CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 21, NO. 7, 2005, 1005–1014

0300-7995
doi:10.1185/030079905X49653




ORIGINAL ARTICLE

# Cost-effectiveness of levodopa/carbidopa/entacapone (Stalevo*) compared to standard care in UK Parkinson's disease patients with wearing-off

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***Key words:*** **Cost-effectiveness – Levodopa/carbidopa/entacapone – Markov model – NHS – Parkinson's disease – Probabilistic analysis**



## ABSTRACT

*Background and methods:* A Markov model was developed to evaluate the cost-effectiveness of levodopa/carbidopa/entacapone (LCE;Stalevo*), in the treatment of patients with Parkinson's disease (PD) and end-of-dose motor fluctuations (wearing-off). LCE, with or without other antiparkinsonian medications, was compared to UK standard care, comprising traditional levodopa/dopa-decarboxylase inhibitor (DDCI) with other antiparkinsonian medications (e.g. selegiline or dopamine agonists) added as needed. The costs and outcomes of both treatments were projected over a period of 10 years from the perspective (a) of society as a whole and (b) of the UK National Health Service (NHS). Sensitivity analyses, including second-order Monte Carlo simulations, were performed to assess the confidence level of the primary results.

*Results:* Treatment with LCE produced an average gain of +1.04 quality-adjusted life-years (QALYs) per patient (2.57 vs. 1.53) in the base-case analysis (discount rate 3.5%). This gain was accompanied by a reduction in the total 10-year direct cost of care to society of £10 198 per patient (~ €14 800). From the societal perspective, therefore, LCE was dominant, producing better clinical outcomes with lower costs. This dominance was reiterated in all sensitivity analyses of society-focused analysis, including a shortening of the time-frame to 5 years.

Although treatment with LCE resulted in an increase in direct costs per patient of £3239 (£25 756 versus £22 517) to the NHS over the 10-year period analysed, the incremental cost-effectiveness ratio (ICER) of LCE was only £3105 per QALY gained (~ €4500). All ICERs to the NHS remained below £3800 per QALY gained in univariate sensitivity analyses applying different discount rates. When a shorter, 5-year, time-horizon was analysed, the NHS-related ICER for LCE was £6526 per QALY gained. All these ICERs are within the range usually considered to indicate

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acceptable or highly acceptable cost effectiveness (defined as < £30 000 per QALY gained).

The results of the Monte Carlo simulations indicated that the likelihood of LCE being either 'dominant' or more effective at an 'acceptable cost' from either the societal or the NHS perspective was high, exceeding 96% in the base-case sensitivity analysis, and was 93% even when all the uncertainties associated with the model were taken into consideration simultaneously. In particular, compared to standard care, the probability that LCE would provide better outcomes at a lower cost to society as a whole was 77% in the base-case sensitivity analysis and 72% in the scenario involving the highest degree of uncertainty.

*Conclusions:* In the UK the use of LCE to treat PD patients with wearing-off is beneficial to individual patients and likely to offer money savings to society as a whole, compared with UK standard therapy. The added cost of the medication itself is exceeded by the savings made in other direct costs of PD, mainly those relating to social care or PD-related private expenditures.



## Introduction

In patients with Parkinson's disease (PD) symptom severity is generally associated with decreased quality of life and increased cost of care. Following the 'honeymoon' period, the emergence of 'wearing-off' symptoms is a pivotal stage in the progression of Parkinson's disease (PD). As a matter of fact, the subsequent course of many such patients is one of increasing disability and dependency, leading to further decline in the quality of life and an increase in the direct costs of treatment[1–4].

Levodopa/carbidopa/entacapone (LCE; Stalevo*) is a recent addition to the PD armamentarium, comprising levodopa, the dopa-decarboxylase inhibitor (DDCI) carbidopa and the catechol-O-methyl-transferase (COMT) inhibitor entacapone, in one formulation. By blocking both major metabolic pathways of levodopa peripherally, LCE optimises levodopa therapy, increasing the bioavailability and extending the half-life of levodopa significantly[5]. LCE is approved for use in the European Union and the USA for the treatment of PD patients with end-of-dose motor fluctuations not stabilised by standard levodopa/DDCI products alone[6].

