Estimating the value of novel interventions for Parkinson's disease: an early decision-making model with application to dopamine cell replacement


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 study considered future dopamine cell replacement therapies for patients with Parkinson's disease (PD), such as a stem cell-based approach that replaces dead neurons with healthy ones, restores deficient transmitter release, and reconstructs neuronal circuitries.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with PD.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1999 and 2006. PD costs and resource consumption were derived from a study published in 2002. No dates were reported for the sources of the treatment costs. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A state transition model was constructed to simulate patients’ disease progression from PD diagnosis to end of life. Specifically, disease progression was defined as a continuous temporal function and each health state was defined by the Hoehn and Yahr (HY) stage of PD (I, II, III, IV and V). The time horizon of the analysis was 25 years. Disease progression was estimated as a function of initial disease severity (HY stage), difference in time between first and last visits and age at diagnosis. It was modelled through a multivariate, ordinary least-squares regression. The model assumed an initial progressive improvement in disease due to dopamine cell replacement for 2 years, followed by a stationary period of up to 5 years after grafting, after which disease progression followed its preoperative trend. Since most of the patients were in HY Stages III and IV, the cost-effectiveness analysis was run mainly for these two cohorts of patients.
Outcomes assessed in the review

The outcomes assessed from the literature were:

data on disease progression, which were based on the characteristics of a cohort of PD patients (i.e. age at onset, age at PD diagnosis, age at time of last visit, PD duration at first neurological assessment, PD duration at time of last visit, and proportions of patients in different HY stages at both the first and most recent visits);

survival;

increased PD mortality in comparison with the general population;

the health state utilities according to HY stage;

the effectiveness of a future cell-based therapy for PD; and

the frequency of complications such as haematoma and dyskinesias.

Study designs and other criteria for inclusion in the review

Since no details on the methods and conduct of a systematic review of the literature were provided, the primary studies might have been identified selectively. Data on disease progression came from a cohort of 79 PD patients (48 men, 31 women) randomised from the Department of Neurology of the Lund University Hospital in Sweden. In particular, the change in HY between the first and most recent visits in this cohort of patients was used to estimate disease progression, which also depended on HY Stage and age at PD diagnosis. Survival was derived from Swedish life tables. The utilities were estimated using the generic EuroQol (EQ-5D) scale, based on the time trade-off approach. Treatment effectiveness came from a study that involved a series of 14 patients (12 men, 2 women) with idiopathic PD who had received intrastratal grafts of dopamine-rich human embryonic ventral mesencephalic tissue. The rate of complications was retrieved from a published review.

Sources searched to identify primary studies

Not reported.

Criteria used to ensure the validity of primary studies

Not reported.

Methods used to judge relevance and validity, and for extracting data

Not reported.

Number of primary studies included

Seven primary studies provided the clinical data.

Methods of combining primary studies

The primary estimates appear to have been combined through a narrative approach.

Investigation of differences between primary studies

Not reported.

Results of the review
In terms of disease progression:

the age at onset was 56.8 (+/- 12.3) years;

the age at PD diagnosis was 58.6 (+/- 11.9) years;

the age at time of last visit was 69.2 (+/- 11.3) years,

the PD duration at first neurological assessment was 4.3 (+/- 4.0) years, and

the PD duration at time of last visit was 12.4 (+/- 6.1) years.

At the first visit, 34.2% of patients were HY Stage 1, 31.6% were Stage II, 22.8% were Stage III, 10.1% were Stage IV and 1.3% were Stage V.

At the most recent visit, 2.5% of the patients were HY Stage 1, 25.3% were Stage II, 20.3% were Stage III, 22.8% were Stage IV and 29.1% were Stage V.

No patient in the cohort died during the study follow-up.

The increased PD mortality in comparison with the general population was 1.8 for patients younger than 64 years and 1.5 for those aged 64 and older.

