Assessing the cost-effectiveness of new pharmaceuticals in epilepsy in adults: the results of a probabilistic decision model
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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
Treatments for epilepsy were examined in adults in three situations:

- monotherapy for newly diagnosed patients,
- monotherapy for refractory patients, and
- combination therapy for refractory patients.

Since the analysis separately considered the treatment of partial and generalised seizures, six scenarios were finally considered. For the treatment of generalised seizures, the following comparisons were made:

- valproate and lamotrigine as monotherapy for newly diagnosed patients;
- valproate and lamotrigine as monotherapy for refractory patients; and
- lamotrigine or topiramate as combination (adjunctive) therapy for refractory patients.

For the treatment of partial seizures, the following comparisons were made:

- carbamazepine, valproate, lamotrigine, oxcarbazepine, and topiramate as monotherapy for newly diagnosed patients;
- carbamazepine, valproate, lamotrigine, oxcarbazepine as monotherapy for refractory patients; and
- lamotrigine, gabapentin, levetiracetam, oxcarbazepine, tiagabine, topiramate as combination (adjunctive) therapy for refractory patients.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of adults with epilepsy.

Setting
The setting was secondary care. The economic study was carried out in the UK.
Dates to which data relate
The effectiveness data were obtained from studies published between 1990 and 2002. The resource use data and costs came from studies and sources published in 1998 and 2002. The prices used were those estimated in 2002 - 2003.

Source of effectiveness data
The effectiveness data were derived from a synthesis of completed studies and authors' assumptions.

Modelling
A state transition model (semi-Markov process) was constructed to represent the treatment of epilepsy as a series of discrete states through which the patients progressed. A key feature of the model was that the estimated probability that the patient would progress to the next state in the treatment sequence varied depending on how long the patient had been in his or her current state. The states represented the following treatment sequence: newly diagnosed patients start with monotherapy, those who do not respond switch to a different monotherapy, subsequent failure to respond results in treatment with combination therapy, and those who still do not respond ultimately receive a maintenance therapy. Patients could die because of epilepsy or any other reasons at any stage in the model.

In the model, patients only remained on a treatment if they responded adequately. Response was defined as "a patient both tolerating the study drug and being seizure free" for monotherapy for newly diagnosed patients, and as "a patient tolerating the study drug and achieving a 50% reduction in seizure frequency compared to a baseline period" for monotherapy for refractory patients and combination therapy.

The time horizon of the model was 15 years and cycles of 6 months were considered. A simplified version of the model was reported.

Outcomes assessed in the review
The outcomes assessed from the literature were the probabilities of treatment failure and response, mortality rates and utility values.

Study designs and other criteria for inclusion in the review
A systematic review of the literature was undertaken to identify primary estimates of response rates. These were then combined by a meta-analysis of clinical trials. Details of all clinical trials included in the review were provided. No clinical trial data were available for monotherapy for refractory patients with generalised seizure, thus the data were presented using a general category of "monotherapy" versus "combination therapy" without distinguishing between newly diagnosed patients and refractory patients. Other sources of data appear to have been identified selectively and were the National General Practice Study of Epilepsy, an open-label follow-up study, and national and epilepsy-specific sources. The utility values came from a non-randomised audit of 125 patients starting a new adjunctive AED, who completed the EQ-5D questionnaire after 6 months.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
The use of clinical trials ensures the validity of the efficacy estimates.

Methods used to judge relevance and validity, and for extracting data
Only clinical trials based on an intention to treat analysis were included in the review.
Number of primary studies included
Thirty-three studies were used to estimate the effectiveness data.

Methods of combining primary studies
In the meta-analysis, Bayesian hierarchical modelling was used to derive the absolute treatment differences, based on the available mixed comparisons because of the lack of head-to-head comparative data.

Investigation of differences between primary studies
Not reported.

Results of the review
The average proportions of patients responding are reported below.

In the case of treatment of partial seizures and monotherapy for newly diagnosed patients:
- lamotrigine, 0.40 (95% CI: 0.30 - 0.50);
- oxcarbazepine, 0.43 (95% CI: 0.31 - 0.55);
- carbamazepine, 0.41 (95% CI: 0.31 - 0.51);
- valproate, 0.42 (95% CI: 0.31 - 0.53);
- phenytoin, 0.42 (95% CI: 0.30 - 0.55);
- topiramate, 0.44 (95% CI: 0.32 - 0.56).

In the case of treatment of partial seizures and monotherapy for refractory patients:
- lamotrigine, 0.44 (95% CI: 0.23 - 0.67);
- carbamazepine, 0.47 (95% CI: 0.24 - 0.71);
- valproate, 0.44 (95% CI: 0.23 - 0.68).

