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A Cost-Effectiveness Decision Model for Antiepileptic Drug Treatment in Newly Diagnosed Epilepsy Patients

Pieter D. Knoester, PharmD, PhD,[1] Charles L. P. Deckers, MD, PhD,[2] Eveline H. Termeer, MSc,[3] Arjo J. Boendermaker, MSc,[4] Irene A. W. Kotsopoulos, MD, PhD,[5] Marc C. T. F. M. de Krom, MD, PhD,[5] Toine Keyser, MD, PhD,[3] Willy O. Renier, MD, PhD,[3] Yechiel A. Hekster, PhD,[3] Hans L. Severens, PhD[4,5]

[1]Erasmus MC, Rotterdam, The Netherlands; [2]SEIN, Zwolle, The Netherlands; [3]University Medical Centre Nijmegen, Nijmegen, The Netherlands; [4]Maastricht University, Department of Health Organisation, Policy and Economics, Maastricht, The Netherlands; [5]University Hospital Maastricht, Maastricht, The Netherlands

ABSTRACT

Objective: To establish cost-effectiveness of antiepileptic drug (AED) treatment strategies of newly diagnosed patients with epilepsy.

Methods: A decision analysis was carried out comparing effectiveness and treatment cost of six treatment strategies comprising carbamazepine (CBZ), lamotrigine (LTG), and valproate (VPA) as first-line and second-line drugs. Three outcome groups were defined: complete success, partial success, and failure. Data on seizure control and failure due to adverse effects were derived from the literature. Data on resource use and costs were collected for each outcome group by means of a patient survey.

Results: Cost data were obtained from 71 patients. Cost increased from complete success to failure outcome groups. The probability of obtaining complete success varied from 64% (VPA–CBZ strategy) to 74% (LTG–VPA strategy). The strategy LTG–VPA was more effective than the least expensive strategy CBZ–VPA, but at higher costs per additional effectively treated patient. Probabilistic sensitivity analysis confirmed these findings to be robust. Subsequent analysis showed that changing inclusion criteria used in the selection of the studies from the literature had a major effect on cost-effectiveness ratios of the various strategies. The probability that LTG first-line therapy is the most cost-effective option remains small, even defining a high cost-effectiveness threshold. Nevertheless, LTG second-line strategies can be cost-effective depending on the willingness to pay for patient improvement.

Conclusions: Only a few studies satisfied our inclusion criteria for employment in our decision model. Our model supports the use of conventional AEDs as first-line options for patients with newly diagnosed epilepsy. LTG second-line therapy is likely to be the most cost-effective option in case society is willing to pay more than €6000 for an additional successfully treated patient. This study also illustrates that, with the data presently available, the outcome of decision analysis for AED treatment choice depends on the inclusion criteria used to select trials. Prospective real-life studies are needed in which first- and second-line treatment strategies are compared with respect to both effectiveness and costs.

Keywords: cost-effectiveness, decision tree model, epilepsy, lamotrigine.

Introduction

Carbamazepine (CBZ), phenobarbital, phenytoin, and valproate (VPA) have been the leading antiepileptic drugs (AEDs) for more than 30 years. Several new AEDs have, however, been introduced during the last decade.

In order to be licensed, these new AEDs had to demonstrate efficacy as adjunctive therapy in so-called intractable patients, that is, in patients with inadequate seizure control despite optimal therapy. Once a new compound is licensed and has demonstrated its effectiveness in daily practice, it will often be compared with the existing compounds in monotherapy trials for patients with newly diagnosed epilepsy. Lamotrigine (LTG), one of the new AEDs, has been involved in several of these comparative monotherapy trials [1–4]. A main advantage of LTG over conventional AEDs seems to be its favorable tolerability profile, leading to fewer treatment failures, fewer cognitive side effects and a better disease-related quality of life in patients with newly diagnosed epilepsy [4–6].

These results may contribute to a more widespread use of LTG. Nevertheless, the acquisition cost of LTG is several times higher than that of conventional AEDs. In this era of constrained health-care resources, health authorities are beginning to demand economic justification for new AEDs. The purpose of this study is

Address correspondence to: Pieter D. Knoester, Erasmus MC, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: p.knoester@erasmusmc.nl

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to establish the cost-effectiveness of LTG in patients with newly diagnosed epilepsy. In this study, the cost-effectiveness of LTG is compared with CBZ and VPA through a decision analytic approach. Drug-specific effectiveness data were derived from randomized clinical trials and observational studies published in the international literature. Patient data on cost consumption were collected for patients in one out of three different outcome groups via a patient questionnaire.