The health state utility was 0.90 for Stage I, 0.60 for Stage II, 0.30 for Stage III, 0.20 for Stage IV and 0.11 for Stage V.

Concerning treatment effectiveness, the 2-year postoperative data on grafted patients showed that clinical disease progression, in terms of HY stages, had ceased in 8 patients and was reversed in 6 patients. Specifically, after treatment, 0% of the patients were HY Stage I, 7.1% were Stage II, 42.9% were Stage III, 28.6% were Stage IV and 21.4% were Stage V.

The frequency of haematoma was 5% and that of dyskinesias 15%.

Measure of benefits used in the economic analysis

The summary benefit measure used was the cumulative number of quality-adjusted life-years (QALYs). These were estimated by combining the expected adjusted survival with utility weights in the decision model. Both series of data were derived from the literature. The benefits were discounted at an annual rate of 3%.

Direct costs

The authors did not explicitly state the perspective adopted in the study but the analysis included the direct costs associated with inpatient care, outpatient care, pharmaceuticals, investigations, transport and home help. The intervention costs (transplantation) covered procedural costs and the costs of haematoma and dyskinesias. The unit costs and the quantities of resources used were not presented separately. However, the costs were stratified by HY stage and by age (less or more than 64 years). All costs associated with the treatment of PD were derived from a published study. The costs and resource consumption of novel treatments were derived from clinical trials and other studies, and some assumptions were also made. Discounting was relevant, as the long-term costs were evaluated, and an annual rate of 3% was used. The price year was 2002.

Statistical analysis of costs

The costs were treated deterministically.

Indirect Costs

The indirect costs were not considered.
Currency
Swedish kroner (SEK). These were presented in euros (EUR). The exchange rate was SEK 9.19 = EUR 1.00.

Sensitivity analysis
A univariate sensitivity analysis was carried out to assess the robustness of the cost-utility ratios to variations in the time horizon (10, 20 and 30 years), discount rate (0 to 5%), treatment efficacy (+/- 50%), occurrence of haematoma and dyskinesias (+/- 100%), the inclusion of medical costs only, and the utility weights (derived using the visual analogue scale method). Alternative values were mainly based on authors' opinions. A threshold analysis was also performed to determine the price premium (profit or compensation for intervention developmental costs).

Estimated benefits used in the economic analysis
During a 25-year time horizon, the cumulative QALYs for patients who were preoperative HY Stage III were 2.880 in the control group and 3.753 in the intervention group (difference 0.873).

For patients who were preoperative HY Stage IV, the cumulative QALYs were 2.183 in the control group and 3.316 in the intervention group (difference 1.133).

Cost results
During a 25-year time horizon, the expected costs for patients who were preoperative HY Stage III were EUR 158,943 in the control group and EUR 156,467 in the intervention group (difference -EUR 2,476).

For patients who were preoperative HY Stage IV, the expected costs were EUR 186,279 in the control group and EUR 163,558 in the intervention group (difference -EUR 22,721).

Thus, the intervention costs were more than offset by a reduction in other direct costs, mostly related to home help.

Synthesis of costs and benefits
The costs and benefits were combined by calculating incremental cost-utility ratios. However, in the base-case analysis, the novel intervention for PD dominated usual care, which was both less effective and more expensive.

The authors also used two commonly used thresholds (EUR 38,000 and EUR 70,000 per QALY) to assess the size premium for intervention developmental costs. The analysis showed that the maximum price premium to remain cost-effective ranged from EUR 12,000 to EUR 64,000 according to thresholds of EUR 38,000 to EUR 70,000 and depending on whether all costs, or only medical direct costs, were included in the analysis.

The sensitivity analysis showed that the base-case results were sensitive to variations in the time horizon (the intervention was less cost-effective with shorter the time horizons), treatment effect, and the method used to derive utility weights in the cohort of HY Stage III patients. The results were more stable for HY Stage IV patients. However, the intervention remained cost-saving or cost-effective for most variations in model parameters. The incremental cost per QALY for the intervention over control was higher than EUR 50,000 in only three cases. Specifically, with a time-horizon of 10 years for HY Stage III patients (EUR 66,192 per QALY), with a reduction of 50% in treatment effect for HY Stage IV patients (EUR 69,870 per QALY), and using the visual analogue scale to elicit preferences for HY Stage III patients (EUR 92,216).

