.20 and was statistically significant, (p<0.001).

Clinical conclusions
The CGI and GDS outcome measures both showed a statistically significant clinical improvement for the propentofylline group compared to the placebo group. The GBS scores were not statistically significantly different, although this outcome measure was not used in the cost-effectiveness analysis.

Measure of benefits used in the economic analysis
The benefit measure adopted was incremental change in the disease staging measures, CGI and GDS. The paper did not state how these measures were administered.

The GDS was administered at baseline, whereas the CGI was not because it measures only change from baseline. Both were administered throughout the trial at each 12 week interval patient visit, and, finally, at the 48 week endpoint.

Direct costs
The costs reflect data collected over the 48-week clinical trial duration. As the trial was European, errors in health care resource use differences to those practised in Canada were minimised by mapping and grouping patients by their GBS score to the Alberta Resident Classification System (RCS) at each twelve-week interval. Participants were assigned at
an average reported level rather than individually, as the authors did not have access to this information. This classification indicates average home care resource use. For those in residential and nursing homes, the long-term care cost of the homes was used, irrespective of resident diagnosis. Resource use classification was defined as none, low, medium or high.

Drug and dispensing cost was based on actual drug usage rather than prescribed drugs. The quantity of drug actually used was not stated.

Costs of adverse events were based on an estimated physician time usage. This was taken from the "Schedule of fees for Alberta physicians". The quantity of time used was not reported.

The trial performed a Caregivers Activity Time Survey to estimate the amount of informal care giving time. The quantity of time was not stated in the paper. Informal care was derived using shadow pricing techniques applied to the cost of providing formal, but similar, home care services. It was assumed that informal care was a substitute for, or prevented formal home care.

Seven out of the 539 trial participants were not included in the cost analysis due to having "extreme values" in their estimation of informal care giving time. Four were from the propentofylline group and three from the placebo group.

No discounting was performed as the data relate to a time period of less than a year.

**Statistical analysis of costs**

All statistical tests were evaluated at the 5% level of significance and were based upon intention to treat.

Analysis was performed on the total average cost per patient, and average patient outcome per patient. Justification of statistical techniques was stated and the parametric tests were used for variables because of the large sample size. Non-parametric bootstrapping methods were used to evaluate the statistical significance of the cost-effectiveness ratios.

The RCS mapping method was validated using correlation tests (Chi square and Spearman coefficient), and to test for differences in the RCS distribution between the study groups.

**Indirect Costs**

Indirect costs were not included.

**Currency**

Canadian dollars (Can$) for 1994/95.

**Sensitivity analysis**

Sensitivity analysis was used to test key assumptions regarding home care services and the validity of the mapping methodology.

For home care services, if the patient was initially categorised as requiring no home care personal services, then it was assumed in the sensitivity analysis that they would receive some, although the new quantity of resource use was not stated. Another RCS mapping methodology was employed to establish whether the categorisation changed significantly to alter the results.

Patients dropped due to "extreme values" were included to establish their impact on the overall results.

No other sensitivity analysis, such as varying unit costs, effectiveness, and prescribed as opposed to actual drug usage, was performed. The authors justified varying only three factors as they made very few assumptions and so sensitivity analysis would be limited.
Estimated benefits used in the economic analysis
Using the CGI outcome measure, the propentofylline group had a 0.16 increase, whereas the placebo group had a 0.06 decrease, resulting in an incremental difference of 0.22, (p=0.03).

Using the GDS outcome measure, the propentofylline group had a 0.12 increase compared to a 0.07 decrease in the placebo group, resulting in an incremental difference of 0.19, (p<0.001).

The length of follow-up was 48 weeks and no extrapolation beyond this time period was undertaken. Adverse events were not reported although they have been costed in the costing analysis.

Cost results
No discount rate was applied to the costs, which were measured over a 48 week time period. Adverse events were incorporated into the costing total.

For the societal perspective, the average cost of treatment for the propentofylline group was Can$16,224, and for the placebo group was Can$15,770. The incremental cost was Can$454.

For the Ministry of Health perspective, the average cost of treatment for the propentofylline group was Can$4,759, for the placebo group was Can$3,163 and the incremental cost was Can$1,596, (p<0.0001).

For an informal caregiver perspective, the average cost of treatment for the propentofylline group was Can$11,465, for the placebo group was Can$12,607 and the incremental cost was -Can$1,142.

The Ministry of Health perspective was broken down into the cost of personal care, home support, assessment/case management, nursing home care, treatment of adverse events and treatment medication.

The costs that were statistically different between the two groups were those for treatment for adverse events and average total cost to the Ministry of Health.

