Seizure 1999; **8**: 8–13
Article No. seiz.1998.0248, available online at http://www.idealibrary.com on IDEAL

Adjunctive therapy in epilepsy: a cost-effectiveness comparison of two AEDs

C. E. SELAI*, K. SMITH & M. R. TRIMBLE

Raymond Way Neuropsychiatry Unit, Institute of Neurology, Queen Square, London WC1 N3BG, UK

Correspondence to: C. E. Selai, Raymond Way Neuropsychiatry Unit, Institute of Neurology, Queen Square, London WC1N 3BG, UK

The objective of this study was to compare the relative cost-effectiveness of two AEDs by a prospective clinical audit. Patients starting on the adjunctive therapies lamotrigine and topiramate were recruited from the out-patient epilepsy clinics at Queen Square. Three interview were scheduled: baseline; three months follow-up and six months from baseline. Of the 81 patients recruited, a total of 73 patients completed all three interviews. An intention to treat analysis was performed on the data. Seizure severity and frequency were assessed using the National Hospital Seizure Severity Scale. Side-effects, adverse events and reasons for stopping medication were also recorded.

At the third interview, a total of 47/73 (64%) were still on the prescribed adjunctive drug. Outcome was assessed by two methods: the $>$ 50% seizure reduction cited in the literature and a more stringent assessment of patient 'satisfaction' which we defined operationally on clinical criteria. Using this definition, a total of 10/73 (14%) patients were 'satisfied'. The relative costs of starting patients on each of the two AEDs were calculated, both drug costs and the costs of adverse events (the latter were defined as events requiring urgent medical attention). The costs of the two drugs were compared. A number of methodological issues relating to cost comparison are discussed. Outcome and pharmaco-economic studies need to assess more than reduction in number of seizures. They should take into account variables important for quality of life including side-effects and adverse events.

Key words: outcome; quality of life; cost-effectiveness; lamotrigine; topiramate.

INTRODUCTION

In recent years, the costs of medical care in general, and the costs of antiepileptic drugs in particular, have come under close scrutiny[1]. Whilst approximately 70% of patients are well controlled on monotherapy, with standard antiepileptic drugs (AEDs), for the remaining 30% of patients polytherapy is considered. Costs rise because combinations of AEDs often include the newer compounds and the unit cost of these is much greater than that of the older, more established AEDs. Costs of polytherapy are also higher because of increased side-effects, additional medical interventions and more extensive drug monitoring.

To assess the cost effectiveness of any intervention, data are needed for both cost and effectiveness (outcome) of therapy. Such data on the pharmaco-economic aspects of medical treatment are, however, extremely scant. Health economists have attempted to develop decision-analytic models using the meagre data available supplemented by clinical opinion and including various assumptions and estimates. Whilst economists' methods include extensive use of models, it is argued that the conclusions of such studies are unsatisfactory and a move away from such modelling in health care has been predicted[2].

Recent studies have attempted to look at the cost of epilepsy in the UK[3] and the cost-effectiveness of adjunctive therapy in epilepsy[4]. In both of these studies, a number of assumptions were made and many of the costs were estimated. A recent retrospective, cross-sectional cost-of-illness study, conducted in France, Germany and the UK, showed that higher seizure frequencies were associated with higher direct and indirect costs and with reduced quality of life (QOL) for patients with epilepsy[5]. A retrospective audit of patients starting on lamotrigine showed that, at 6–8 years follow-up, 86% of those patients still living were no longer taking these add-on drugs[6]. In another

*E-mail: cselai@ion.ucl.ac.uk

1059–1311/99/010008 + 06 $12.00/0

audit[7], where efficacy was defined as >50% reduction in seizure frequency, 36% of patients receiving lamotrigine benefitted according to this criterion. These studies did not take account of side-effects or a broader appraisal of patient satisfaction.

