Pramipexole v. levodopa as initial treatment for Parkinson's disease: a randomized clinical-economic trial

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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
Initial pramipexole treatment was compared with initial carbidopa-levodopa treatment in patients with early Parkinson's disease (PD). Pramipexole was taken as 0.25-mg, 0.5-mg or 1.0-mg tablets (or matching placebo) 3 times daily. Carbidopa-levodopa was taken as 12.5/50-mg or 25/100-mg capsules (or matching placebo). If needed, the doses were escalated over the next 10 weeks to 4.5mg pramipexole or 150/600 mg carbidopa/levodopa.

Type of intervention
Pharmacologic treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with early PD. No information on inclusion or exclusion was provided.

Setting
The setting was secondary care (outpatient). The economic study was carried out in the USA.

Dates to which data relate
Enrolment occurred between October 1996 and August 1997. The costs were estimated from sources ranging between 1995 and 2002, and were adjusted to 2002 US dollars.

Source of effectiveness data
The effectiveness data were 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
The authors stated that the trial methods and clinical outcome results have been published elsewhere. This abstract reports only those details published in the current publication. Further details may be obtained from the related studies (see 'Other Publications of Related Interest' below for bibliographic details).

The authors did not report that power calculations were used to rule out the influence of chance. The study sample comprised 301 patients treated with either pramipexole with levodopa placebo (151 patients) or carbidopa-levodopa...
with pramipexole placebo (150 patients). It was unclear how this sample was selected. The authors reported basic comparison data for the participants. The average age was 61 years, 65% were male and 95% were Caucasian.

**Study design**
The study was a randomised controlled trial. There was a 10-week dosage escalation period, and from week 11 through to 2 years patients remained on the same dosage. The patients were followed every 3 months over the 2-year period. The study was based at 17 sites in the USA and 5 sites in Canada. The authors did not report that blinding to any degree was carried out. Missing data, caused by loss of follow-up, was imputed assuming a linear increase in use and cost based on the pre-termination experiences. The levodopa group lost 19 (13%) patients, while the pramipexole group lost 23 (15%) patients. Withdrawals in the two groups occurred at similar times.

**Analysis of effectiveness**
The primary outcome of the trial was time to first occurrence of dyskinesias, wearing off and on-off effects. Data were analysed according to intention to treat. The only reported statistically significant difference was in the preference scores at baseline, and the authors made adjustments to correct for this difference.

**Effectiveness results**
The authors did not report the effectiveness evidence here (the reader is referred to the section 'Estimated benefits used in the economic analysis' reported below.

**Clinical conclusions**
The authors did not report the clinical evidence here.

**Measure of benefits used in the economic analysis**
Secondary outcomes included changes in the Unified Parkinson Disease Rating Scale, quality of life scales, adverse events and economic outcomes. Health preferences were estimated using the EuroQol EQ-5D system and EuroQol visual analogue scale (EQ-VAS), which measured quality-adjusted life-years (QALY-e and QALY-v, respectively). The participants of the clinical study gave valuations (self-administered) at baseline and 10, 26, 52, 78 and 102 weeks after randomisation.

**Direct costs**
The analysis was carried out from a "quasi-societal" perspective. The participants were asked to complete a health care use diary, recording all medical resource use as it occurred. This diary collated both direct and indirect costs including provider visits, outpatient procedures, tests and surgeries, acute hospitalisations, emergency department visits, medications, durable medical equipment, homes aid, long-term care, rehabilitation, and the number of days missed from gainful employment. The authors stated that time costs or productivity costs outside the traditional labour market were not collected. The quantities were measured throughout the clinical trial, while the prices were estimated from a variety of sources including published material and local health care facilities from between 1995 and 2000. The costs were then adjusted to 2002 prices using the Consumer Price Index. The authors stated that they did not adjust the 2nd year costs for inflation or discount the costs or effects because of the "relatively short 2-year time horizon”.

**Statistical analysis of costs**
Extensive statistical analyses were performed. These included chi-squared tests to compare proportions and t-tests to compare means. Tests were conducted to account for the non-normality of distributions, although these did not affect the significance of the results. All tests were 2-tailed and used a significance level of 5%.

**Indirect Costs**
See also the ‘Direct Costs’ section. Lost wages were obtained from population census data and stratified by age. The total lost income was estimated as the total number of days missed from work multiplied by the appropriate daily wage.

**Currency**

US dollars ($).

**Sensitivity analysis**

One-way sensitivity analyses were used to assess the impact of the cost of pramipexole being 50% of the base-case cost, and low and high estimates for the cost of levodopa. The authors also used confidence ellipses in the cost-effectiveness plane and cost-effectiveness acceptability curves to assess the impact of uncertainty on the results.

**Estimated benefits used in the economic analysis**

The authors reported that the cumulative effects gained measured in QALY-e were about twice those obtained when measured using QALY-v.

QALY-e gains were 0.1511 (95% confidence interval, CI: 0.0952 - 0.2069) in the pramipexole group and 0.1311 (95% CI: 0.0896 - 0.1727) in the levodopa group.

