Cost minimization analysis of antiepileptic drugs in newly diagnosed epilepsy in 12 European countries


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
Different drugs for epilepsy were evaluated. Lamotrigine (LTG) was compared with older anti-epilepsy drugs (AEDs), in particular carbamazepine (CMZ), phenytoin (PHT) and valproate (VPA).

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The target population comprised adult patients with newly diagnosed epilepsy.

Setting
The setting was primary and secondary care. The economic study was conducted in 12 Western and Central European countries (Belgium, Czech Republic, France, Italy, The Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, Turkey and UK).

Dates to which data relate
The effectiveness evidence came from trials published between 1985 and 1998. Resource use was evaluated through a panel of experts and was published in the paper. The price year was not stated.

Source of effectiveness data
The effectiveness data were derived from a review of published studies and from opinion-based estimates.

Modelling
A decision analytic model was constructed to represent the treatment pathways for patients with newly diagnosed epilepsy and to calculate the total costs. The pathways differed according to the patients' tolerance of AEDs and whether add-on drugs were used. The time horizon of the study was one year. An expert panel estimated the choice of drugs for first and second-line therapy for both partial and generalised epilepsy, as well as the treatment patterns, for each country.

Outcomes assessed in the review
The authors stated that the evidence shows that all drugs have similar effectiveness in terms of freedom from seizure. Thus, the input parameters used to evaluate resource use were the prevalence of side effects, drug tolerability and the
average dose prescribed in the trials.

**Study designs and other criteria for inclusion in the review**
Although the inclusion criteria were not explicitly stated, randomised controlled trials (RCTs) were included.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
The authors stated that 7 RCTs had been published since 1983, but only 5 contained data that allowed a cost-minimisation analysis.

**Methods of combining primary studies**
The primary studies were combined using a narrative method. Since none of the trials compared all four drugs directly, the cost-consequences were assessed separately for the five individual trials, in each country.

**Investigation of differences between primary studies**
The authors performed five different analyses for each country since the RCTs differed in many ways (protocol, sample size, follow-up time, comparators and withdrawal rates).

**Results of the review**
The clinical trials demonstrated similar effectiveness. Therefore, the trial results were used to estimate resource use.

The prevalence of side effects was 8.5 to 74% with CMZ, 56% with LTG, 10.3% with PHT (for "half" of the patients), and 10.9 to 49.4% with VPA, although in some trials it was not stated.

Drug tolerability (withdrawal rates) was not reported homogeneously. It was 11 to 49% with CMZ, 9 to 35% with LTG, 3 to 29% with PHT, 5 to 26% with VPA.

The average doses prescribed in the trials were described heterogeneously (mg/day in some, mg/kg in others). Examples of average doses were 600 mg/day CMZ, 100 or 200 mg/day LTG, 300 mg/day PHT and 924 mg/day VPA.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions for the model.

**Estimates of effectiveness and key assumptions**
It was assumed that 60% of patients suffered from partial epilepsy, and that patients who develop side effects would consult their general practitioner (GP) (or specialist in Turkey). Also, patients receiving CBZ, PHT or VPA would have their AED levels checked, and if a change of medication was needed then both a GP and specialist would be consulted.
The expert panel estimated the different first- and second-line treatments for each country and for each type of epilepsy (partial or generalised). They also estimated the proportion of patients treated with second-line monotherapy after the failure of first-line monotherapy.

**Measure of benefits used in the economic analysis**
As this was a cost-minimisation analysis, the study only evaluated the cost implications of the different strategies and assumed equal effectiveness. Therefore, no summary measure of benefit was used.

**Direct costs**
Discounting was not carried out. This was appropriate given the short-term horizon of one year. The quantities and the costs were analysed separately. The categories of costs included were drug acquisition costs, medical consultations (GP and specialists), medical investigations (laboratory tests, serum AED determinations) and hospitalisations (percentage of patients hospitalised, length of stay and emergency admissions). Although the economic perspective was stated to have been societal, it actually appears to have been that of the health service. The authors excluded the costs of treating the side effect symptoms, and rare and serious adverse events. The costs of initial investigations were also excluded, as they were common to all drugs.

The quantities of resource use for the different treatment pathways were estimated, based on a consensus panel of experts in each country, then derived using modelling. The authors stated that the unit costs were obtained from published sources and charging schedules, as described elsewhere (see Other Publications of Related Interest). Neither the dates of the resource consumption exercise nor the price year were reported.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not evaluated.