Topiramate is one of the most recent drugs to be licensed as an add-on therapy for the treatment of partial epilepsies. A double-blind, randomized placebo controlled study suggested that 24% of patients on topiramate had a greater than 50% decrease in seizure frequency[8]. A high rate of side-effects (41%) was reported, which led to the withdrawal of the drug in 41% of the patients. In order to explore the potentially interesting clinical differences between topiramate and lamotrigine, in efficacy and side-effects, we conducted an audit survey to examine the pharmaco-economic consequences of their administration in clinical practice. Our perspective is to compare the reality of clinical practice with a pharmaco-economic model and to examine the way that different end-points may lead to differing drug costs, especially in relation to QOL.

MATERIALS AND METHODS

Design

Given the limitations of theoretical models, we planned the current prospective, follow-up study to compare the outcome of patients starting on two new AEDs (lamotrigine and topiramate). Patients were approached after their medical consultation and the study was explained to them. For convenience, patients who were willing to take part were offered the choice of a telephone interview at home as an alternative to a face-to-face interview at the hospital and most patients chose this option. The timing of the interviews was: (1) baseline; (2) 3 months from baseline and (3) 6 months from baseline.

Main outcome measures

The National Hospital Seizure Severity Scale[9] was used to assess seizure frequency and seizure severity. This scale is administered by a health professional during an interview with both patient and a witness to the seizures. It contains seven seizure-related factors and generates a score from 1 to 27.

Drug-related sequelae: Side-effects, adverse events and reasons for stopping medication were also recorded.

Quality of Life (QOL): QOL was measured by the QOLAS[10,11] and the EuroQol instrument[12] but these data will be reported elsewhere.

Patient satisfaction: Patients were deemed 'satisfied' if they fulfilled all of the following criteria: (1) still on drug at $t = 3$; (2) experiencing no side-effects; (3) had no adverse-events; and (4) had a greater than 50% reduction in seizures.

Costs: Patients were asked at follow-up interviews for dates of stopping medication. Costs for any epilepsy-related event were included in our analysis. The costs for the two drugs were found in the current edition of *MIMS*[13]. Costs relating to adverse events were obtained from the *OHE Compendium of Health Statistics*[14], from Health Authority sources and other public bodies as appropriate. Costs were calculated on an 'intention to treat' basis[15]. For the group of patients who were lost to follow-up, data concerning their continuation (or otherwise) with medication were taken from the patients' notes. The costs of medication for these patients could be ascertained and were thus included. Data on side-effects and adverse events, however, were not incorporated since interviews had not been completed and these data were not systematically recorded in the patients' notes.

Costs of 'adverse events': In our operational definition of 'satisfaction', all epilepsy-related adverse events were included but, for the cost-effectiveness comparison, only those events were taken into account where medical advice was sought and a cost was therefore incurred. An example of such an event is the development of a skin rash which resulted in extra GP and/or clinic visits.

Cost-effectiveness comparison: In order to compare the cost-effectiveness of the different drugs, we used the cost-effectiveness ratio published in the pharmaco-economic paper[4]. The formula used in this paper is as follows:

$$\begin{aligned} CER &= \textit{Cost per successfully treated patient} \\ &= \textit{Cost per patient of treatment divided by the} \\ &\quad \textit{percentage of successfully treated patients.} \end{aligned}$$

RESULTS: PART I — DESCRIPTIVE

A total of 81 adult patients were recruited into the study. All patients were receiving one or more anticonvulsants and were prescribed the new medication because of continuing seizures. Of these, 73 attended for both follow-up interviews and eight failed to attend follow-up. Those lost to follow-up were incorporated and an 'intention to treat analysis' was performed[15]. We thus report the full outcome of those patients ($n = 73$) who started on the two drugs and who completed all three interviews; the eight patients who were lost to follow-up are incorporated into the cost-effectiveness analysis. Of the 73 patients, 26 were started on lamotrigine (14 male) and 47 on topiramate (28 male). Of the eight patients lost to follow-up, six were on lamotrigine and two on topiramate. There were no sig-

Table 1: Individual data for patients at the 6 months follow-up.

