The cost-effectiveness of pregabalin in the treatment of fibromyalgia: US 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.

CRD summary
The study examined the cost-effectiveness of pregabalin for treatment of severe fibromyalgia compared with placebo, duloxetine, milnacipran, gabapentin, tramadol and amitriptyline. The authors concluded that pregabalin was more beneficial and less expensive than the other available treatments for severe fibromyalgia, except when compared to amitriptyline. The study used valid and transparent methodology that should ensure the validity of the authors’ conclusions.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The study examined the cost-effectiveness of pregabalin for treatment of severe fibromyalgia compared with placebo, duloxetine, milnacipran, gabapentin, tramadol and amitriptyline.

Interventions
The interventions were pregabalin (150mg and 225mg twice daily), duloxetine (60mg once or twice daily), milnacipran (50mg and 100mg twice daily), gabapentin (600mg three times a day), tramadol (50mg, up to 200mg/day) and amitriptyline (50mg once daily). The background comparator was no treatment (placebo).

Location/setting
USA/primary and secondary care.

Methods
Analytical approach:
The analysis was based on a cost-effectiveness model with two parts: a decision tree model corresponding to the initial 12-week treatment period; and a medium-term Markov model based on response rates and treatment discontinuation. The overall time horizon was one year. The authors stated that a societal perspective was adopted.

Effectiveness data:
Two different approaches were used to estimate clinical inputs. First, evidence on the comparison between pregabalin and placebo for the first 12 weeks was taken from three published randomised controlled trials (RCTs). Second, the efficacy of other agents over placebo in the short-term was estimated by means of a systematic review of RCTs in various electronic databases. Estimates of efficacy were calculated using the indirect comparison methodology and pooled meta-analytic methods. A subgroup of patients with severe fibromyalgia (visual analogue pain score >6.5 and Fibromyalgia Impact Questionnaire >59 at baseline) was considered. Response rates were key inputs of the model and were defined as an improvement more than 30% in the pain score and a score of much improved or very much improved in the Patient Global Impression of Change questionnaire. The long-term likelihood of maintaining a therapeutic response was based on other published studies and the same drop-out rate and response loss of pregabalin was applied to all other comparisons (given the lack of valid data).

Monetary benefit and utility valuations:
Not considered.

Measure of benefit:
Responder days was used as the benefit measure.
Cost data:
The economic analysis included costs of medications, health care services associated with management of fibromyalgia and productivity losses due to fibromyalgia. Drug costs were estimated using effective drug consumption and reimbursement data from official nationwide databases. Both branded and generic formulations were considered. Other healthcare resources were estimated from a cross-sectional observational study of the burden of fibromyalgia in USA. Costs of these items were valued using Medicare and Medicaid payment rates. Productivity losses for patients and their caregivers were based on costing algorithms. In particular, generalised linear regression models were applied to assess the relationship between severity scores and annualised direct and indirect costs. Costs were in USA dollars ($).

Analysis of uncertainty:
One-way sensitivity analyses were carried out to identify influential inputs and to examine the robustness of model assumptions. A subgroup analysis was performed to assess whether baseline characteristics of the patient population were associated with better cost-effectiveness.

Results
Over one year, the expected total societal costs were $38,358 with placebo, $37,565 with pregabalin 150mg and $36,418 with pregabalin 225mg. The corresponding responder days were 59.58, 119.16 and 121.78. Both dosages of pregabalin were dominant over placebo, which was simultaneously less effective and more expensive.

The costs and responder days of the other treatments were: $38,001 and 90.27 with duloxetine 60mg; $38,476 and 92.51 with duloxetine 120mg; $37,788 and 90.03 with gabapentin; $37,041 and 109.96 with tramadol; $36,464 and 129.76 with amitriptyline; $38,380 and 72.09 with milnacipran 100mg; and $38,197 and 66.38 with milnacipran 200mg. Pregabalin 150mg was dominant over both duloxetine dosages, gabapentin and both milnacipran dosages, had an incremental cost per responder day of $57 compared to tramadol, but was dominated by amitriptyline. Pregabalin 225mg dominated all treatment except amitriptyline, which was the preferred treatment with an incremental cost per responder day of $6.

Greater cost savings were associated with pregabalin in subgroups of patients with severe fibromyalgia, use of sleep or anxiety medications and sleep problems at baseline.

Sensitivity analysis showed the robustness of base case findings to variations in key inputs. Compared to amitriptyline, pregabalin was cost effective when studies of amitriptyline that reported heterogeneous efficacy results and a small sample size were excluded from the meta-analysis. The probability of response after 12 weeks of treatment was a key input of the model.

Authors’ conclusions
The authors concluded that pregabalin was more beneficial and less expensive than the other available treatments for severe fibromyalgia, except when compared to amitriptyline.

CRD commentary
Interventions:
The authors justified the selection of the comparators. The comparators were appropriate as the analysis considered not only drugs officially prescribed for management of fibromyalgia but also older agents that were not indicated for fibromyalgia but had been recommended in treatment guidelines.

Effectiveness/benefits:
Data on short-term treatment effects for the comparison between pregabalin and placebo were obtained from a pooled analysis of three randomised controlled trials that were briefly described and should have ensured high internal validity. These were selected by the authors on the basis of their quality and provided estimates for the required subgroup of patients (severe fibromyalgia). A systematic review of the literature was conducted for treatment effect of other medications and only RCTs were selected. No head-to-head studies were found and the whole analysis had to be based on an indirect comparison using placebo as common comparator. There were differences in the selected studies that might have biased the results (acknowledged by the authors) but the results were quite stable to changes in model parameters. Long-term efficacy was assumed to be equal for all treatments and this might have been conservative against pregabalin. The summary benefit measure was disease specific and captured the intermediate impact of...
treatments on patients’ health. A more comprehensive benefit measure such as quality-adjusted life-years (QALYs) would have been more appropriate and would have enabled cross-disease comparisons.

Costs:
The economic analysis adopted a broad perspective. It appeared that all relevant cost categories were taken into account. Data sources were appropriate and consistent with the USA health care system. For example, the large observational study used for resource use (excluding drugs) was likely to have been a valid source and was representative of the USA context. No breakdown of cost items was reported for non-drug health care costs, which were appropriately related to disease severity. A similar approach was used for calculation of indirect costs. Reflation exercises in other time periods were not possible as the price year was not reported explicitly.

Analysis and results:
The study results were presented extensively (total and incremental findings were reported). Incremental cost-effectiveness ratios were calculated to identify the optimal treatment strategy. The issue of uncertainty was investigated using a deterministic approach that considered variations in key inputs of the model. The results of the sensitivity analyses were illustrated clearly and discussed. A clear description of the decision model was provided. The authors stated that a previous economic evaluation conducted in the UK had shown the cost-effectiveness of pregabalin but was based on a cost per QALY analysis. Some limitations were acknowledged and these mostly related to use of indirect comparisons with some heterogeneous studies and the need for assumptions. The study results may be relevant to other settings with similar drug relative prices and comparable other costs.

Concluding remarks:
The study used valid and transparent methodology that should ensure the validity of the authors’ conclusions.

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