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
This study examined the cost-effectiveness of pregabalin versus placebo, duloxetine, gabapentin, tramadol, or amitriptyline, for the treatment of fibromyalgia. Pregabalin 450mg was consistently more cost-effective than pregabalin 300mg and both doses were cost-effective over placebo and duloxetine, for a population with severe disease. The study was well conducted and the issue of uncertainty was addressed well, but the lack of an incremental analysis greatly limits the authors’ conclusions.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
This study examined the cost-effectiveness of pregabalin versus placebo, duloxetine, gabapentin, tramadol, or amitriptyline for the treatment of fibromyalgia, focusing on patients who were experiencing severe pain.

Interventions
The interventions were pregabalin 300mg or 450mg, duloxetine 60mg or 120mg, gabapentin 1,200mg, tramadol 200mg, and amitriptyline 50mg. No intervention (placebo) was the comparator.

Location/setting
UK/primary care.

Methods
Analytical approach:
The analysis was based on a decision tree, followed by a Markov model with a three-year time horizon. The authors stated that the perspective of the UK National Health Service (NHS) was adopted.

Effectiveness data:
The clinical data were identified in two ways. The efficacy of pregabalin (both doses) against placebo was from three large multicentre randomised controlled trials (RCTs), with similar designs and patient populations. These trials were selected by the authors. The remaining clinical data were identified by a literature review of clinical trials and the data were pooled in meta-analyses. Placebo was the common comparator for indirect comparisons. The response rate was the key clinical endpoint and it was defined as an improvement of 30% or more on the Numeric Rating Scale for pain and a score of either one or two on the Patient Global Impression of Change questionnaire. A one-year open-label extension of a pregabalin clinical trial was used for the long-term outcomes. Some assumptions were needed due to a lack of data on long-term outcomes for the other drugs.

Monetary benefit and utility valuations:
The utility values were derived from data collected, using the Short Form (SF-36) Health Survey, during the three pregabalin RCTs.

Measure of benefit:
Quality-adjusted life-years (QALYs) and the rate of responders were the summary benefit measures and they were discounted yearly at a rate of 3.5%.

Cost data:
The economic analysis included the costs of drugs, general practitioner visits, laboratory tests, and referrals to a specialist. The data on resource consumption were from published sources. Drug prices were from the British National Formulary (BNF) and the dosages were based on clinical trials and BNF recommendations. The costs associated with the model health states were based on data from two published studies. All costs were in UK pounds sterling (£) and were discounted at an annual rate of 3.5%. The price year was 2008.

Analysis of uncertainty:
Univariate and probabilistic sensitivity analyses were carried out on the key model inputs. A scenario was considered where the resource use among responders was lower than that among non-responders. The long-term drop-out rate for duloxetine and the response rate for amitriptyline were varied and subgroup analyses were performed for different patient populations.

Results
In patients with severe pain and those with severe fibromyalgia, for pregabalin 300mg over placebo the additional costs were £656.85, the proportion of responders was 3.40, and the QALYs were 0.028. The incremental cost per additional responder was £193.12 and the incremental cost per QALY gained was £23,166.

For pregabalin 450mg over placebo, the incremental cost per additional responder was £187.84 and the incremental cost per QALY gained was £22,533.

The cost-effectiveness ratios for pregabalin 300mg were £168.63 over duloxetine 60mg, £122.37 over duloxetine 120mg, £318.63 over gabapentin, and £1,031.40 over tramadol. For pregabalin 450mg they were £160.25 over duloxetine 60mg, £117.51 over duloxetine 120mg, £357.37 over gabapentin, and £817.56 over tramadol.

The cost-utility ratios for pregabalin 300mg were £20,228 over duloxetine 60mg, £14,679 over duloxetine 120mg, £38,222 over gabapentin, and £123,724 over tramadol. For pregabalin 450mg they were £19,224 over duloxetine 60mg, £14,096 over duloxetine 120mg, £35,737 over gabapentin, and £98,072 over tramadol.

Both pregabalin treatments were dominated by amitriptyline, which was less expensive and more effective.

The key drivers of the model were the efficacy and utility values. The sensitivity analyses showed that these results were generally stable.

Authors' conclusions
The authors concluded that pregabalin 450mg was consistently more cost-effective than pregabalin 300mg and both doses were cost-effective over placebo and duloxetine, for a population with severe disease.

CRD commentary
Interventions:
The authors stated that pregabalin was the first drug to be approved for the treatment of fibromyalgia in the USA and its efficacy and safety profile was widely documented in clinical trials. The other drugs were selected to represent the drug classes used to treat fibromyalgia while there was no licensed treatment; the selection of these comparators was valid.

Effectiveness/benefits:
The sources of evidence appear to have been valid. RCTs are considered to be appropriate due to their methodological strengths and the systematic search of sources should have ensured the selection of the most appropriate evidence for the other drugs. Some key details, such as the sample size, of the trials were reported. No head-to-head comparisons between intervention drugs were found and the analysis was based on indirect comparisons, using placebo as the common comparator, but it was not clear if this indirect comparison was actually conducted as its methods were not reported. The authors discussed the issues around the definition of the response rate for this patient population. QALYs were appropriate to capture the impact of the disease on a patient's health. Utility weights were based on data from the patients in the pregabalin trials, using a standard algorithm to convert SF-36 scores and this was appropriate.
Costs:
The categories of costs were consistent with the economic viewpoint. The unit costs, quantities of resources, price year, and discount rate were clearly reported. Little information on the data sources was provided and the methods of these cost studies were not described. The costs were treated stochastically in the probabilistic sensitivity analysis.

Analysis and results:
The results were clearly presented, but an incremental analysis was not conducted. This was not appropriate as the interventions appear to have been mutually exclusive options for the same patient population. Each of the pregabalin doses was compared separately with each of the other active interventions and not with each other. It was unclear whether this was due to issues with the indirect evidence or other methodological limitations, but the lack of an incremental analysis affects the validity of the results. The issue of uncertainty was satisfactorily investigated by means of different approaches. The authors noted that the cost-effectiveness of pregabalin might have been underestimated as there was limited data available on the medical resource use for patients who responded to treatment compared with those who did not. They acknowledged that there was a lack of direct head-to-head trials comparing the treatments and there was variation in the definition of the response rate. This means that caution is required in drawing conclusions from some of the cost-effectiveness results.

Concluding remarks:
The study was well conducted and the issue of uncertainty was addressed well, but the lack of an incremental analysis greatly limits the authors' conclusions.

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