In double-blind, randomised, controlled trials it has been shown that combining levodopa/DDCI with entacapone increases 'on' time and attenuates wearing-off type motor fluctuations, as measured by patient diaries, Clinical Global Impression of Change (CGI-C) and the extensively validated Unified Parkinson's Disease Rating Scale (UPDRS). The daily levodopa requirement is reduced[7–11] and quality of life improved[12–14]. In the most recently completed trial, the TC INIT study, more than 70% of patients treated with LCE regarded themselves (as indicated by the CGI-C) as clinically improved compared to previous therapy with standard levodopa products and motor fluctuations were decreased in more than 80% of patients. Although the clinical improvement was similar in both study treatment groups (LCE vs. separate tablets of levodopa/DDCI + entacapone), patients rated their quality of life as significantly better on LCE with the mean difference between treatments being 9.8 mm (SD ± 20.9) on a 100 mm visual analogue scale ($p < 0.001$). Furthermore, 81% preferred LCE to the separate tablets[15].

Treatment with levodopa/DDCI and entacapone has been shown to be well-tolerated in controlled trials[7–11]. Experience gained up to September 2004 from more than 580 000 patient-years of exposure in post-marketing use has not given rise to particular safety concerns (Data on file, Orion Pharma International). More specifically entacapone has not been associated with liver function abnormalities and there is no need for liver function monitoring, unlike with tolcapone, the other COMT inhibitor available for treating PD[9,16,17].

Cost-effectiveness analyses of levodopa/DDCI used in combination with entacapone have concluded that the treatment strategy represents an effective use of healthcare resources, with a high likelihood of being 'dominant' (i.e. providing better outcomes at lower cost) versus reference therapy in some countries[18–20]. We now report the results of a cost-utility analysis of LCE in the context of UK National Health Service (NHS) provision, based on a Markov model of PD and the use of Monte Carlo simulation technique.

## Methods

Cost-utility analysis of LCE was carried out using a Markov model supplemented by the use of Monte Carlo simulation technique[21–25]. LCE was compared to UK standard care in typical PD patients with wearing-off type fluctuations and with a mean age of 66 years at treatment start. The present model was adapted for the UK setting based largely on the earlier work of Linna *et al*.[20].

### Model structure and perspective of the analysis

The model describes the transition of patients (i.e. the average course of disease) receiving either LCE (with or without other antiparkinsonian medications, such

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as selegiline or dopamine agonists) or UK standard care, through the seven modified Hoehn and Yahr (H&Y) stages[26] for 10 years or until death, which was defined as the absorbing state of the model. Standard care consisted of individually tailored treatment with traditional levodopa/DDCI products, to which other antiparkinsonian medications are added as needed. The 10-year total time horizon of the model was divided into shorter 6-month cycles, corresponding to the duration of follow-up in randomised, placebo-controlled pivotal trials of entacapone[7–11].

All analyses were conducted from two perspectives – that of the UK society as a whole and from the point of view of the NHS as the provider of health services.

## Model parameters

Cost and preference-based health-related quality-of-life (utility) values were assigned to each state of the Markov model (i.e. the modified H&Y stages). UK-specific direct costs were derived from the 1998 cross-sectional study of Findley *et al*.[27]. In that study, a random sample of 125 GP practices within 36 Regional Health Authorities (RHAs) and equivalents were approached by 42 different hospitals/specialist clinics, to subscribe all their PD patients to a survey. The sample thus derived was nationally representative both geographically and in terms of categories of the Under-Privileged Area economic deprivation score. Seventy-six of the practices approached distributed patient questionnaires to a total of 777 patients. Of those, 440 patients returned their questionnaires with useable data. The respondents were distributed across all H&Y stages; approximately a third of the respondents had been diagnosed with PD 6–10 years ago and 41% had been diagnosed during the previous 4 years. Fifty-two per cent of the respondents were men; 72 were less than 65 years of age. In addition to the self-completed portion of the questionnaire, which explored health and social care resource use, participants contributed to a an interview undertaken by a PD nurse specialist, designed to elicit details of, among other things, medications, PD status including H&Y stage when 'on' and state of mind/cognitive function (by Mini Mental State Examination). GP records were also examined for relevant data, including demographic details and current and concomitant medications.

Costs were differentiated into NHS costs, social services costs and private PD-related expenditures (see Appendix) and reported by age and H&Y stage. Together these three sources of cost comprise the total direct costs of PD borne by society. The study confirmed for the UK a finding previously reported for some other European countries, namely that the costs of PD increase with age, and, more particularly, with disease severity.

The original 1998 NHS costs of Findley *et al*.[27] were adjusted to 2003 cost levels based on the UK Consumer Price Index (CPI) for Health. Other costs were adjusted based on the CPI overall index. Base-case cost input values are summarised in the Appendix, which also includes a graphical representation of the principles of the model and a description of the different types of costs included.