**Currency**
US dollars ($). Conversion rates for each of the 12 currencies were tabulated in the original paper.

**Sensitivity analysis**
Several one-way sensitivity analyses were performed to test whether and how changing any of the assumptions affected the overall results. The ranges selected were derived from authors' assumptions.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
Detailed data on resource consumption for each treatment pathway in each country and on the unit costs were given, but the total costs of the strategies for the 12 countries were not reported. The authors stated that treating a patient with LTG as first-line therapy was between two- and four-fold more expensive then treatment with CMZ, PHT or VPA, which share similar costs, over the first year (although in the abstract the difference reported was between two- and three-fold). The results were consistent in all the countries considered, despite the variation in the medical treatment of newly diagnosed epilepsy. The authors stated that the results were similar among the five different analyses carried out with each trial data.
The sensitivity analysis revealed that, although the results were sensitive to changes in the frequency of hospitalisation, drug dose, acquisition cost, frequency of follow-up visits and the proportion of patients on polytherapy, the overall conclusions of the analysis were not altered. Various assumptions that increased the cost of polytherapy increased the absolute costs of all drugs, thereby reducing the ratio of the cost differences among them.

**Synthesis of costs and benefits**
The costs and benefits were not combined.

**Authors’ conclusions**
Throughout Europe, the direct costs of prescribing lamotrigine (LTG) to patients with newly diagnosed epilepsy are likely to be two to four times higher than the cost incurred with carbamazepine (CBZ), phenytoin (PHT) and valproate (VPA), which are similar to one another.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparators appears to have been appropriate, as the drugs chosen seem to have been the usual classical therapies for epilepsy in the countries studied. Although the authors stated that several new drugs have been licensed for epilepsy, it is unclear why they chose to evaluate only LTG from all of the available newer drugs.

**Validity of estimate of measure of effectiveness**
The authors stated that the trials demonstrated similar effectiveness among the four evaluated drugs, but they did not report the effectiveness results from these trials. No details of the methodology of the review (e.g. sources, inclusion criteria) were provided, which make the results less transparent. If similar effectiveness had been statistically demonstrated, it was appropriate to undertake a cost-minimisation analysis, as the authors did.

**Validity of estimate of measure of benefit**
No estimate of benefit was used as the benefit was assumed to be equal. The benefits were based on cost differences only.

**Validity of estimate of costs**
The authors stated that, although the direct medical costs were incorporated into the paper, the perspective of society as a whole was chosen. However, the indirect costs, such as productivity losses, were not evaluated. Some costs that were common to all drugs (such as the initial work-up of the patients) were excluded from the analysis. Other excluded costs were the treatment of symptoms of side effects (generally handled by changing the dose or treatment), and rare and serious side effects.

Although resource use and practice pattern for each treatment path were reported in detail from the expert panel results, and the unit costs for each country were reported, an important omission of the paper was the total cost of each drug strategy in each country. The method by which the expert panel reached consensus was not stated. The authors only reported the relative cost differences between LTG and the other drugs, but it is difficult to evaluate their absolute impact and impossible to evaluate it by country. Thus, it is difficult for the reader to interpret the results and to adapt them to their own setting.

The sensitivity analysis was reported in a narrative. It revealed that, although the results were sensitive to changes in some parameters, the overall conclusions of the analysis were not altered. The price year was not stated, which hinders reflation exercises to other time periods or settings. It was stated that the unit costs were derived from published sources and charging schedules, but the authors did not provide a reference for this. The authors also reported the costs and charges, but did not differentiate between them.
Other issues
The authors reported some differences between the RCTs (e.g. sample size, follow-up time, comparators and withdrawal rates), but did not evaluate them in a quantitative way. They also did not evaluate the impact of the heterogeneity on the results.

Implications of the study
The finding that LTG is more costly than the other alternatives applies to all the health care systems considered in the study, despite variations in unit costs and medical practice. The differences in the side effect profile and tolerability observed among the four drugs are too small to affect the direct costs of treatment substantially. Choosing to treat such patients with expensive new AEDs, the clinical benefits of which are unclear, is likely to significantly increase the overall costs of treatment to both the health care system and to society as a whole.

The authors also made other recommendations. First, a broader evaluation of outcomes including, for example, productivity loss and quality of life, may reveal differences that were not considered in the study and should be further investigated. Second, the validity of this study can only be confirmed by comparing the results with a prospective economic appraisal of the use of AEDs in a naturalistic setting.

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Other publications of related interest

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