Cost-effectiveness of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: a Canadian perspective

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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
The study examined two treatments for neuropathic pain (NeP) associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN). The treatments were gabapentin (between 900 and 3,600 mg/day) and pregabalin (between 150 and 600 mg/day). In particular, the analysis focused, in the base-case, on a dosage of 2,400 mg for gabapentin and 430 mg for pregabalin.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised two hypothetical cohorts, one of patients with DPN and one of patients with PHN. Only patients with moderate or severe pain were considered.

Setting
The setting was primary and secondary care. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness data were derived from studies published between 1998 and 2006. The resource use data were derived from a survey carried out in 2003 and published in 2005. The price year was 2004.

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

Modelling
A published Markov model was used to assess the costs and benefits of the two treatments in hypothetical cohorts of 1,000 patients with either DPN or PHN over a time horizon of 12 weeks. The cycle length was one day as pain was managed from day to day. The three health states of the model were based on pain scores for NeP, which are generally rated on an 11-point scale (0 being no pain; 10 being worst imaginable pain). Thus, the model health states were "no or mild pain" (pain score < 4), "moderate pain" (pain score >= 4 but < 7) and "severe pain" (pain score >= 7 to 10). No absorbing state such as death was considered, as all patients were assumed to stay alive during the simulation. A schematic representation of the model was provided.
Outcomes assessed in the review
The outcomes estimated from the literature were treatment effect (defined as the change from baseline in pain intensity) and the utility values associated with the model health states.

Study designs and other criteria for inclusion in the review
The primary studies appear to have been identified selectively rather than through a systematic review of the literature. Data on treatment effectiveness came from three randomised clinical trials (RCTs), which were extensively described in terms of their inclusion criteria, the demographics of patients enrolled, and the baseline values of pain scores. Two clinical trials were selected for gabapentin (109 and 84 patients, respectively) and one for pregabalin. Globally, there were 105 patients with DPN treated with pregabalin and 84 treated with gabapentin, while there were 36 patients with PHN treated with pregabalin and 109 treated with gabapentin. The utility weights were derived from a cross-sectional survey in a sample of 126 NeP patients enrolled by 19 general practitioners in three Canadian provinces (Alberta, Quebec and Ontario) which completed the EuroQol EQ-5D.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
The use of RCTs ensures a high internal validity of the clinical estimates.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Four primary studies provided the data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
The authors stated that no head-to-head studies were found for the comparison between pregabalin and gabapentin, thus the efficacy data had to be based on different clinical trials. It was stated that these studies were similar in terms of the patients' baseline characteristics, age, pain scores and gender. However, no test of heterogeneity was carried out to corroborate this statement.

Results of the review
In patients with DPN, the mean changes from baseline in pain intensity over 12 weeks ranged from -13.3% (+/- 2.0) to -52.6% (+/- 4.7) with pregabalin and from -17.1% (+/- 2.9) to -39.7% (+/- 4.3) with gabapentin.

In patients with PHN, the mean changes from baseline in pain intensity over 12 weeks ranged from -14.7% (+/- 2.3) to -58.2% (+/- 6.4) with pregabalin and from -17.3% (+/- 2.5) to -36.0% (+/- 3.3) with gabapentin.

The utility values were 0.71 for "no or mild pain", 0.47 for "moderate pain" and 0.20 for "severe pain".

Adverse events and discontinuation were similar in the RCTs and were not considered in the model.
Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
The key assumption of the model was that all patients were perfectly compliant over the 12-week period. Another assumption was that non-pharmacological treatments did not confer any benefit. Finally, diabetic patients were assumed to have their diabetes controlled.

Measure of benefits used in the economic analysis
The summary benefit measures used were the quality-adjusted life-years (QALYs) and the number of days with no pain or mild pain. The QALYs were calculated by weighting utility values derived from the literature against the time spent in each health state. The change in pain score and the number of days with moderate or severe pain were also reported as model outputs. Discounting was not necessary given the short-term time horizon.

Direct costs
The viewpoint of the analysis might have been that of the third-party payer, although this was not explicitly stated. The categories of costs included in the analysis were study drugs, diagnostic tests, outpatient care, general physician and specialist visits, and non-pharmacological treatments. Diagnostic tests included computed tomography scan, magnetic resonance imaging, nerve conduction studies, quantitative sensory testing, Doppler sonography, electromyography, glycosylated haemoglobin, creatinine and complete blood count. Non-pharmacological treatments included physical therapy, drug infiltration, nerve block, transcutaneous electrical nerve stimulation and the implementation of a spinal stimulator. The unit costs were presented separately from the quantities of resources used. Resource use was derived from an Internet-based survey of 80 Canadian physicians (50 general practitioners, 10 anaesthesiologists, 10 endocrinologists and 10 neurologists) involved in the routine treatment of NeP patients. The survey was carried out in 2003. Drug dosages were estimated from the RCTs used to derive treatment effectiveness. The costs were mainly obtained from the Ontario Health Insurance Plan schedule of benefits and fees. Discounting was not relevant as the costs were incurred over a short timeframe. The price year was 2004.

Statistical analysis of costs
The cost estimates were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered.

Currency
Canadian dollars (CAD).