Medication dosages for levodopa and for LCE were calculated from the work of Keränen *et al*.[3] and of Brooks and Sagar[10] in PD patients with wearing-off, and adjusted in accordance with the authors' personal clinical expertise (Lees, Findley). The weighted daily average dose of levodopa associated with the standard care of such patients was assumed to be 672 mg (range of means 400–700 mg per H&Y stage) and the weighted average dose frequency was 4.8 doses/day (range 3.2–5.2). All stated doses refer to means in the total wearing-off population, which is the target group of LCE treatment under the currently approved labelling. In each case, dose frequency and dosage reached a maximum at H&Y stage III–IV and then declined. It was assumed that use of LCE reduces the mean daily levodopa requirement by 10%; this represented a conservative assumption based on clinical experience and controlled trials of entacapone[28].

Medication costs were assigned using the NHS prices of levodopa/DDCI and LCE valid on 1 January 2005[29]. Thus, the cost of LCE was £0.724 per tablet, regardless of the strength of tablet used. The cost of levodopa/DDCI in the model was £0.001 per 1 mg (of levodopa) based on the proprietary levodopa/DDCI formulations co-careldopa (Du Pont, Letchworth Garden City, Herts, UK) and co-beneldopa (Roche, Welwyn Garden City, Herts, UK). The costs for all other PD medications were derived from Findley *et al*.[27], indexed to 2003 values and assumed to be same for both arms of the model.

Preference-based health-related quality-of-life values (i.e. utilities for each H&Y stage) were taken from the work of Schrag *et al*.[30], as mean EuroQoL (EQ-5D) summary indices. These mean utilities by H&Y stage are summarised in the Appendix.

A utility of zero and zero costs were attached to the absorption state ('dead'). In the base-case analysis, both costs and utilities were discounted at 3.5%.

Six-month transition probabilities between H&Y stages were derived from levodopa- and placebo-controlled pivotal trials of entacapone[7,8]. These probabilities were adjusted by incorporating in all H&Y stages the probability of death, derived from the mortality of the UK general population (www.statistics.gov.uk) and the patients' sex and age. A 2.3-fold increase in mortality was assumed for patients with PD compared with the UK age- and sex-adjusted general population[31,32]. As UK-specific data were not available, the initial distribution

of patients by H&Y stage at treatment start was based on data from fluctuating PD patients in a naturalistic burden of illness study conducted by Keränen *et al*.[3].

### Sensitivity analyses

Univariate sensitivity analyses were used to evaluate the effect of varying the discount rate from 3.5% used in the base-case to either 0% or 5% for both costs and utilities. Separately, the significance of the duration of the analysis period was explored by carrying out an analysis based on a 5-year period (with discount rate 3.5%).

In addition, a second-order Monte Carlo simulation with 1000 iterations was performed to explore other parameter-related uncertainties. At each iteration the values of the parameters were drawn at random from the respective distributions of costs, utilities, transition probabilities and initial H&Y distributions.

Skewness of the cost data was taken into consideration by drawing the cost estimate for each H&Y stage randomly from the complete set of the individual patient data values of Findley *et al*.[27] in the Monte Carlo simulation process. Within each H&Y stage, utility values were assumed to follow a normal distribution, dictated by the mean and standard deviations reported for a sample of PD patients in the UK by Schrag *et al*.[30]. Sampling of the utility values was undertaken from this normal distribution. Uncertainty around the trial-based transition probabilities and the initial distribution of patients by H&Y stage was accounted for in a similar fashion. The transition probabilities were modelled using β-distributions[20], where the means were the point estimates obtained from controlled trials of entacapone. Sampled transition probabilities of a chance node were adjusted to add up to 1 using the method of Sendi and Clemen[33]. The same procedure was undertaken for the initial H&Y distribution of the base case.

A value of £30 000 per quality-adjusted life-year (QALY) gained was used as the threshold of acceptable incremental cost-effectiveness, as usually applied by the UK National Institute of Excellence (NICE)[34].

All analyses were performed with DATA Pro Health, release 11 (TreeAge Software Inc., Williamstown, MA, USA).

## Results

The results of the base-case analysis are summarised in Table 1. From the broader, societal perspective, which takes the total direct costs of PD into account, LCE was a dominant choice. Compared with standard therapy, LCE produced better clinical outcomes with a gain of +1.04 QALYs, while reducing total direct costs by £10 198 per patient per decade (~ €14 800). From the perspective of the NHS, the additional QALYs of LCE versus standard care were achieved at an incremental cost of £3105 per QALY gained (~ €4500).

The base-case data proved robust in univariate sensitivity analyses, as well as sensitivity analysis relating to the chosen time horizon (Table 2). From the perspective of society, LCE was dominant irrespective of the discount rate used, and also when the analysis period was shortened from 10 to 5 years. The incremental cost per QALY from the perspective of the NHS remained less than £3800 at all other discount rates applied. On a 5-year time perspective, LCE provided 0.46 QALYs more than standard therapy, resulting in an incremental cost of £6526 per QALY gained on LCE.

