The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable 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 valproate, lamotrigine and topiramate. Drug dosages and preparations were used as the clinician would use them 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 valproate as a better standard treatment option than carbamazepine (i.e. patients with generalised 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 January 1999 with the last follow-up data being available in January 2006. The resource use data related to the same time period. The 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 a 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 716 patients were finally recruited and agreed to participate. Of these, 239 were assigned to lamotrigine, 239 to topiramate and 238 to valproate. Seventeen patients were excluded from all analysis either because they had no follow-up data (3) or they had a subsequent diagnosis other than epilepsy (14).
Study design
The authors designed a randomised controlled trial that was based at multiple centres across the UK. Patients were randomised to the three treatment groups in a ratio of 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 the patients. A minimisation procedure was then used to allocate the patients to the groups. Blinding was not carried out. The patients were followed for up to 6 years.

Analysis of effectiveness
The 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. Comparison of the groups revealed that they were "well balanced", and there were no reported statistically significant differences. A further 18 patients were lost to follow-up during the study, 16 because they declined further follow-up and 2 for other reasons. 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.

Effectiveness results
The authors reported that the results presented in the paper were supplemented by figures available online. A limited number of results are presented in this abstracts. The reader should refer to the paper for a full overview of the results.

For time to treatment failure there were significant differences between drugs. Valproate was the better option. The hazard ratio between topiramate and valproate was 1.57 (1.19 to 2.08) and that between lamotrigine and valproate was 1.25 (0.94 to 1.68).

When restricted to patients identified as having generalised epilepsy syndrome, the case for valproate was more marked. The hazard ratio between valproate and topiramate was 0.53 (0.37 to 0.76) and that between valproate and lamotrigine was 0.65 (0.45 to 0.93).

Pairwise comparisons showed valproate to be the preferred option in terms of 1-year remission. The hazard ratio between topiramate and valproate was 0.93 (0.76 to 1.15) and that between lamotrigine and valproate was 0.76 (0.62 to 0.94).

When restricted to patients identified as having generalised epilepsy syndrome, the case for valproate was again more marked. The hazard ratio between lamotrigine and valproate was 0.68 (0.53 to 0.89) and that between topiramate and valproate was 0.82 (0.64 to 1.06).

The authors noted that differences between intention to treat and per protocol analyses were due to patients who had treatment failure with topiramate switching to valproate. The results for the 2-year outcomes were consistent with those for 1 year.

Clinical conclusions
The authors concluded that valproate was more effective than lamotrigine and topiramate, and that the effect seemed greater when the analysis was restricted to a sub-set of patients.

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". 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 165 adult patients who provided complete EQ-5D responses at 2 years. A detailed description of the methods used for quality of life outcomes was reported to have been published in a supplementary paper (Marson et al. 2007, see 'Other Publications of Related Interest' below for bibliographic details). The number of seizures avoided was also used as a summary measure of health benefit.

**Direct costs**
Only limited details of the cost-effectiveness analysis were reported in the current report. The authors stated that further details are available (Marson et al. 2007). The analysis focused on the patients' use of resources and classified use as either consumption of antiepileptic drugs, resource use associated with the treatment of adverse events needing hospitalisation, or the use of other health care and social services resources.

**Statistical analysis of costs**
There was no report of a statistical analysis of the costs and quantities being carried out.

**Indirect Costs**
There was no report of productivity costs being 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.

**Estimated benefits used in the economic analysis**
Valproate resulted in 1.648 QALYs and 44.1 seizures.

Topiramate resulted in 1.809 QALYs and 75.1 seizures.

Lamotrigine resulted in 1.701 QALYs and 120.9 seizures.

Topiramate gave 0.161 additional QALYs and lamotrigine gave -0.108 QALYs.

Topiramate gave 31.0 additional seizures and lamotrigine gave 45.8 additional seizures.

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

In a table relating to QALYs, the costs were reported as valproate 1,390, topiramate 1,568 and lamotrigine 1,906. This gives an incremental cost of 178 for topiramate and 338 for lamotrigine.

In a table relating to seizures avoided, the costs were reported as valproate 1,136, topiramate 1,568 and lamotrigine 1,761. This gives an incremental cost of 432 for topiramate and 193 for lamotrigine.

**Synthesis of costs and benefits**
The incremental cost per QALY gained for topiramate relative to valproate was 1,106.

Lamotrigine was dominated by topiramate in terms of the cost and QALYs.

Valproate dominated (lower cost and few associated seizures) both topiramate and lamotrigine in terms of the seizures avoided.

**Authors' conclusions**

"For patients with generalised onset seizures or seizures that are difficult to classify, valproate is significantly more effective than topiramate for treatment failure and significantly more effective than lamotrigine for 12-month remission". Valproate was also the dominant technology when seizures avoided was the primary measure of health benefit.

**CRD COMMENTARY - Selection of comparators**
The authors compared valproate, lamotrigine and topiramate antiepileptic drugs. Valproate was reported to be a well-established technology that is generally used as first-line treatment. The other two technologies were reported to be relatively newly available; the extent to which they were already being used in the study setting was unclear.

**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. 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 was increased by including both intention to treat and per protocol analyses. However, as a caution it is worth mentioning that the text suggests 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**
Few details of the costing analysis were reported. The authors noted that further details are available in an associated paper. The reader is referred to this publication to find out more about the validity of the costing analysis. However, the analysis, as reported, appears to have addressed the perspective of the health care provider and measured resource use on an individual basis.

**Other issues**
The authors were unable to draw conclusions with other studies in this area as there is a general lack of evidence available. Generalisability to other settings was not addressed and, although the clinical study may generalise to other settings, it is not possible to draw the same conclusion about the costing analysis without further information. The authors acknowledged that they were unable to match the target for recruitment as indicated by the power calculations. However, as event rates were higher than expected, they were still able to draw statistically meaningful conclusions. They noted that a potential factor inhibiting recruitment was the reluctance of clinicians to introduce women of child bearing age to a study in which they may have been randomised to a drug which is associated with a high rate of foetal malformation. 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, but it was unclear whether these resources provided additional information or simply presented the existing information more clearly. The reader is referred to these sources directly to assess their relevance.

**Implications of the study**
The authors recommend that "valproate should remain first-line treatment" for patients such as those studied in this trial. They also recommend further work to assess newly available drugs as they emerge and to explore monotherapies that classify patients by epilepsy syndrome (owing to the sub-group analyses carried out within this study).

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**Other publications of related interest**
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adolescent; Adult; Anticonvulsants /adverse effects /economics /therapeutic use; Child; Child, Preschool; Cost-Benefit Analysis; Epilepsy, Generalized /drug therapy /physiopathology /prevention & control; Female; Follow-Up Studies; Fructose /adverse effects /analogs & derivatives /therapeutic use; Humans; Male; Quality-Adjusted Life Years; Time Factors; Treatment Failure; Triazines /adverse effects /therapeutic use; Valproic Acid /adverse effects /therapeutic use

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