	Topiramate	Lamotrigine
Still on drug	31/47 (65%)	16/26 (61%)
Side-effects[a]	23/47 (48%)	10/26 (38%)
Adverse events[b]	4/47 (8%)	1/26 (3%)
50% reduction Ss	15/47 (32%)	10/26 (38%)
Number of patients 'satisfied'[c]	7/47 (15%)	3/26 (11%)
Seizure-free patients	3/47 (6%)	4/26 (15%)
No interview @ $t = 3$	2	6

[a] Side-effects as reported by patients and attributed by them to the add-on therapy.
[b] Serious adverse events are epilepsy related requiring urgent medical care.
[c] Our operational criteria for 'satisfied' were: (1) still on the drug at $t = 3$; (2) experiencing no side-effects; (3) had no adverse events; and (4) had a greater that 50% reduction in seizures.

nificant differences between the mean ages of patients on the two drugs: lamotrigine mean age = 37 (SD 9.8); topiramate mean age = 39 (SD 12.6).

Seizures at baseline

Most of the patients had either non-convulsive seizures or both convulsions and other seizure types. Of the 73 patients, 39 patients were experiencing convulsions (53%). The number experiencing convulsions for each drug was lamotrigine = 13 (50%) and topiramate = 26 (55%).

Status at 3 months follow-up

At 3 months follow-up, 21 were still on lamotrigine (81%) and 31 remained on topiramate (66%).

Status at 6 months follow-up

At the last follow-up, 16 (61%) of the patients were still on lamotrigine 31 (66%) on topiramate. Table 1 shows individual data for the 73 patients at 6 months follow-up. The side-effects reported by the patients are shown in Table 2. Reasons for stopping the drugs at any point are given in Table 3.

RESULTS: PART 2 — COSTINGS (DRUGS AND INDIRECT COSTS)

The costs of the drugs for each patient, on an intention to treat basis, for the 6 month period are shown in Table 4. This table shows two alternative costs for topiramate: the first includes *all* epilepsy related costs, and the second costing shows this sum minus the costs for admission for elective, in-patient video-telemetry. These costs, concerning only three patients, greatly inflated the total cost for topiramate. No patient in the lamotrigine group had undergone video-telemetry during the study. The total costs divided by the number of patients 'satisfied' are shown in Table 5. In Table 6 we compare the cost-effectiveness of these drugs.

Table 7 shows the differences in the costing of the two drugs when we compare a conventional measure of successful treatment (a > 50% reduction in seizures), with our more stringent outcome of patient 'satisfaction'.

Table 2: Side-effects reported by patients at $t = 2$ and/or $t = 3$.

	Lamotrigine	Topiramate
Cognitive effects		
Tingling		3
Slowness of thought—	1	2
Judgement impaired		1
Memory	3	6
Speech		1
Stutters		2
Cognitive slowing		3
Headache	2	1
Concentration	1	4
Vision	5	4
Dizzy	1	6
Confusion	2	
Mood		
Tired	2	8
Depression	1	4
Emotional problems		1
Irritable		1
Tearful		1
Sleepy		1
Fear		1
Short temper		2
Apathy		1
Moody		1
Withdrawn		1
Violent	1	
Behavioural		
Psychosis		1
Other		
Appetite		3
Increase in accidents		1
Stressed		1
Balance	2	2
Constipation		1
Hair loss		1
Weight loss		3
Weight gain	2	
Physical harm		1
Bad back	1	
Stiffness	1	
Bruising	1	
Urinary incontinence	1	
Rash	3	

Table 3: Patients' stated reasons for stopping drug.