The results of the probabilistic sensitivity analyses employing the random sampling of costs and utilities (with other variables held constant) are presented in Figure 1 (societal analysis) and Table 3 (NHS analysis). From the perspective of society, the analysis indicated that the probability of LCE being dominant (i.e. providing better clinical outcome at a lower cost) was 77% (base-case Monte Carlo simulations). At the acceptability threshold of £30 000 per QALY gained there was a 99% probability of LCE being either dominant or effective at acceptable cost. From the NHS perspective, the likelihood of LCE offering a cost-effectiveness ratio within an acceptable range was 97%.

***Table 1.*** *Results of the base-case analysis for a hypothetical 10-year evaluation of the cost-effectiveness of LCE (± other antiparkinsonian medications added as needed) versus standard care (levodopa/DDCI ± other antiparkinsonian medications added as needed) in patients with PD with wearing-off symptoms in the UK. Costs and utilities discounted at 3.5%.*

| | Societal perspective | | | NHS perspective | | |
|---|---|---|---|---|---|---|
| | Total direct costs (£) | QALYs | ICER (£/QALY) | NHS costs (£) | QALYs | ICER (£/QALY) |
| LCE | 59 563 | 2.571 | | 25 756 | 2.567 | |
| Standard care | 69 761 | 1.529 | | 22 517 | 1.524 | |
| Difference: LCE – standard care | –10 198 | +1.042 | Dominant | +3239 | +1.043 | 3105 |

ICER = Incremental cost-effectiveness ratio, i.e. the cost at which one additional QALY was gained (with LCE)
'Dominant' = better clinical outcomes plus lower costs

***Table 2***. *Univariate sensitivity analyses of the base-case scenario. LCE therapy remained dominant in all analyses from the societal perspective and well within conventional bounds of cost-effectiveness from the NHS perspective*

| | Societal perspective | | NHS perspective | |
|---|---|---|---|---|
| | Cost (£) | QALYs | Cost (£) | QALYs |
| Discount rate 5% | | | | |
| LCE | 54 781 | 2.39 | 24 281 | 2.40 |
| Standard care | 63 532 | 1.46 | 20 692 | 1.46 |
| Difference: LCE – standard care | –8751 | +0.93 | +3589 | +0.96 |
| Outcome | LCE dominant (better outcome, lower cost) | | ICER £3731† | |
| Discount rate 0% | | | | |
| LCE | 68 486 | 2.95 | 29 748 | 2.93 |
| Standard care | 80 617 | 1.71 | 25 428 | 1.69 |
| Difference: LCE – standard care | –12 131 | +1.24 | +4320 | +1.24 |
| Outcome | LCE dominant (better outcome, lower cost) | | ICER £3478† | |
| 5-year time period* | | | | |
| LCE | 34 200 | 1.70 | 15 500 | 1.70 |
| Standard care | 37 300 | 1.23 | 12 500 | 1.24 |
| Difference: LCE – standard care | –3100 | +0.46 | +3000 | +0.46 |
| Outcome | LCE dominant (better outcome, lower cost) | | ICER £6526† | |

* discount rate 3.5%
† ICER = incremental cost-effectiveness ratio, i.e. the cost at which one additional QALY was gained with LCE

