The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial

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
The authors assessed five antiepileptic drugs. These were carbamazepine, gabapentin, lamotrigine, oxcarbazepine and topiramate. The drug dosages and preparations were used as they would be by a clinician in everyday practice.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with suspected epilepsy. Patients were included if they "had a history of two or more clinically definite unprovoked epileptic seizures in the previous year and if the recruiting clinician regarded carbamazepine as a better standard treatment option than valproate (i.e. patients with partial onset seizures)". Patients were excluded if "the clinician or patient felt that treatment was contraindicated, if all seizures had been acute symptomatic seizures (including febrile seizures), they were aged 4 years or younger, or if there was a history of progressive neurological disease".

Setting
The setting was outpatient care. The economic study was carried out in the UK.

Dates to which data relate
Patient recruitment began in December 1999 and the last follow-up data were available in January 2006. The resource use data related to the same time period. A price year was not reported.

Link between effectiveness and cost data
The costing related to the same sample of patients as that used in the effectiveness study.

Study sample
Sample size calculations indicated that, to achieve 90% power to detect differences over a follow-up period of 2.5 years with a significance level of 5%, the authors needed 445 patients per treatment group. A total of 1,721 patients were finally recruited and agreed to participate. Of these, 378 were allocated to carbamazepine, 377 to gabapentin, 378 to lamotrigine, 210 to oxcarbazepine, and 378 to topiramate. Forty-nine patients were excluded from the analysis post randomisation (44 had a subsequent diagnosis other than epilepsy and 5 had no follow-up data).
Study design
The authors designed a randomised controlled trial based at multiple centres across the UK. The patients were randomised to the treatment groups in a ratio of 1:1:1:1:1. Randomisation was carried out by the clinician telephoning a central randomisation service and providing patient identifying information. The centre, gender, and treatment history (newly diagnosed and untreated, treated with ineffective monotherapy, relapse after remission) were used to stratify patients. A minimisation procedure was then used to allocate the patients to the groups. Blinding was not carried out. The patients were followed up at 3 months, 6 months and 1 year, and at successive yearly intervals for up to 6 years. Oxcarbazepine was added to the study only after the trial had been running for some time. Therefore, analyses were carried out both with and without this drug.

Analysis of effectiveness
Analysis was carried out on an intention to treat basis, supplemented by per-protocol calculations. The primary outcomes were:

- the time from randomisation to treatment failure (stopping the randomised drug because of inadequate seizure control and/or intolerable side-effects; or the addition of other antiepileptic drugs), and
- the time from randomisation to a 1-year period of remission of seizures.

Extensive clinical and demographic data were collected at baseline. A comparison of the groups revealed that they were "well balanced"; there were no reported statistically significant differences. A further 39 patients were lost to follow-up during the study, 38 because they declined further follow-up and one patient who had left the country. Time-to-event data were reported to have used cumulative incidence analysis and Cox proportional hazard models; cumulative incidence was used as log rank tests were not considered appropriate. The authors reported that follow-up was 94% complete.

Effectiveness results
Numerous results were presented in the paper, of which a small selection of relevant results has been presented in this abstract.

For time to treatment failure, there were significant differences between drugs when comparisons were made over the whole period. Lamotrigine was reported as being "better than all other drugs for pairwise comparisons", carbamazepine and oxcarbazepine were intermediate, and gabapentin and topiramate were the poorest performing drugs.

The sensitivity analysis revealed that including only patients with definite partial seizures, or including patients subsequently withdrawn as "not epilepsy", did not affect the results.

The hazard ratio for treatment failure due to unacceptable events was 0.62 (0.46 to 0.83) between lamotrigine and carbamazepine, 0.62 (0.46 to 0.84) between lamotrigine and topiramate, and 0.6 (0.44 to 0.81) between gabapentin and carbamazepine.

Carbamazepine was most likely to be associated with treatment failure due to unacceptable adverse events.

Gabapentin was most likely to be associated with treatment failure due to inadequate seizure control and carbamazepine the least likely. The hazard ratio between gabapentin and carbamazepine was 2.45 (1.81 to 3.32).

The intention to treat analysis revealed statistical differences for 12-month remission, with gabapentin and topiramate the least favoured options and carbamazepine the most preferred treatment.

There was no evidence that relative treatment effects differed across age groups.

Clinical conclusions
The authors concluded that "for patients with partial onset seizures that need monotherapy, we have found lamotrigine to be significantly better for time to treatment failure than the current standard treatment, carbamazepine".

**Measure of benefits used in the economic analysis**
The authors used quality of life measured by "a battery of previously validated generic and epilepsy-specific measures" as a summary measure of health benefit. For adults, the Newly Diagnosed Epilepsy Quality of Life (NEWQOL) questionnaire was used. EQ-5D responses were used to measure quality-adjusted life-years (QALYs). The final analysis was based on 1,009 adult patients who provided complete EQ-5D responses at 2 years. The authors reported that details of the methods used in assessing quality of life outcomes were given online (web appendix, web figure 1, web tables 2 and 3. The number of seizures avoided was also used as a summary measure of health benefit.

**Direct costs**
Few details of the cost-effectiveness analysis were given in the current report. The authors stated that further details are available online. The perspective of the analysis was not reported. The analysis focused on the patients' use of resources and classified use as either consumption of antiepileptic drugs, resource use associated with the management of adverse events needing hospitalisation, and use of other health care and social services resources. A table giving details of disaggregated costs was reported to be available online.

**Statistical analysis of costs**
A statistical analysis of the costs and quantities was not reported to have been carried out.