Authors' conclusions
A novel therapeutic approach for Parkinson's disease (PD), such as dopamine cell replacement therapy, could be cost-effective in the Swedish health care system. There could be room for a price premium in Hoehn and Yahr (HY) Stage III-IV patients with early onset PD.
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was appropriate given that the novel approach was compared with usual care. However, usual care was not described in detail. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The clinical estimates used to populate the decision model were derived from published studies. Such studies might have been identified selectively as the authors made no mention of a systematic review of the literature. However, most of the sources were selected to find the most recent data on Swedish patients, thus they appear to have been appropriate for the objective of the study. Few details on the primary studies were reported. The authors noted that the clinical data were mainly derived from real life clinical practice rather than from clinical trials, which might be artificial and which would not reflect actual treatment patterns in a naturalistic environment. Some of the key model inputs were varied in the sensitivity analysis because of the uncertainty surrounding some estimates. A limitation of the analysis was the small sample of patients included in the main sources of data (both for the cohort of patients used to estimate disease progression and for the cohort of patients used to obtain treatment effect).

Validity of estimate of measure of benefit
QALYs are an appropriate measure of benefit since they incorporate two dimensions of health, survival and quality of life, which are relevant for patients with PD. The utility values were reported for all health states and some information on the sources of the utility data was provided. Further, the use of an alternative instrument to elicit quality of life scores was investigated in the sensitivity analysis. QALYs can be compared with the benefits of other health care interventions. The QALYs were discounted, in accordance with recommendations for economic evaluation.

Validity of estimate of costs
Only direct medical costs were included in the analysis. Limited information on the analysis was provided as most costs were derived from published studies. The costs were presented as macro-categories. Direct non-medical costs were excluded from the sensitivity analysis, and none of the analyses investigated the potential inclusion of indirect costs. The costs were likely to reflect the Swedish setting, thus caution will be required if extrapolating the results of the economic analysis to other contexts. The authors provided details of the total costs associated with different categories of costs and different health states. The authors reported the price year, thus facilitating reflation exercises in other time periods.

Other issues
The authors noted that some aspects of their analysis were similar to those of other published studies. However, no direct comparisons with other studies were made. The issue of the generalisability of the study results to other settings was not explicitly addressed and only a few sensitivity analyses were performed. This could limit the external validity of the analysis. The authors pointed out the validity of their decision model, which fulfilled most of the requirements recommended in the literature. Further, a unique aspect of the analysis was the estimate of the profit required to cover the development costs of the new technology. However, in general, there was high uncertainty around the cost-effectiveness estimates, as changes in some model parameters had a strong impact on model results and the efficacy data were based on a very small sample of patients.

Implications of the study
The results of this preliminary study support the use of a stem cell-based approach for the treatment of patients with PD. Future analyses are needed to corroborate the results of this study.

Source of funding
Supported by the Swedish Research Council, Skane County Council’s Research and Development Foundation, and the Kock, Soderberg, and Rut and Erik Hardebo Foundations.
Bibliographic details

PubMedID
16798054

DOI
10.1016/j.parkreldis.2006.04.006

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Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Aged, 80 and over; Cost-Benefit Analysis; Decision Making; Disease Progression; Dopamine /physiology; Genetic Therapy /economics; Humans; Middle Aged; Models, Econometric; Neurons /physiology /transplantation; Parkinson Disease /economics /surgery /therapy; Quality of Life; Sensitivity and Specificity; Stem Cell Transplantation /economics

AccessionNumber
22006002008

Date bibliographic record published
30/04/2007

Date abstract record published
30/04/2007