	Lamotrigine ($n = 10$)	Topiramate ($n = 15$)
Poor seizure control	2 (20%)	4 (26%)
Cognitive side-effects	0	6 (40%)
Other side-effects	6 (60%)	5 (34%)
Other reasons	2 (20%)	0

Table 4: Costs, for the 6 month period, of starting patients on each of the drugs.

	Drug therapy		Adverse events	Total cost	Cost per patient
Topiramate	£14 745 $n = 47$	£556[a] $n = 2$	£20 088	£35 389	£722
Topiramate[b] (without telemetry unit costs)	£14 745 $n = 47$	£556[a] $n = 2$	£7813	£23 114	£472
Lamotrigine	£10 111 $n = 26$	£1377[a] $n = 6$	£7303	£18 791	£587

[a] Cost for patients who did not complete full follow-up interviews at 6 months.
[b] This is the cost for topiramate minus the costs for the patients having in-patient telemetry. No patients on lamotrigine incurred a telemetry cost.

Table 5: Cost of patients on each drug, divided by number of patients 'satisfied' at the end of the 6 months follow-up period.

	Number satisfied	Percentage satisfied	Total cost divided by number of 'satisfied'pts in each drug
Topiramate ($n = 49$)	7	14	£5055
Topiramate (without telemetry cost) ($n = 49$)	7	14	£3302
Lamotrigine ($n = 32$)	3	9	£6263

Table 6: Cost effectiveness (C/E) comparison of each of the drugs.

	Cost per patient	Percentage satisfied	C/E
Lamotrigine	£587 × 2 = 1174/	9 =	£130
Topiramate (without telemetry costs)	£472 × 2 = 944/	14 =	£67

Table 7: Cost per patient: difference between 'satisfied' and 50% seizure reduction.

	Lamotrigine		Topiramate without telemetry	
'Satisfied'	£6263	$n = 3$(9%)	£3302	$n = 7$(14%)
50% seizure reduction	£1879	$n = 10$(31%)	£1541	$n = 15$ (31%)

Sensitivity analysis

We did not perform a sensitivity analysis because we are presenting actual, prospective, clinical data. We do, however, discuss the methodological issues concerning what costs to include and we present data both including and excluding the cost of an elective, in-patient admission. Since our paper is already concerned with questions of methodology, our conclusions are tentative and these data do not lend themselves to the systematic calculation of uncertainty. Moreover, the methods of sensitivity analysis remain relatively underdeveloped and the subject of some debate[16].

DISCUSSION

In this study we have carried out an audit of patients treated with one of two new anticonvulsant drugs. The drugs were added to existing medications in patients with difficult to control seizures. The situation with monotherapy may be different, but to date most patients given these drugs receive them as polytherapy.

The study is not a double-blind or back-to-back comparison and we acknowledge that such studies are needed and important. However, we are presenting empirical data, derived from clinical experience, and based upon careful follow-up over 6 months. Nearly all of the follow-up studies that are published concentrate on seizure reduction as the outcome measure. Further, most studies, following initial investigations carried out for the purpose of drug regulation, are retrospective in design[17]. Here, we have attempted to achieve two outcomes: first, a prospective evaluation and, second, to incorporate measures of patient satisfaction into our follow-up which we believe are more important indicators of outcome above and beyond simple measures of reduction of seizure frequency, the usual variable measured.

We have used some objectively defined methods of assessment (The National Hospital Seizure Frequency and Severity scale and the EQ-5D), but we have also conducted in-depth interviews inviting patients to discuss their feelings about their treatment and their responses to various side-effects. All of the interviews were carried out by a single interviewer using a protocol to ensure consistency of data elicitation. Of the patients who were still on the drug at 6 months follow-up, only 14% were 'satisfied' according to our operational definition.

We compare the figure obtained using this measure of outcome with the figure obtained using the more usually reported measure of outcome, namely a decrease in seizure frequency. While many studies identify the number of patients who have achieved a reduction in seizure frequency, few emphasize QOL measures or patient satisfaction.