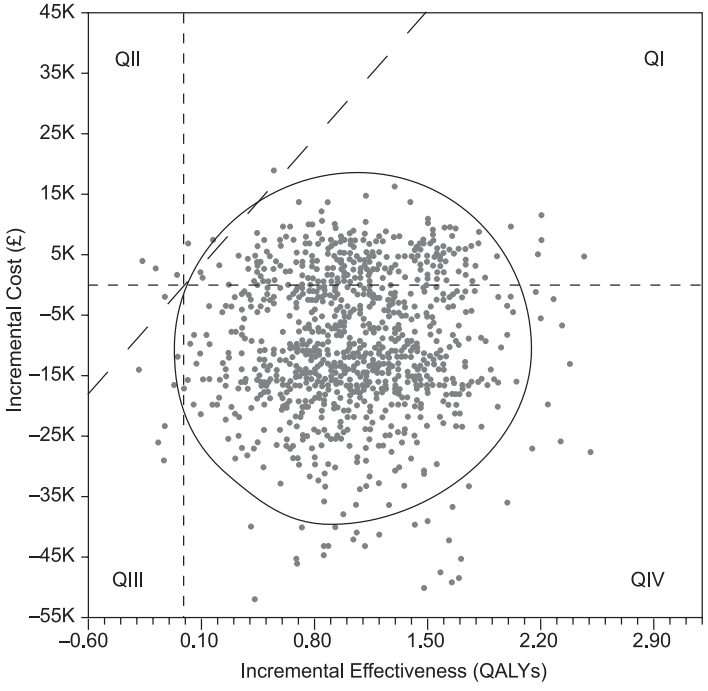


***Figure 1.*** *Probabilistic sensitivity analysis of the base-case scenario with 3.5% discount rate analysed from a societal perspective using Monte Carlo simulation with 1000 iterations and random sampling of total direct costs and utilities for each of the H&Y stages. The scatterplot of the ICER values for LCE indicated a 99% probability of LCE being either dominant (better outcome at lower costs) or more effective at an acceptable incremental cost (total proportion of all dots in quadrants QI and QIV in the area below the dashed willingness-to-pay [WTP] slope). The probability that LCE resulted simultaneously in better outcomes and in net savings to society was 77% (QIV)*

In the second type of Monte Carlo simulation, with random sampling of costs, utilities and transition probabilities, there was a 72% probability of LCE being dominant from a societal perspective. In a further 24% of simulations LCE offered better clinical outcome with an acceptable incremental cost per QALY (i.e. ICER < £30 000). The overall probability of the cost-effectiveness results favouring LCE thus exceeded 95%, a finding that was robust to variations in discount rate. Inferiority (i.e. worse outcome plus greater cost) was demonstrated in < 2% of simulations in the societal analysis, regardless of the discount rate applied.

In the complementary analysis undertaken from the NHS perspective LCE was dominant in 135 of the 1000 simulations (14%) and provided additional QALYs at a cost of less than £30 000 per QALY in a further 779 simulations (78%). Thus, the overall probability that LCE was superior to standard therapy or offered greater effectiveness at acceptable expense was 92%. The chance of inferiority was < 4%. The probability of superiority or an acceptable ICER of LCE versus standard therapy exceeded 90% at discount rates of 0% or 5%.

Figure 2 and Table 4 illustrate the scenario of greatest uncertainty in which the costs, utilities, transition probabilities and initial H&Y distribution were all

***Table 3.*** *Probabilistic sensitivity analysis of the base-case scenario (discount rate 3.5%) from the NHS perspective. LCE ICER results of the Monte Carlo simulation with 1000 iterations, with random sampling of NHS costs and utilities at each H&Y stage*

| Treatment consequences with LCE vs. 'standard care' | | | | |
|---|---|---|---|---|
| Quadrant | Effectiveness: QALYs on LCE | Cost to NHS (£) on LCE | LCE ICER (£/QALY) | % |
| IV | More | Less | Dominant | 13.3 |
| I | More | More | < 30 000 | 83.3 |
| I | More | More | > 30 000 | 1.9 |
| III | Less | Less | n.a. | 0.1 |
| II | Less | More | Inferior | 1.4 |

n.a. = not applicable

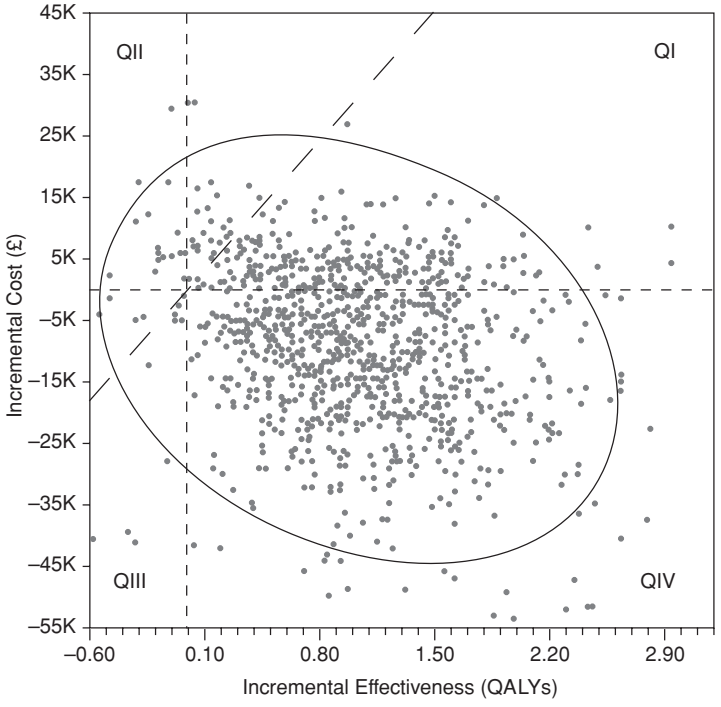


***Figure 2.*** *Probabilistic sensitivity analysis exploring the scenario with the greatest degree of uncertainty involved. Analysis was carried out from the societal perspective using 3.5% discount rate and Monte Carlo simulation with 1000 iterations. Initial H&Y distribution, transition probabilities, total direct costs and utilities were all randomly sampled from the respective distributions derived from PD patients in the UK. The scatterplot indicated a 94% probability of LCE being either dominant (better outcome at lower costs) or more effective at an acceptable incremental cost (dots in quadrants QI and QIV in the area below the dashed willingness-to-pay [WTP] slope). The probability that LCE resulted in better quality of life for patients and net savings to society was 72% (QIV)*