The incremental effectiveness (DeltaQALY-e) of pramipexole was 0.0200 (standard error, SE=0.0347).

QALY-v gains were 0.0603 (95% CI: 0.0230 - 0.0976) in the pramipexole group and 0.0686 (95% CI: 0.0394 - 0.0979) in the levodopa group.

The incremental effectiveness (DeltaQALY-v) of pramipexole was -0.0083 (SE=0.0241).

**Cost results**

The authors reported that the use of health care resources and costs was similar in the treatment groups.

Drug cost was the only cost category with a statistically significant difference between the two groups (mean difference $1,870; p<0.0001). The mean cost of days lost from work was not statistically significantly different.

The mean total cost was $9,412 in the pramipexole group and $7,274 in the levodopa group. The difference was $2,138, (p=0.07).

**Synthesis of costs and benefits**

The incremental cost-effectiveness of pramipexole compared with levodopa using the EQ-5D was $106,900 per QALY-e gained.

When using the EQ-VAS, pramipexole was dominated by levodopa (cost more and gained fewer QALYs).

For EQ-5D data, the probability that the incremental cost-effectiveness ratio falls in the definitely adopt region is 0.298. The probability that it falls in the ambiguously adopt region is 0.207, and in the definitely do not adopt region 0.495.

For EQ-VAS data, the probability that the incremental cost-effectiveness ratio falls in the definitely adopt region is 0.065. The probability that it falls in the ambiguously adopt region is 0.08, and in the definitely do not adopt region 0.855.

When one QALY is worth $50,000, pramipexole was associated with a welfare loss of $1,140 (SE=2,096) when using the EQ-5D and a welfare loss of $2,552 (SE=$1,667) when using the EQ-VAS.
When one QALY is worth $100,000, pramipexole was associated with a welfare loss of $2,966 (SE=2,707) when using the EQ-5D.

The probability that pramipexole is welfare enhancing changed with both the costs of pramipexole and the costs of levodopa.

Authors' conclusions
Both treatments had similar patterns of health service usage. The authors concluded that, over the first two years of therapy, it is "unlikely that pramipexole is welfare-enhancing even for very high valuations of a QALY" (quality-adjusted life-year via the EuroQol-visual analogue scale). Pramipexole was more likely to be welfare enhancing using EuroQol EQ-5D valuations.

CRD COMMENTARY - Selection of comparators
The authors chose to compare initial pramipexole treatment with initial levodopa treatment in patients with early PD. This choice was explicitly justified with a discussion of alternative treatments and an explanation that the chosen two treatments represented the "two most plausible competing alternatives" to "best approximate routine clinical practice". You should determine if this represents a valid comparison in your setting.

Validity of estimate of measure of effectiveness
The authors used a randomised controlled trial to compare the technologies of interest. This method allows the authors to minimise systematic differences between the patient groups. In this specific case, the preference weights were normalised and gains and losses measured from baseline for each person. The groups were otherwise comparable at analysis. Although the sample was not reported in great detail, the sample certainly appears to have been representative of the study population since it comprised sufferers of early stage PD. Extensive statistical analyses were carried out. To fully assess the internal validity of the clinical study the reader should refer to the two clinical papers where it is reported in full (see 'Other Publications of Related Interest' below for bibliographic details).

Validity of estimate of measure of benefit
The estimation of benefits (QALY-e and QALY-v) was obtained directly from the effectiveness analysis. The authors used the study to compare the valuations obtained from each way of measuring QALYs. These analyses enabled the authors to make appropriate comparisons and draw sensible conclusions that well reflected uncertainty in health preference valuation. This methodology also enables broader comparisons with a variety of health care technologies.

Validity of estimate of costs
The authors adopted a "quasi-societal perspective". They achieved this through estimating costs over a range of categories including the loss of economically productive time at work. The costs and the quantities were reported separately, thus enabling the authors to gain a good understanding of the cost drivers. A sensitivity analysis was carried out to assess the impact of changes in cost.

Other issues
Extensive analyses were used to explore the extent of uncertainty in the estimates of benefit. These included the use of confidence ellipses, cost-effectiveness acceptability curves and sensitivity analyses. The issue of generalisability was addressed as one of the limitations of the study, with the authors acknowledging that the results are generalisable only to the extent that the participants are similar to patients in routine clinical practice. Other limitations highlighted included the ability of self-reported utilisation diaries to capture all health service use, and the fact that the costs were proxy costs rather than true opportunity costs. Nevertheless, the authors were able to correct for some potential limitations. For instance, adjustments were made to correct for the different ranges of the QALY scales. The conclusions related principally to the methods of preference elicitation and uncertainty, and those drawn related well to the evidence contained within the paper.
Implications of the study
The authors did not make any recommendations following their study, although they highlighted that further work on the "optimal use and interpretation of direct, holistic preference measures and pre-scored health state classification" would be beneficial.

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Other publications of related interest


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