Sensitivity analysis
Univariate and multivariate sensitivity analyses were carried out to assess the robustness of the base-case results to variations in model inputs such as drug doses, time horizon, utility scores for specific conditions, pre-treatment pain score and treatment costs. The authors reported all the alternative values used in the sensitivity analysis. Confidence intervals (CIs) around cost-effectiveness and cost-utility ratios were also reported. These were based on 100 simulations of 1,000 patients each (first-order uncertainty).

Estimated benefits used in the economic analysis
In patients with DPN, the expected QALYs were 0.1150 (+/- 0.0003) with gabapentin and 0.1197 (+/- 0.0003) with pregabalin. The difference was 0.0047 QALYs in favour of pregabalin.
In patients with PHN, the expected QALYs were 0.1125 (+/- 0.0004) with gabapentin and 0.1211 (+/- 0.0003) with pregabalin. The difference was 0.0086 QALYs in favour of pregabalin.

In patients with DPN, the expected number of days with no or mild pain was 30 (+/- 0.3) with gabapentin and 36 (+/- 0.3) with pregabalin. There were 6 extra days of no pain or mild pain with pregabalin.

In patients with PHN, the expected number of days with no or mild pain was 27 (+/- 0.3) with gabapentin and 36 (+/- 0.3) with pregabalin. There were 9 extra days of no pain or mild pain with pregabalin.

**Cost results**

In patients with DPN, the expected costs per patient were CAD 837.53 with gabapentin and CAD 818.49 with pregabalin.

In patients with PHN, the expected costs per patient were CAD 720.61 with gabapentin and CAD 667.07 with pregabalin.

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies. However, pregabalin dominated gabapentin, which was both less effective and more expensive.

The 95% CI of the incremental cost per day with no or mild pain ranged from dominant to CAD 13 for patients with DPN and from dominant to CAD 3 for patients with PHN.

The 95% CI of the incremental cost per QALY ranged from dominant to CAD 15,708 for patients with DPN and from dominant to CAD 3,325 for patients with PHN.

The results of the sensitivity analysis basically confirmed the base-case analysis, although the cost-effectiveness ratios were somewhat sensitive to the gabapentin dose. Reducing the dosage of gabapentin to 1,800 mg (2,400 mg), but assuming equal efficacy, led to a reduction in the costs associated with gabapentin, thereby increasing the cost-effectiveness ratio for pregabalin. However, in general, pregabalin was found to be cost-effective. Even in a worst-case scenario with the cost of gabapentin 900 mg and the efficacy of gabapentin 1,800 mg, the analysis suggested that pregabalin remained cost-effective with an incremental cost per QALY of CAD 31,148 for DPN and CAD 20,101 for PHN. The incremental cost-effectiveness ratios generally remained well below commonly accepted cost-effectiveness thresholds.

**Authors’ conclusions**

Pregabalin was a cost-effective or cost-saving treatment strategy compared with gabapentin in the treatment of neuropathic pain (NeP) associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) in Canada.

**CRD COMMENTARY - Selection of comparators**

The rationale for the choice of the comparators was clear. Both drugs were widely used treatments for NeP in patients with either DPN or PHN. The dosages used were reported and alternative dosages were considered in the sensitivity analysis. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness data were derived from published studies. A systematic review of the literature was not undertaken because the primary sources were identified selectively so as to include the three clinical trials of pregabalin versus gabapentin. The information on utility weights was obtained from a sample of Canadian patients, which were appropriately selected in order to obtain data relevant to the setting of the analysis. Extensive information on the primary studies was provided. For example, the authors reported the sample size of the RCTs, the dosages administered
and the trial inclusion criteria.

Some assumptions were also made to simplify the decision model, but the impact of changes in these assumptions was not investigated. Although RCTs represent a robust source of clinical evidence, the authors noted that clinical effectiveness was not obtained from head-to-head clinical trials. Thus, indirect comparisons were made and this might represent a limitation of the analysis. The authors noted that patients enrolled in the trials were comparable at baseline in terms of their demographic and clinical factors, which strengthens the validity of the comparison. The authors acknowledged that a limitation of the clinical analysis was the small sample size for patients with PHN receiving pregabalin. The issue of uncertainty surrounding key clinical data was extensively addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
Two benefit measures were used in the analysis. The use of QALYs was particularly appropriate as quality of life is an important aspect of health for patients suffering from NeP. Moreover, QALYs can be compared with the benefits of other health care interventions. The approach used to calculate QALYs and the details of the sources of the utility weights were reported. The use of Canadian patients to obtain utility scores strengthens the analysis.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective of a third-party payer, although this was not explicitly stated. The costs were derived from the national health care payer in Canada. Extensive information on the unit costs and quantities of resources used was provided, which will help in replicating the analysis in other settings. The cost estimates were specific to the context of the analysis but alternative costs were used in the sensitivity analysis. The use of a large sample of experts to obtain resource use appears to have been appropriate, but these data should be considered as specific to the Canadian setting. The price year was reported, which will facilitate reflation exercises in other time periods.

Other issues
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. In general, the economic analysis should be considered specific to the Canadian context; it may not be easily transferable to other countries. The study referred to patients suffering from NeP associated with either DPN or PHN and this was reflected in the authors’ conclusions. The authors pointed out some potential limitations of the analysis, which were mainly related to the use of assumptions and the sources of some data. The results of the base-case analysis and the sensitivity analysis were extensively reported.

Implications of the study
The study results support the use of pregabalin for the treatment of NeP due to DPN or PHN.

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