**Indirect Costs**
Productivity costs were not reported to have been estimated.

**Currency**
UK pounds sterling (£).

**Sensitivity analysis**
Bootstrapping was used to generate cost-effectiveness acceptability curves. The number of repetitions used was not stated. The authors also used high and low cost estimates, but these were not fully explained or reported. Further details of the methods underlying this analysis were reported to be available online.

**Estimated benefits used in the economic analysis**
Results excluding oxcarbazepine:
- carbamazepine resulted in 1.477 QALYs and 52.6 seizures;
- topiramate resulted in 1.501 QALYs and 63.1 seizures;
- lamotrigine resulted in 1.564 QALYs and 41.7 seizures;
- gabapentin resulted in 1.491 QALYs and 69.8 seizures.

Results including oxcarbazepine:
- carbamazepine resulted in 1.491 QALYs and 50.9 seizures;
- oxcarbazepine resulted in 1.611 QALYs and 32.0 seizures;
topiramate resulted in 1.541 QALYs and 59.4 seizures;
lamotrigine resulted in 1.563 QALYs and 50.9 seizures;
gabapentin resulted in 1.480 QALYs and 85.3 seizures

Cost results
The costs were difficult to interpret from the paper.

Costing relating to the analysis excluding oxcarbazepine:
in a table relating to QALYs, the costs were reported as carbamazepine 1,226, topiramate 2,009, lamotrigine 2,257, gabapentin 2,561;
in a table relating to seizures avoided, the costs were reported as carbamazepine 1,266, topiramate 2,008, lamotrigine 2,134, gabapentin 2,4941.

Costing relating to the analysis including oxcarbazepine:
in a table relating to QALYs, the costs were reported as carbamazepine 1,095, oxcarbazepine 1,839, topiramate 1,930, lamotrigine 2,078, gabapentin 2,573;
in a table relating to seizures avoided, the costs were reported as carbamazepine 1,151, oxcarbazepine 1,815, lamotrigine 1,946, topiramate 2,059, gabapentin 2,594.

Synthesis of costs and benefits
In all analyses topiramate and gabapentin were either dominated or least preferred by extended dominance (more costly with fewer associated outcomes).

With analyses including oxcarbazepine, lamotrigine was either dominated or not preferred because of principles of extended dominance.

With analyses excluding oxcarbazepine, the incremental cost for lamotrigine was 11,851 per QALY gained, or 80 per seizure avoided.

The incremental cost for oxcarbazepine was 6,200 per QALY gained, or 35 per seizure avoided.

Authors’ conclusions
Lamotrigine has better tolerability. This lends support to lamotrigine being used as a first-choice treatment for most patients with partial epilepsy. The economic analysis lends further support to lamotrigine being preferred to the current first-line treatment (i.e. carbamazepine).

CRD COMMENTARY - Selection of comparators
The authors compared carbamazepine, gabapentin, lamotrigine, oxcarbazepine and topiramate antiepileptic drugs. Carbamazepine was reported to be the first-line choice of treatment for partial onset epilepsy. The other technologies were reported to be relatively newly available; the extent to which they were already being used in the study setting was unclear. Oxcarbazepine became available and was introduced as a technology of interest part way through the study.

Validity of estimate of measure of effectiveness
The authors designed a randomised controlled trial to help minimise the possibility of systematic differences between patients in the two treatment groups. This was achieved by the finding that the study groups were "well balanced". The
authors noted that they were not able to introduce blinding and suggested that this may have created a bias in the results with regards to the reporting and assessment of symptoms. However, the authors discussed this possible limitation well, and explained clearly why they had made the decision to leave patients and clinicians unmasked. The study sample comprised both newly diagnosed patients and those with treatment failure and so was representative of the study population. The internal validity of the study is increased by including both intention to treat and per protocol analyses, and by separating the analysis to include and exclude oxcarbazepine, as the two analyses had different power to detect significant differences. The author aimed to create a study that had high external validity in order to maximise the applicability of the results to general practice. They did this through making the entry criteria very inclusive and encouraging clinicians to use dosages and preparations as they would in everyday practice. The text would suggest that the hazard ratios presented for time-to-event were obtained using cumulative incidence analysis, however, the presentation of log rank test statistics could lead to confusion.

**Validity of estimate of measure of benefit**
The authors used a disease-specific measure (seizures avoided) as well as a generic measure of well-being (QALYs). These two measures ensure that comparisons can be made across a broad range of health care-related technologies. However, the authors noted that the analysis of EQ-5D data was based only on patients for whom they had complete data and that this may, therefore, introduce the potential for response bias.

**Validity of estimate of costs**
Only limited details of the costing analysis were reported. The authors noted that further details, especially disaggregated costs, are available online. The reader is referred to the online material for more information about the validity of the costing analysis. However, the analysis reported seemed to address the perspective of the health care provider and measured resource use on an individual basis.

**Other issues**
The authors were able to draw some conclusions with other studies, although they noted that this was the only study of such size and duration in this area. In particular, they noted no evidence of any interaction between age and drug treatment groups and suggested that this result differed from previous work. The authors acknowledged that they were unable to match the target for recruitment as indicated by the power calculations. However, as event rates were high than expected and they were able to extend the duration of the trial, they were still able to draw statistically meaningful conclusions. The results and conclusions were well discussed and the conclusions were an accurate reflection of the results presented. The authors made reference to some figures on the Web; it was not always clear whether these resources provided additional information or simply presented the existing information more clearly. The reader is referred directly to these sources to assess their relevance.

**Implications of the study**
The authors recommend that "the National Institute for Clinical Excellence should now reconsider its guidance about the first-line antiepileptic drug for patients with partial onset seizures". They also recommend further and continuing work to assess the cost-effectiveness of newly available drugs.

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