The correlation between RCS and GDS clinical observations was moderate (the Spearman coefficient was 0.545, p<0.001) suggesting that higher resource use was associated with patients with later disease stages.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio was used, defined by the difference in average total cost divided by the difference in the change in health status of patients across the two groups.

The incremental cost-effectiveness ratios for three perspectives were given:

Ministry of Health: GDS, Can$8,400; CGI, Can$7,121;
informal caregiver: GDS, -Can$6,011; CGI, -Can$5,098; and
societal perspective: GDS, Can$2,384; CGI, $2,023.

Boot strapping for a 95% confidence interval on the cost-effectiveness ratio was presented only for the societal CGI result and was Can$2,018 per CGI (±/ 67,897). This demonstrates that it was not statistically significant from zero.

The sensitivity analysis performed did not significantly alter the overall results.

Authors' conclusions
The results were not measured in QALYs and therefore could not be compared to other dementia treatments or other types of healthcare intervention.
The extra cost of propentofylline treatment was partially offset by savings in home care and informal care giving. The authors believed that informal care giving cost savings might have been overstated because of the assumption that each hour of informal care substituted an equal amount of home care services. They accepted that, in reality, this was unlikely to be true.

Propentofylline has a statistically significant beneficial treatment effect compared to placebo, although the cost difference was not significantly different. The authors consequently concluded that propentofylline could be cost-effective.

The authors reported that other studies have found cost savings by using propentofylline when only formal healthcare costs have been incorporated. However, these studies extrapolated benefits and costs beyond the time span available for existing data.

CRD COMMENTARY - Selection of comparators
The selection of comparators was based upon data availability i.e. a placebo-controlled trial. However, there may be a subtle difference between the effectiveness of having placebo and the assumed "standard care" that the authors believed was happening. It is likely that if there was a placebo effect, propentofylline may have been more effective than assumed in the trial. The user of the database should interpret the results alongside current practice in their own healthcare setting. The article does not define "standard care" explicitly.

Validity of estimate of measure of benefit
Benefit measures were limited to those available in the trial. Unfortunately the disease specific nature of the two measures used in the study, CGI and GDS, limits the generalisability of the results across other countries and comparison against other health care interventions.

The external validity of the study may be limited as 61% of trial participants were categorised into Group A (low resource use) of the RCS. However, only 11% of dementia patients in Canada's general population are in this category.

The GDS and CGI are ordinal scales but had to be interpreted as cardinal measures.

It is not possible from this paper to comment on the quality of the clinical trial on which the effectiveness data were based. However, the trial was randomised and had broad inclusion criteria. The authors in this paper undertook appropriate statistical tests.

Validity of estimate of costs
Costs were reported in Canadian dollars and related to the years 1994 to 1995. Although the trial data were European, the authors have attempted to minimise errors in resource use differences that may occur in a Canadian setting by linking functional ability of trial participants to appropriate RCS categories. No description was given regarding quantity of resources used, limiting the ability of the reader to convert costs to their own health care setting. The exclusion of the "extreme care time" patients seems reasonable as they were a very small number and were similar across the two groups.

The trial provided the only source of data that included global function measures and caregiver information so that resource usage could be estimated. The RCS was the only available source to link the trial participants to resource usage in Canada. It may not therefore be sensitive to small resource use shift patterns.

The societal perspective was the addition of informal care giving costs to the Ministry of Health costs. However, the informal care cost was not the cost of providing informal care, such as time off work, missed job opportunity, or lack of leisure time. The assumed cost was the cost of actual formal home care and caution should be taken regarding the assumption that the two are a one to one equivalent substitution.

The authors undertook limited sensitivity analysis around the parameters, in particular quantity of resource use and unit prices. This limits the potential to generalise the results to other countries.
Discounting was not performed and this is acceptable, as the time span was under one year. However, the price year was not clearly reported and it is not clear how prices were adjusted to a common price year.

**Other issues**
The study correctly reported the use of incremental cost-effectiveness ratios, especially as the increased benefit of using propentofylline was associated with a higher cost. The authors made no inference as to whether the resulting ratio provided good value for money to health care decision makers.

The authors did comment accurately on the limitations of the study and its interpretation, such as the external validity and generalisability to the "real world" which is reported above.

**Implications of the study**
Health care decision makers should be cautious when using this article to aid decision-making regarding the use of propentofylline. The patient group is for people aged over 50 with mild or moderate Alzheimer disease and/or vascular dementia. For an UK NHS perspective, the Ministry of Health results provide the decision maker with a pure health and social care system perspective. However, interpretation of the societal costs should be made carefully. The study covers less than one year and more data are needed about the longer-term efficacy of propentofylline and its cost-effectiveness. Obvious cost driver factors to include in such analyses would be residential and nursing home admissions over time.

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