A cost-utility analysis of adjunctive treatment with newer antiepileptic drugs in the UK
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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
Five adjunctive antiepileptic drugs (AEDs) were studied. More specifically, clobazan (non-proprietary), gabapentin (Neurontin; Parke-Davis, UK), lamotrigine (Lamictal; GlaxoSmithKline, UK), topiramate, (Topamaz; Janssen-Cilag, UK) and vigabatrin (Sabril; Aventis Pharma, UK).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study comprised outpatient, adult patients with epilepsy.

Setting
The setting was the community. The economic study was carried out in London, UK.

Dates to which data relate
The dates to which the data related were not reported in the study. Further details may be available in other articles (Selai 1999 and/or Selai 1998., see 'Other Publications of Related Interest' below for bibliographic details). The unit costs were expressed in 2002 UK pounds.

Source of effectiveness data
The effectiveness data were derived from a single study

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used for the effectiveness data.

Study sample
A total of 125 patients with intractable epilepsy were recruited. Of these, 20 were receiving clobazan, 17 gabapentin, 26 lamotrigine, 47 topiramate and 15 vigabatrin. No power calculations were reported. The patients were approached at a tertiary referral centre in London after their medical consultation.

Study design
This was a single-centred, prospective, non-randomised observational study. The patients were asked to complete
questionnaires at baseline, and 3 and 6 months from baseline. Between interviews they were asked to keep a record of side effects, adverse events and any other epilepsy-related contacts with health services. All patients were followed up for 6 months. No method of blinding was reported.

**Analysis of effectiveness**
The analysis of effectiveness was conducted on an intention to treat basis. During the interviews, the National Hospital Seizure severity scale was used to assess seizure frequency and seizure severity. Patient quality of life was measured by the Quality of Life Assessment Schedule and the EQ5D instruments.

The mean age (standard deviation, SD) of the patients was 37.3 (SD=8.2) years in the clobazan group, 36 (SD=11) years in the gabapentin group, 37 (SD=9.8) years in the lamotrigine group, 38 (SD=12.6) years in the topiramate group, and 35 (SD=12) years in the vigabatrin group. The proportion of men was 40% in the clobazan group, 47% in the gabapentin group, 54% in the lamotrigine group, 59% in the topiramate group, and 67% in the vigabatrin group. All patients were experiencing seizures at baseline, despite being treated with one or more AEDs. The mean number of seizures per month was 31.76 (SD=62.46) with clobazan, 21.05 (SD=31.74) with gabapentin, 19.29 (SD=34.06) with lamotrigine, 25.36 (SD=41.17) with topiramate, and 31 (SD=62.4) with vigabatrin. The percentages of patients with convulsive seizures were 35% (clobazan), 29% (gabapentin), 50% (lamotrigine), 55% (topiramate) and 40% (vigabatrin), respectively. No adjustments for confounding factors were reported.

**Effectiveness results**
At 6 months, 78 patients were still on their prescribed drug. Of these, there were 9 (45%) on clobazan, 10 (59%) on gabapentin, 17 (65%) on lamotrigine, 31 (66%) on topiramate and 11 (73%) on vigabatrin. These differences were not statistically significant.

A detailed analysis of patient outcomes was reported in Selai (2002).

The mean utility values (EQ5D) for each treatment group were similar in magnitude at baseline and did not differ statistically. The values were 0.8435 (SD=0.0484) for clobazan, 0.8341 (SD=0.0505) for gabapentin, 0.8762 (SD=0.0277) for lamotrigine, 0.8479 (SD=0.0267) for topiramate and 0.8833 (SD=0.0294) for vigabatrin.

Compared with baseline, only patients treated with topiramate had a statistically significant increase in their EQ5D utility scores, (p<0.05).

The mean EQ5D scores at 6 months were 0.8260 (SD=0.0364) with clobazan, 0.7629 (SD=0.0608) with gabapentin, 0.8200 (SD=0.0444) with lamotrigine, 0.9117 (SD=0.0186) with topiramate and 0.8927 (SD=0.0313) with vigabatrin.

**Clinical conclusions**
Only topiramate and vigabatrin patients showed an increase in EQ5D scores, but only the first result was statistically significant.

**Measure of benefits used in the economic analysis**
Quality-adjusted life-years (QALYs) were used in the cost-utility analysis. The instrument used to measure this was the EQ5D. For this, guidelines laid down by the developers of this instrument were followed, using the UK general population tariff obtained by the time trade-off method.

**Direct costs**
The unit costs were reported for AEDs, contact with medical personnel, and for test and diagnostics. The resource quantities were not reported separately. The quantities and costs were estimated using actual data (questionnaires and patient notes). When a patient could not provide the dose of their medication, the average of the usual daily dose stipulated in the British National Formulary was used. Prices were also obtained from this source. Specialty-specific
hospital stays, outpatient visits, consultations, epilepsy-related visits to accident and emergency departments and to
general practitioners were recorded, as were visits from district nurses or social services. The dates during which the
quantities were collected were not reported. If necessary, the costs were inflated using Hospital and Community Health
Services inflation indices. The price year was 2002. Discounting was not relevant as the follow-up period was 6 months.