In the case of treatment of partial seizures and combination therapy:
- placebo (monotherapy), 0.12 (95% CI: 0.09 - 0.16);
- gabapentin, 0.23 (95% CI: 0.13 - 0.35);
- levetiracetam, 0.32 (95% CI: 0.23 - 0.43);
- lamotrigine, 0.23 (95% CI: 0.13 - 0.34);
- oxcarbazepine, 0.39 (95% CI: 0.27 - 0.52);
- tiagabine, 0.27 (95% CI: 0.18 - 0.37);
- topiramate, 0.33 (95% CI: 0.23 - 0.43).

In the case of treatment of generalised seizures and monotherapy:
- lamotrigine, 0.62 (95% CI: 0.55 - 0.68);
valproate, 0.68 (95% CI: 0.58 - 0.76).

In the case of treatment of generalised seizures and combination therapy:

placebo (monotherapy), 0.19 (95% CI: 0.07 - 0.39);

topiramate, 0.43 (95% CI: 0.22 - 0.67).

The mean utilities were:

successful on 1st monotherapy, 0.94 (standard error, SE=0.024);

successful on combination therapy, 0.90 (SE=0.020);

no response to therapy, 0.84 (SE=0.029).

The mortality rate per 1,000 patients per year was 28 for successful on first monotherapy and 40 for other patients.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
Patients with partial seizures who failed 1st-line therapy were assumed to receive carbamazepine as 2nd-line (monotherapy) and gabapentin as 3rd-line (combination therapy).

Measure of benefits used in the economic analysis
The summary benefit measure was the quality-adjusted life-years (QALYs). These were estimated using the decision model. The expected survival was combined with utility weights derived from the literature. Discounting was performed at an annual rate of 1.5%.

Direct costs
The cost analysis was performed from the perspective of the NHS. Thus, only the direct medical costs were taken into consideration. The health services considered in the analysis were general practitioner visits, outpatient visits and hospitalisations. The costs were reported but information on the resource use data was unclear. Only drug dosages were reported in detail. The costs and resource use data were derived from published studies. Discounting was relevant, owing to the long timeframe of the decision model, and an annual rate of 6% was used. The costs were reported for the price year 2002 - 2003.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

Indirect Costs
The indirect costs were not considered.

Currency
UK pounds sterling ()

Sensitivity analysis
Distributions were assigned to each parameter used in the model. Using a second-order Monte Carlo simulation, estimates of expected costs and QALYs associated with each of the treatment options for 1,000 simulations were generated. The ranges of values were derived from published sources. Cost-effectiveness acceptability curves were then constructed to indicate the probability of each treatment being the most cost-effective for a range of maximum values that the UK health system could be willing to pay for an additional QALY.

Estimated benefits used in the economic analysis
The estimated QALYs for monotherapy for newly diagnosed patients with partial seizure were:

9.392 for carbamazepine,
9.404 for valproate,
9.382 for lamotrigine,
9.415 for oxcarbazepine, and
9.430 for topiramate.

The estimated QALYs for monotherapy for refractory patients with partial seizure were:

8.865 for carbamazepine, and
8.856 for valproate and lamotrigine.

The estimated QALYs for combination therapy for refractory patients were:

8.716 for placebo (monotherapy),
8.747 for gabapentin,
8.746 for lamotrigine,
8.758 for tiagabine,
8.794 for oxcarbazepine,
8.775 for levetiracetam, and
8.777 for topiramate.

The estimated QALYs for monotherapy in newly diagnosed patients with generalised seizure type were:

9.814 for valproate, and
9.748 for lamotrigine.

The estimated QALYs for combination therapy in refractory generalised seizure type patients were:

8.737 for placebo (monotherapy), and
8.807 for topiramate.

Cost results
The estimated costs for monotherapy for newly diagnosed patients with partial seizure were:
4,428 for carbamazepine,  
4,572 for valproate,  
6,133 for lamotrigine,  
6,294 for oxcarbazepine, and  
7,838 for topiramate.

The estimated costs for monotherapy for refractory patients with partial seizure were:  
5,599 for carbamazepine,  
5,728 for valproate, and  
6,749 for lamotrigine.

The estimated costs for combination therapy for refractory patients were:  
5,064 for placebo (monotherapy),  
5,861 for gabapentin,  
5,926 for lamotrigine,  
6,133 for tiagabine,  
6,400 for oxcarbazepine,  
6,984 for levetiracetam, and  
7,026 for topiramate.

The estimated costs for monotherapy in newly diagnosed patients with generalised seizure type were:  
4,288 for valproate, and  
6,675 for lamotrigine.

The estimated costs for combination therapy in refractory generalised seizure type patients were:  
5,064 for placebo (monotherapy), and  
7,471 for topiramate.

**Synthesis of costs and benefits**

Incremental cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies. Dominated alternatives are not reported.