***Table 4.*** *Probabilistic sensitivity analysis accounting for the greatest degree of uncertainty from an NHS perspective (i.e. Monte Carlo simulation [1000 iterations] with random sampling of costs, utilities, transition probabilities and initial H&Y distribution). Discount rate 3.5%*

| Treatment consequences LCE vs. 'standard care' | | | | |
|---|---|---|---|---|
| Quadrant | Effectiveness: QALYs on LCE | Cost to NHS (£) on LCE | LCE ICER (£/QALY) | % |
| IV | More | Less | Dominant | 10.1 |
| I | More | More | < 30 000 | 82.6 |
| I | More | More | > 30 000 | 4.4 |
| III | Less | Less | n.a. | 0.6 |
| II | Less | More | Inferior | 2.3 |

n.a. = not applicable

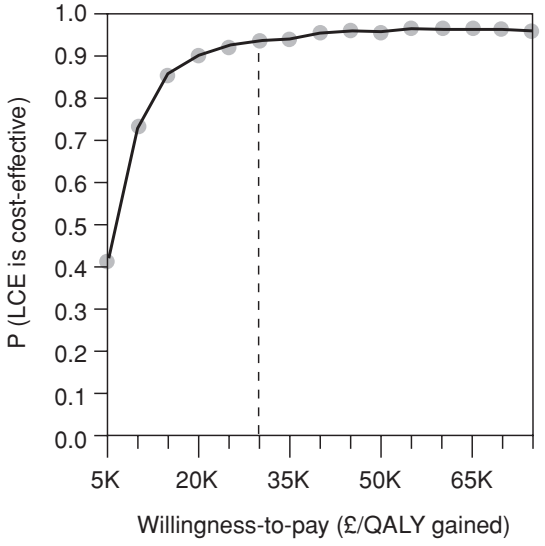


***Figure 3.*** *Cost-effectiveness acceptability curve – NHS perspective; the scenario of greatest uncertainty (four randomly sampled variables). The vertical dotted line identifies a nominal willingness-to-pay (WTP) of £30 000 per QALY: in the given scenario, at this specific threshold, LCE is cost effective in > 90% of cases. In the base case the corresponding figure was 97%. From the present curve it can be seen that even when applying a clearly lower threshold for marking societal WTP, e.g. £15 000 per QALY gained, the probability that LCE is cost-effective would still exceed 85%*

randomly sampled from the respective distributions within a single analysis (discount rate 3.5% as in base-case). In this instance LCE was dominant in 722 simulations (i.e. with a probability of 72%) from a societal perspective (Figure 2) and effective at an additional cost not exceeding £30 000 per QALY in 216 simulations (22% probability). The probability of LCE being inferior to standard therapy was < 2%. The corresponding percentages in the NHS analysis (Table 4) were 10%, 83% and < 3%, respectively.

The data may also be portrayed as an acceptability curve that depicts the likelihood of cost-effectiveness of a new treatment option (in our case LCE) versus the existing standard at various thresholds of societal willingness-to-pay (WTP)[34–36]. This principle is illustrated in Figure 3, which shows the LCE cost-utility acceptability curve derived from the last of the Monte Carlo simulations from the NHS perspective (i.e. the scenario of greatest uncertainty). As noted earlier, the probability of LCE being cost-effective at a WTP threshold of £30 000 per QALY was 93% in this scenario. Inspection of the acceptability curve (Figure 3) reveals that there is a > 85% probability that LCE is cost-effective even when WTP is set at £15 000 per QALY gained.

Similar acceptability curves derived from the base-case Monte Carlo simulations revealed that there was a > 90% probability that the incremental cost of LCE in relation to the additional benefit gained (1.04 QALYs) would be acceptable even at a WTP threshold as low as £8000 per QALY gained from the societal perspective, and £15 000 per QALY gained from the NHS perspective.

