Economic evaluation of oral treatments for neuropathic pain
Soledad Cepeda M, Farrar J T

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
Four treatments for neuropathic pain were evaluated:

- amitriptyline (average dose 75 mg/day, range evaluated 25 to 200 mg/day);
- carbamazepine (average dose 800 mg/day, range evaluated 600 to 2,400 mg/day);
- gabapentin (average dose 2,400 mg/day, range evaluated 900 to 3,600 mg/day); and
- tramadol (average dose 200 mg/day, range evaluated 100 to 400 mg/day).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with neuropathic pain from postherpetic neuralgia or diabetic neuropathy who were free of cardiovascular, hepatic and renal disease.

Setting
The setting was secondary care. The economic study was conducted at the Javeriana School of Medicine in Bogota, Colombia.

Dates to which data relate
The effectiveness and resource use evidence was derived from studies published between 1980 and 2005. The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies.

Modelling
A decision tree analysis, based on evidence from trials, was used to calculate the costs and benefits of the four strategies. A standard decision tree modelled the cost and effects of the strategies over a 1-month period. For each strategy, a patient could obtain pain relief and/or could develop major or minor side effects with the treatment. The two final health outcomes were pain relief or no pain relief. The amitriptyline arm also included the risk of developing myocardial infarction.
Outcomes assessed in the review
The outcomes assessed were the probability of having pain relief, the probability of having minor side effects and the probability of having major side effects. Major side effects were defined as resulting in the need to stop the medication as a result of side effects or a risk of myocardial infarction.

Study designs and other criteria for inclusion in the review
The study designs included in the review were firstly systematic reviews. Randomised double-blind clinical trials published after the latest search reported in the meta-analyses were also included. Studies were excluded from the review if they were reports of trials which were open or single masked, or if the trials evaluated combined therapies. The authors reported that since randomised controlled trials are not always the best resource for evaluating side effects, additional non-random studies were included to evaluate safety. They also reported that since there was limited evidence of the treatment effect of carbamazepine for diabetic neuropathy and postherpetic neuralgia, studies that evaluated trigeminal neuralgia were also included.

Sources searched to identify primary studies
The authors searched MEDLINE and the Cochrane Library for systematic reviews.

Criteria used to ensure the validity of primary studies
Randomised controlled trials were only included if they were double blind.

Methods used to judge relevance and validity, and for extracting data
The methodological quality of the studies was assessed by the Oxford Scale. This evaluated the quality of blinding, information on the randomisation procedure and the report of withdrawals. The method used to select and assess the relevance of the studies was not described.

Number of primary studies included
Twelve meta-analyses and four randomised, double-blind clinical trials were included in the analysis of effectiveness and safety. One further study was included to estimate the risk of myocardial infarction.

Methods of combining primary studies
The authors combined the results by extracting from the studies the number of patients who had at least 50% pain relief, and then calculating the probability. They updated the probability of meta-analyses by adding the results of the randomised trials, using the reciprocal of the squared standard error of each study as weights.

Investigation of differences between primary studies
The authors investigated differences between the primary studies. They reported the p-value of the Q statistic used to estimate homogeneity (P<0.05 indicative that the studies are not homogeneous).

Results of the review
For amitriptyline:
the probability of having 50% or more pain relief was 0.68,
the probability of having minor side effects was 0.80, and
the probability of having major side effects was 0.07.
For carbamazepine:

the probability of having 50% or more pain relief was 0.63,
the probability of having minor side effects was 0.44, and
the probability of having major side effects was 0.05.

For gabapentin:

the probability of having 50% or more pain relief was 0.40,
the probability of having minor side effects was 0.65, and
the probability of having major side effects was 0.10.

For tramadol:

the probability of having 50% or more pain relief was 0.59,
the probability of having minor side effects was 0.43, and
the probability of having major side effects was 0.12.

Measure of benefits used in the economic analysis

The outcome measure used in the economic analysis was the average health utility score. Health utilities were applied to pain, myocardial infarction and side effects. The utility of pain was derived from the Health Utilities Index Mark 3.
The utilities for myocardial infarction and minor side effects were derived from published studies. The authors noted a number of assumptions in their valuation of health utilities. First, they assumed that pain relief equated to a utility of 1. They also assumed that minor side effects continued throughout the 1-month study and that patients with major side effects suspended their treatment and, therefore, did not obtain pain relief. It was also assumed that the disutility of health states relating to minor side effects were the same for all types of minor effects.

Direct costs

Limited resource use data were presented. The authors stated that the cost boundary adopted was that of the third-party payer. Direct costs that were different among the treatment strategies were measured. These included the costs of a month's prescription, a physician office visit, a complete blood count test for patients who received carbamazepine, and inpatient and outpatient care for an episode of acute myocardial infarction. Diagnostic tests for patients with diabetic neuropathy were excluded from this analysis since the costs of the tests were similar in all treatment strategies.