In the case of monotherapy for newly diagnosed patients with partial seizure, carbamazepine was the reference strategy and the incremental cost per QALY was 11,731 with valproate and 126,519 with topiramate. At a maximum willingness to pay for an additional QALY of 30,000, the older AEDs (carbamazepine and valproate) had a probability of being the most cost-effective that ranged from 0.36 to 0.41. The probability of being cost-effective for the newer AEDs (lamotrigine, oxcarbazepine, and topiramate) ranged from 0.02 to 0.16.
In the case of monotherapy for refractory patients with partial seizure, carbamazepine was the reference strategy and the other strategies were all dominated. The probability that carbamazepine was the most cost-effective therapy was 0.75 when the willingness to pay for an additional QALY was 30,000.

In the case of combination therapy for refractory patients, placebo (monotherapy) was the reference strategy and the cost per QALY was 17,095 with oxcarbazepine. The probability that oxcarbazepine was the most cost-effective therapy was 0.65 when the willingness to pay for an additional QALY was 30,000.

In the case of monotherapy in newly diagnosed patients with generalised seizure type, the reference strategy was valproate. The probability that valproate was cost-effective was 0.95 if the maximum willingness to pay for an additional QALY was less than 30,000.

In the case of combination therapy for refractory generalised seizure patients, the reference strategy was placebo (monotherapy) and the cost per QALY was 34,417 with topiramate. At a willingness to pay of 30,000, there was a 0.41 probability that topiramate was cost-effective.

**Authors’ conclusions**

For newly diagnosed patients with partial seizures, carbamazepine and valproate were likely to be the most cost-effective monotherapies. Carbamazepine was likely to be the most cost-effective second-line monotherapy for refractory patients, while oxcarbazepine would probably be the most cost-effective adjunctive therapy for refractory patients if the willingness to pay for additional health benefits was greater than 18,000 per quality-adjusted life-year (QALY). For patients with generalised seizures, valproate was most likely to be cost-effective for newly diagnosed patients. For refractory patients, adjunctive topiramate was more cost-effective than monotherapy alone if the willingness to pay for additional health benefits was greater than 35,000 per QALY. The authors noted that there was considerable uncertainty surrounding the results of the analysis, as the probabilistic analysis highlighted.

**CRD COMMENTARY - Selection of comparators**

The authors justified explicitly the selection of the comparators included in the analysis. All relevant comparators were considered. Two potential AEDs (i.e. phenytoin and vigabatrin) were considered clinically inappropriate and were excluded from the final analysis. A justification for the exclusion of such therapies was provided.

**Validity of estimate of measure of effectiveness**

The effectiveness analysis was based on published evidence. A systematic review of the literature was performed to identify primary estimates of the efficacy of the different treatment options. Details of the sample size and patients characteristics of the included studies were provided. A modelling approach was used to define comparative data because of the lack of head-to-head comparisons between drugs. Extensive details on such an approach were provided. A meta-analysis was used to combine the primary estimates. The validity of the estimates used was ensured by the use of clinical trials. Other model inputs were selectively identified. Some assumptions were also made. A stochastic sensitivity analysis was performed on all model parameters.

**Validity of estimate of measure of benefit**

The use of QALYs as the summary benefit measure was appropriate because it captures the impact of the intervention on the most relevant dimensions of health (i.e. quality of life and extended survival). The source of the utility values was reported. Discounting was applied using the rate recommended by NICE. With QALYs, the benefits estimated in the current study are comparable with those of other health care interventions.

**Validity of estimate of costs**

The costs included were consistent with the perspective adopted. Typical NHS sources were used to derive the costs. No information on the resource use data was provided, which limits the possibility of replicating the cost analysis in other settings. The cost estimates were treated deterministically in the base-case but were given stochastic distributions in the
Monte Carlo simulation. However, these estimates were specific to the study setting. The price year was reported, which aids reflation exercises in other time periods.

Other issues
The authors discussed the strengths and drawbacks of the available evidence. They stated that few economic evaluations had been performed and the much of the literature had been cost-minimisation studies. However, even the most recent economic evaluations had short time horizons or did not consider all relevant alternatives. The authors stated that the results of the deterministic sensitivity analysis were reported elsewhere. It was also stated that variations in the discount rate did not alter the conclusions of the analysis. The issue of the generalisability of the study results was addressed and the authors stated that the weaknesses of the available clinical trial evidence limit the external validity of the analysis.

The authors noted two main limitations of their analysis. First, the impact of drug treatments on the severity, frequency and pattern of occurrence of epileptic seizures was not explicitly addressed. Second, since clinical trials had a short follow-up, the current analysis did not account for the impact of either chronic toxicity or harm from AEDs, or for the potential for drugs to cause teratogenicity or neurodevelopmental harm to children of mothers receiving them.

Implications of the study
The study results suggested that the decision on the optimal AED is complex because of uncertainty in several key clinical variables. The authors stated that the incorporation in the current decision model of the results of the ongoing trial (the Standard and New AEDs trial, SANAD), funded by the UK NHS Health Technology Assessment Programme, could address some of these problems.

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Other publications of related interest


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