In another study[18], we have shown that our patient-specific measures of 'satisfaction' are significantly associated with an improvement in QOL. The fact that we found only 14% of patients 'satisfied' might explain why Walker *et al.*[6] found that 86% of patients (6–8 years follow-up) had stopped taking their new anticonvulsant drugs.

The data at first follow-up indicate that more patients on topiramate experience side-effects and adverse events. However, comparing the two drugs at 6 months follow-up, the number of patients with 50% reduction in seizures and the number of patients 'satisfied' is very similar. We acknowledge

that our 6 months is not long in the life career of a patient with epilepsy, and longer-term data are needed.

It could be argued that our definition of 'satisfied' is too exacting. The most controversial aspect would be the inclusion of side-effects as well as more significant adverse events in this measure. However, the clinical reality is that patients are concerned about the side-effects of drugs, want to discuss them with the researcher, and it is now established that they are a central feature of QOL, and satisfaction with treatment, for patients taking these drugs[19].

Pharmaco-economic analysis

The importance of pharmaco-economic analyses is acknowledged but such studies are in their infancy. We have previously presented data based on a theoretical model[4] of the pharmaco-economic differences between several anticonvulsant drugs[20]. From this model we have taken our cost-effectiveness ratio. However, the results of this previous study show how inaccurate pharmaco-economic models can be when compared with clinical reality[20]. Regarding our pharmaco-economic audit, we would make the following points. First, we have considered the cost of prescribing each of the two drugs as an add-on therapy. This is based upon an intention to treat analysis and is conceptually different from merely working out the actual cost of the drug per patient followed to the end of the study. We therefore take into consideration the full epilepsy-related costs that arise from an initial prescription for each drug which includes the cost of those that drop out of the study (as far as costing the latter was possible).

Second, we have tried to consider what costs should actually be included in a disease-related pharmaco-economic study. There are no gold standards[21]. At the outset we decided to include every epilepsy-related event that occurred during the course of the drug treatment. This decision resulted in more than just direct drug-related (usually adverse) events being costed.

It became apparent when we started to analyse our data that three patients in the topiramate group, but none in the lamotrigine group, had spent a period of time having in-patient telemetry as an elective procedure, either at the National Hospital or the Chalfont Centre for Epilepsy. We show how including such an epilepsy-related expense dramatically alters the pharmaco-economic costings. The issue of which disease-specific costings should go into an analysis is in need of clarification.

Third, we show the dramatic differences between simply presenting pharmaco-economic data as cost per patient treated, compared to cost for reducing seizures by $> 50\%$, compared to cost per patient 'satisfied'. If we just considered the cost of a patient becoming 50% seizure free, without indices of satisfaction (Table 7) the costs drop considerably.

Fourth, we have used a formula for cost-effectiveness taken from our pharmaco-economic study[4]. In that study, the period under consideration was 12 months and we adjusted our data to make them comparable to the published data for a 1 year period. This may have influenced our cost-effectiveness ratios. However, when we compare the cost-effectiveness ratios between the drugs in this study, there are clearly substantial differences and it is unlikely that our adjusting the data in this way accounts for such findings. Again, there are no gold standards but this may be a useful way of examining differences between drugs for future studies.

CONCLUSIONS

We present data from an audit of two new anticonvulsant drugs conducted at a tertiary referral centre to look at treatment satisfaction. Our data suggest that only a minority of patients with intractable epilepsy going on to the newer anticonvulsants derive 'satisfaction' from these drugs when given as an add-on therapy. We have highlighted differences in costs of achieving patient 'satisfaction' between lamotrigine and topiramate which may have relevance for the prescribing of these drugs.

ACKNOWLEDGEMENTS

For assistance with recruitment of patients we gratefully acknowledge: Professor S. Shorvon, Professor J. Duncan, Dr J.W.A. Sander, Dr D. Fish and Dr S. Smith. Thanks also to Dr M. O'Donoghue who provided training in the use of the National Hospital Seizure Severity Scale.