## Discussion

The relative lack of information about the cost of treating PD in the UK may be inferred from the fact that one recent estimate offered a range from £560 000 to £1.6 million per 100 000 head of population, with no distinction between different types of cost[37]. The present exercise, which used UK cost data of relatively recent origins and differentiated NHS costs from other direct costs[27], is thus a pertinent addition to the literature on this subject.

The clinical benefits of combining levodopa/DDCI with entacapone have been amply demonstrated in controlled trials of PD[7–11,38]. Moreover, the benefits of this therapy have been shown to extend to at least 3 years[39], a consideration that supports the results of our present analysis. Our calculations build upon these core clinical data.

The results indicate that the health-economic case for LCE is attractive when the drug is examined in the narrower perspective of the NHS and compelling when examined in the broader societal context. Replacing

traditional levodopa/DDCI with LCE in the standard care of patients with wearing-off provides better quality of life for the patients in the long term. Moreover, this strategy is likely to result in overall savings of ~ £10 200 (~ €14 800) per patient per decade for the society as a whole, as a result of postponing the need for non-NHS-funded care, e.g. institutional residential care. The cost savings will be shared between the formal social care system, the patients themselves, as well as their networks of family and friends. From the viewpoint of the NHS, the additional drug costs from LCE are for the most part recouped by savings in secondary care. Comparison of LCE ICER data from our analysis with ICERs of other interventions examined in earlier NICE appraisals indicate that the cost of using LCE in the manner described by our model is firmly within the bounds considered by NICE to be an effective use of public funds[34]. These findings should be of interest to the UK Department of Health in regards to prioritisation of the provision of chronic care and to the Primary Care Trusts now responsible for contracting and administering the bulk of NHS expenditure in England[40,41].

Uncertainties arising from parameter assumptions, as well as from the model structure itself, are inherent to any modelling exercise[24,42], for which reason sensitivity analyses are needed. The results of all the univariate sensitivity analyses and the various Monte Carlo simulations indicate that the level of confidence associated with the base-case results is consistently high, within the limitations of the input data. These limitations include equal utility of each H&Y stage regardless of treatment, an assumption that may under-represent the benefits of LCE treatment. The use of a range of costs derived from original cost figures of individual patients[27] is a distinctive feature of our analysis and one that enhances the relevance of our estimates as an aid to decision making. The robustness of the results indicates that, within the limits described by our model, clinicians and budget holders contemplating the use of LCE can be highly confident that this treatment strategy will prove beneficial to patients at acceptable cost to the NHS and in most cases even result in overall savings to society. Examination of acceptability curves similar to Figure 3 support this conclusion, even when relatively stringent (i.e. low) thresholds of societal WTP are applied.

As PD is a chronic, relatively slowly progressing disease, a total time horizon of 10 years was considered appropriate to sufficiently reflect the course of disease. However, the relatively advanced age of PD patients at diagnosis, coupled with the increased mortality due to the disease make the time to realisation of the economic benefit of LCE therapy a matter of interest. Estimates from various sources indicate that compared to age- and sex-matched normal populations, PD increases mortality by a factor of 1–2.9[31]. In our model we applied a correction factor of 2.3, derived from UK data[31,32]. This choice of adjustment factor may be regarded as 'conservative' to the extent that the higher the mortality, the shorter the period for the additional benefits to accrue and the lesser the likelihood that LCE will be cost-effective. In the shorter, 5-year, analysis period LCE nevertheless conferred more QALYs than standard care. From the NHS perspective the cost per QALY gained in this 5-year prediction was twice as high as in the 10-year scenario, but was nevertheless well within the range of acceptable costs per QALY implied by earlier NICE evaluations[34]. From the viewpoint of society as a whole, LCE remained dominant even in this shorter time frame, implying that the drug will probably confer net societal savings within the remaining life span of many patients.

Clinical experience of levodopa/DDCI in combination with entacapone, the cost-effectiveness data derived from our model, and the modernisation agenda of the UK NHS would thus all seem to favour the use of LCE to sustain patients in the best possible state of independence for as long as possible. Implementation of such a strategy requires the prompt detection of wearing-off symptoms as early as possible and, once the symptoms have been recognised, the early optimisation of levodopa treatment through the introduction of LCE. Moreover, a recent report indicates that using levodopa/DDCI with entacapone rather than without, is clearly beneficial even for patients who have not yet developed motor fluctuations[27]. This would appear to favour the early use of LCE as an integral part of pharmacotherapeutic strategies for PD beyond the current approved indication. This hypothesis is currently being tested in a multinational, randomised, double-blind, placebo-controlled trial, the STRIDE-PD study, which is being conducted to investigate whether use of LCE as the first levodopa therapy delays the onset of motor complications (e.g. dyskinesias).