The medication costs were derived from the average wholesale prices in the Red Book. The cost of a general practitioner's office visit was obtained from the American Medicare Fee Schedule. The cost of hospital care for an episode of acute myocardial infarction was obtained from an earlier study. The cost of the complete blood count was obtained from the Clinical Laboratory Fee Schedule of the American Medical Association. Discounting was not relevant because of the short time-period of the study. Prices were calculated for the year 2004. Since the costs of inpatient and outpatient care for an episode of acute myocardial infarction were derived from a published study using 2002 prices, these were reflated assuming an inflation rate of 4%.

Statistical analysis of costs

The costs appear to have been treated deterministically.

Indirect Costs
The indirect costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
A Monte Carlo simulation was conducted to explore uncertainty in the model variables. It was assumed that the variables took triangular distributions. Drug effectiveness, safety, the amount of medication needed to achieve pain relief and health state preference for myocardial infarction were all varied. The ranges of probabilities were derived by excluding studies that were outliers. The authors selected the range of costs to be used in the sensitivity analysis.

**Estimated benefits used in the economic analysis**
The average utility scores were 0.807 for amitriptyline, 0.807 for carbamazepine, 0.769 for tramadol and 0.697 for gabapentin.

These were based on a follow-up of 1 month.

**Cost results**
The cost per patient per month was $29 for amitriptyline, $50 for carbamazepine, $98 for tramadol and $270 for gabapentin.

These were based on a follow-up of 1 month.

The incremental cost was:
- amitriptyline, $0;
- carbamazepine, $20;
- tramadol, $68; and
- gabapentin, $241.

**Synthesis of costs and benefits**
An incremental cost-effectiveness analysis was conducted. Tramadol and gabapentin were dominated by amitriptyline and carbamazepine as they were both more expensive and less effective. Amitriptyline dominated carbamazepine since although it was equally beneficial it was cheaper.

The findings remained robust after sensitivity analyses to incorporate likely variations in costs, effectiveness, safety and utility values. Tramadol and gabapentin remained dominated strategies. Amitriptyline remained the cheapest strategy, although the effectiveness of carbamazepine was slightly higher. The incremental cost-effectiveness ratio for carbamazepine compared with amitriptyline was 43.296.

**Authors' conclusions**
Amitriptyline and carbamazepine were more cost-effective than tramadol and gabapentin. They should be considered as first-line treatments for neuropathic pain in patients free of renal or cardiovascular disease.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparators was clear since the treatments are commonly used in current practice. The reader should
consider whether this reflects current practice in their own setting.

**Validity of estimate of measure of effectiveness**
The authors undertook a systematic review of the literature. The methods and conduct of the review were well reported, with details provided of the methods used to judge the validity of the primary studies, combine details of the primary studies, and investigate differences between them. Estimates of effectiveness were derived credibly. In addition, the authors used weights to reflect differences in sample sizes as well as statistics to assess the homogeneity of the results.

**Validity of estimate of measure of benefit**
The measure of health benefit (health utilities) was derived from a decision tree analysis. The utility values were obtained from the Health Utilities Index Mark 3, which is reliable and has been widely validated, and from studies that obtained preferences directly from patients. The authors made several assumptions (see ‘Measure of Benefits Used in the Economic Analysis’).

**Validity of estimate of costs**
It appears that all the categories of costs relevant to a third-party payer perspective have been included in the analysis. However, the unit costs were not presented separately from the quantities of resources used, and this will not enable the study to be replicated in other contexts. The authors limited their analysis to direct costs. Some relevant costs were omitted from the analysis since only costs that differed between the strategies were considered. For example, diagnostic tests for patients with diabetic neuropathy were not included. Since they were excluded because the costs were the same, this omission is unlikely to have affected the authors' conclusions. The costs were derived from published sources. A sensitivity analysis of the costs was undertaken to reflect uncertainty in the data. The price year was reported. Discounting was not carried out, which was appropriate given the short follow-up period.

**Other issues**
The authors did not compare their findings with those from other studies. The issue of generalisability to other settings was not addressed. However, the authors did acknowledge that the results could not be generalised to patients with co-morbidities such as cardiovascular or renal disease in which amitriptyline could be contraindicated.

The authors reported a number of further limitations to their study, which related to the assumptions adopted. Some of these have been highlighted in earlier fields. Painful diabetic neuropathy and postherpetic neuralgia were considered as one entity, although the authors commented that there is evidence that the therapies evaluated produce similar results in multiple types of neuropathic pain. Some potential side effects associated with the treatments were not included. The authors excluded the possibility of decreases in platelet or white blood cell counts associated with the use of carbamazepine, because of limited data. The authors also noted the limitations associated with modelling only 1-month of therapy, but referred to the fact that if they had considered a longer time horizon, the results would have had limited validity because of the lack of evidence. The authors acknowledged that the sample sizes of the primary studies were small, which might have resulted in an overestimation of the treatment effect size and might have biased the findings towards the older treatments for neuropathic pain.

**Implications of the study**
The authors suggested that amitriptyline and carbamazepine should be first-line treatments for neuropathic pain of diabetic or postherpetic origin in patients free of cardiovascular, hepatic or renal disease.

**Source of funding**
Supported by the Colombian Chapter of the International Association for the Study of Pain.

**Bibliographic details**

---

NHS Economic Evaluation Database (NHS EED)
Produced by the Centre for Reviews and Dissemination
Copyright © 2017 University of York