REFERENCES

1. Shorvon, S. Antiepileptic drug monotherapy versus polytherapy: economic aspects. *Epilepsia* 1997; **38** (Suppl. 5): S17–S20.
2. Drummond, M. F. The future of pharmacoeconomics. In: *Quality of Life and Pharmacoeconomics in Clinical Trials*. (Ed. B. Spilker). Philadelphia: Lippincott-Raven, 1996.
3. Cockerell, O. C., Hart, Y. M., Sander, J. W. A. S. and Shorvon, S. D. The cost of epilepsy in the U.K. *Cost of Epilepsy: Proceedings of the 20th International epilepsy Congress. CIBA-GEIGY, Germany, 1995*.
4. O'Neill, B. A., Trimble, M. R. and Bloom, D. S. Adjunctive therapy in epilepsy: a cost-effectiveness comparison of alternative treatment options. *Seizure*; 1995, **4**: 37–44.
5. van Hout, B., Gagnon, D., Souetre, E., Ried, S., Remy, C., Baker, G., Genton, P., Vespignani, H. and McNulty, P. Relationship between seizure frequency and costs and quality of life of outpatients with partial epilepsy in France, Germany,

and the United Kingdom. *Epilepsia* 1997; **38**: 1221–1226.
6. Walker, M. C., Li, L. M. and Sander, J. W. A. S. Long term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. *BMJ*; 1996; **313**; 1184–1185.
7. McDonnell, G. V. and Morrow, J. I. An audit of the new anti-epileptic drugs in clinical neurological practice. *Seizure* 1996; **5**: 127–130.
8. Crawford, P. An audit of Topiramate use in a general neurology clinic. *Seizure* 1998; **7**: 207–211.
9. O'Donoghue, M. F., Duncan, J. S. and Sander, J. W. A. S. The National Hospital Seizure Severity Scale: A further development of the Chalfont Seizure Severity Scale. *Epilepsia* 1996; **37**: 563–571.
10. Kendrick, A. M. and Trimble, M. R. Repertory grid in the assessment of quality of life in patients with epilepsy: The Quality of Life Assessment Schedule. In: *Epilepsy and The Quality of Life*. (Eds M. R. Trimble and W. E. Dodson). New York, Raven Press, 1994.
11. Selai, C. E. and Trimble, M. R. Adjunctive therapy in epilepsy with the new antiepileptic drugs: is it of any value? *Seizure* 1998; **7**: 417–418.
12. EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16**: 199–208.
13. *MIMS*. Monthly index of medical specialities. London, Haymarket, 1997.
14. *Office of Health Economics Compendium of Health Statistics*, 7th Edition. London, Office of Health Economics, 1989.
15. Pocock, S. J. *Clinical Trials: A Practical Approach*. Chichester, John Wiley and Sons, 1983.
16. Briggs, A., Sculpher, M. and Buxton, M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Economics* 1994; **3**: 95–104.
17. Shakespeare, A. and Simeon, G. Economic analysis of epilepsy treatment: A cost minimization analysis comparing carbamazepine and lamotrigine in the UK. *Seizure* 1998; **7**: 119–125.
18. Selai, C. and Trimble, M. R. Quality of Life before and after temporal lobectomy. *Epilepsia* 1998; **39** (Suppl. 2): 63.
19. Cramer, J. Quality of Life and compliance. In: *Epilepsy and The Quality of Life*. (Eds M. R. Trimble and W. E. Dodson). New York, Raven Press. 1994.
20. Selai, C. and Trimble, M. R. (In prep.) Adjuctive therapy in epilepsy: a cost-effectiveness study of four AEDs.
21. Spilker, B. Developing guidelines for pharmacoeconomics trials. In: *Quality of Life and Pharmacoeconomics in Clinical Trial*. (Ed. B. Spilker). 2nd Edition, Philadelphia: Lippincott-Raven, 1996.