Our present assessment of the cost-effectiveness of LCE in the UK is in line with the results of similar evaluations from other industrialised countries[18–20]. If it is assumed that the total PD population of the UK is ~ 100 000 patients, and if 45% of these patients are seen as potential candidates for LCE therapy, then, in addition to providing improved quality of life for patients, the use of this therapy could produce net savings to society of ~ £450 million per decade. The relationship of disease severity and PD-related costs and QoL in other developed countries is similar to that seen in the UK[1,2,4]. Therefore, although caution is always warranted when generalising cost-effectiveness results, it would seem reasonable to anticipate from these UK-derived estimates that LCE therapy is also likely to be a highly cost-effective therapy for PD in many other developed countries, with the potential to be cost-saving for society as a whole.

## Acknowledgement

This study was supported by Orion Pharma, Espoo, Finland. Mr Peter Hughes and Dr Gillian Gummer of Hughes associates, Oxford, UK, assisted in the preparation of the report.

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# Appendix

## Input data for the base-case model, representation of the model and summary of cost types

### *(a) Input data*

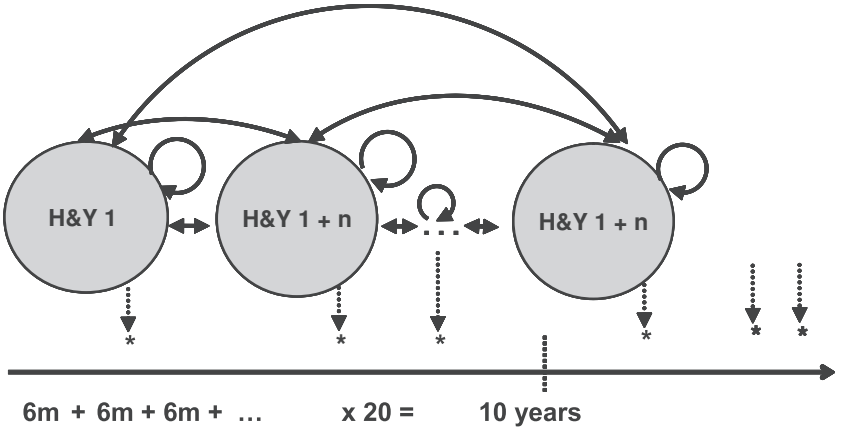
| Costs (at 2003 values)* | Treatment | | H&Y stage 1 | 1.5† | 2 | 2.5† | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|---|
| Mean NHS direct costs £/6 months | Standard care: | Mean | 818 | 830 | 842 | 1170 | 1518 | 2110 | 2379 |
| | | SD | 959 | | 747 | | 2684 | 2457 | 3994 |
| | | Median | 462 | | 619 | | 814 | 1308 | 853 |
| | LCE‡ | | 1146 | 1250 | 1272 | 1662 | 2051 | 2643 | 2891 |
| Mean total direct costs £/6 months | Standard care: | Mean | 1651 | 1680 | 1704 | 2500 | 3420 | 5571 | 9962 |
| | | SD | 2409 | | 2223 | | 4578 | 4629 | 7927 |
| | | Median | 748 | | 966 | | 1464 | 4586 | 11 150 |
| | LCE‡ | | 1979 | 2100 | 2134 | 2992 | 3953 | 6104 | 10 474 |
| Mean utility EQ-5D per health state (independent of treatment) | | Mean | 0.96 | 0.77 | 0.65 | 0.56 | 0.26 | 0.19 | –0.21 |
| | | SD | 0.13 | 0.20 | 0.34 | 0.29 | 0.32 | 0.62 | 0.17 |

* Cost data for 'whole-stage' H&Y categories were derived from the study of Findley *et al*.[27] inflated at 9–11% for total costs and at 17% for NHS direct costs. Inflators were derived from the UK CPI and CPI Health Index, respectively

† Costs for 'half-stage' H&Y categories were inferred from adjacent 'whole-stage' data

‡ Costs in LCE arm (by H&Y) = costs of standard care + LCE mean prescription cost – mean traditional levodopa/DDCI prescription cost

### *(b) Principles of the Markov model*




### *(c) Sources of direct cost*

| | |
|---|---|
| NHS costs | Primary care: drugs, GP visits, home visits by other health professionals<br>Secondary care: hospital in- and outpatient care |
| Social service costs | Home help/support, formal home care, meals on wheels, nursing homes, sitting services, day centres, miscellaneous |
| Private PD-related expenditures | Private residential/nursing home costs, home help services, special equipment, travel, miscellaneous |


CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-3009_4, *Accepted for publication*: 10 May 2005
*Published Online:* 25 May 2005
doi:10.1185/030079905X49653