**Statistical analysis of costs**
The costs were treated stochastically. T-tests were used and SDs were reported.

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

**Currency**
UK pounds sterling ()

**Sensitivity analysis**
A probabilistic sensitivity analysis was carried out to assess the uncertainty surrounding the results due to sampling
variation. A non-parametric bootstrap method was applied.

**Estimated benefits used in the economic analysis**
The mean QALY gains were -0.0175 (SD=0.0526) with clobazan, -0.0712 (SD=0.0600) with gabapentin, -0.0562
(SD=0.0429) with lamotrigine, 0.0638 (SD=0.0274) with topiramate and 0.0093 (SD=0.0273) with vigabatrin.
Incremental benefits were not reported. The duration of health benefits were as in the clinical study.

**Cost results**
The mean total costs were 1,096 (SD=277) for clobazan, 1,248 (SD=125) for gabapentin, 1,502 (SD=311) for
lamotrigine, 1,348 (SD=162) for topiramate and 919 (SD=26) for vigabatrin. Incremental costs were not reported. The
duration considered for the intervention quantities and cost calculations was the same as in the clinical study.

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios (ICERs) were calculated. Only vigabatrin and topiramate resulted in increases in
utility scores. Vigabatrin treatment resulted in a higher utility score gain at lower cost. It dominated clobazan,
gabapentin and lamotrigine.

Adjunctive treatment with topiramate had an ICER of 7,869 per QALY gained when compared with vigabatrin.

Cost-effectiveness acceptability curves from the bootstrap samples were developed. From these, at low values of
willingness to pay for a QALY, adjunctive vigabatrin had the highest probability of being optimal.

At ceiling ratios of over 10,000 per QALY, the adjunctive topiramate treatment had more than 50% chance of being
optimal. This probability equals 76% when the ceiling ratio is 30,000 per QALY.

**Authors' conclusions**
Topiramate had an incremental cost-effectiveness ratio (ICER) of 7,869 per quality-adjusted life-year (QALY) gained
when compared with vigabatrin. It also had more than 50% chance of being optimal if the ceiling ratio was above
10,000 per QALY.
CRD COMMENTARY - Selection of comparators
As the authors did not provide any explicit justification, it was unclear why these particular AEDs were chosen as the comparators. The reader should decide if they represent current practice in their own setting.

Validity of estimate of measure of effectiveness
This was a non-randomised observational study, a design which was not entirely appropriate for the study question. Details of the clinical study were reported in a separate paper, thus it is not possible to comment on the internal validity of the study. However, the authors acknowledged some limitations to their study. Specifically, the non-randomised nature of the study and different group sizes at baseline, although the group characteristics seemed not to differ at baseline. The analysis was conducted on an intention to treat basis. However, the study sample sizes were small and lacked power to detect statistically significant differences in effects. The study sample seems to have been representative of the study population.

Validity of estimate of measure of benefit
The authors derived a summary measure of benefits. The measure of benefits used was the health utility (QALYs) measured over a 6-month period using the EQ-5D questionnaire with UK-based weights. According to the authors, this instrument has a good capacity to discriminate between groups of patients after different events. However, they reported that the small changes found when measuring changes in utilities over the follow-up period might have been due to the general population tariffs used in the study.

Validity of estimate of costs
The analysis was performed from the perspective of the National Health Service paying for treatment. It appears that all the relevant cost categories and relevant have been included in the analysis. The unit costs were presented separately, thus enhancing the reproducibility of the study to other settings. Resource use information was derived from patient interviews and the authors acknowledged that this might have led to recall bias. No statistical analysis of the resource use quantities was reported. However, a statistical analysis of the costs was performed and means and standard errors were reported.

Other issues
The non-parametric bootstrap method was applied to assess the uncertainty surrounding the results on account of sampling variation. Results of these replications on the cost-effectiveness plane were presented and cost-effectiveness acceptability curves were developed. The authors compared their results with those from other studies. The issue of generalisability was addressed implicitly when reporting that the study was based in a single centre and it would be useful to replicate it in other centres. Another limitation reported was the short follow-up for a chronic disease. Studies with longer follow-up, to assess the impact of AEDs in the long run, are warranted.

Implications of the study
The findings of the study suggest that topiramate has an incremental cost-effectiveness ratio within conventionally accepted thresholds. Although associated with some limitations, observational studies provide a valuable source of information for the economic evaluation of AEDs as an alternative to modelling with hypothetical populations.

Source of funding
None stated.

Bibliographic details
Other publications of related interest


Indexing Status
Subject indexing assigned by CRD

MeSH
Anticonvulsants /administration & dosage /adverse effects /economics /pharmacology /therapeutic use; Cost-Benefit Analysis; Costs and Cost Analysis; Epilepsy /drug therapy /prevention & control; Phenytoin /administration & dosage /economics /therapeutic use; Piracetam /administration & dosage /economics /therapeutic use; Primidone /administration & dosage /economics /therapeutic use; Quality-Adjusted Life Years; Valproic Acid /administration & dosage /economics /therapeutic use; Vigabatrin /administration & dosage /economics /therapeutic use

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