Six treatment strategies are compared in this study, that is, CBZ first-line monotherapy followed by either VPA or LTG in case CBZ fails because of either a lack of seizure control or adverse effects, VPA first-line monotherapy followed by either CBZ or LTG in case VPA fails because of either a lack of seizure control or adverse effects, and LTG first-line monotherapy followed by either CBZ or VPA in case LTG fails because of either a lack of seizure control or adverse effects.

Methods

Study Design

This article details a cost-effectiveness analysis evaluating first- and second-line treatment strategies in patients with newly diagnosed epilepsy. The analysis uses a decision tree as a modeling instrument. In accordance with Dutch guidelines on pharmacoeconomic research, a societal perspective was adopted for the economic evaluations [7]. The time span comprises the first year of treatment.

Decision Tree Model

A decision tree analysis (software program DATA; TreeAge Software, Williamstown, MA) was used as a model to depict potential clinical pathways and outcomes within the first year of treatment. Figure 1 shows the structure of the model. Three first-line drugs are studied: CBZ, VPA, and LTG. Six treatment strategies are evaluated comprising all possible variations of first- and second-line treatment with these three agents. In the model the effectiveness of the first drug is evaluated after 6 months. When a patient is seizure-free and does not experience unacceptable adverse effects, the patient continues with the first-line drug for the remaining 6 months. If there are unacceptable side effects on the first drug, the patient is switched directly to a second drug in monotherapy. In case of inadequate seizure control, the second-line treatment is first added to the first-line drug. In this case, the first-line drug is withdrawn after 2 months and second-line monotherapy is used for the last 4 months of the study. Thus, the assumption is made that at the end of the first year all patients are in one of three outcome groups, that is, complete success, partial success, or failure. Complete success implies the patient being seizure-free. Partial success is defined as a reduction in seizure frequency of more than 50% compared with baseline. Failure is defined as inadequate seizure control (i.e., less than 50% seizure reduction) or the occurrence of unacceptable adverse effects.

Decision Model Input

Path probabilities, reflecting the effectiveness of the different treatment strategies, were based on literature data. A limited number of studies with comparable study designs reporting effectiveness of these drugs as first-line therapy were selected from the available full-published comparative monotherapy studies. The inclusion criteria used for this selection procedure were:

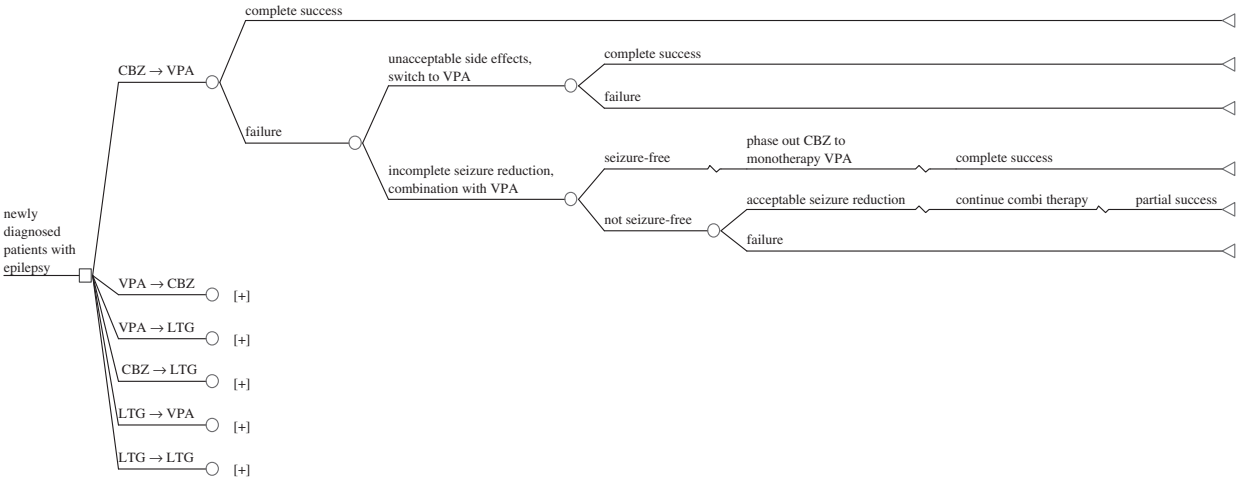

Figure 1 Decision tree model. The model is shown for the first-line strategy carbamazepine (CBZ) followed by valproate (VPA) in case of failure (CBZ → VPA). The structure of the model applies to all strategies. Circles represent change nodes. Triangles represent outcome groups, in which patients remain for the duration of the first year of treatment. LTG, lamotrigine.

- study participants had to be more than 12 years of age with newly diagnosed epilepsy;
- seizures had to be partial and/or generalized tonic–clonic seizures;
- starting dosages and titration schedules had to be in accordance with present guidelines;
- evaluation period of at least 24 weeks;
- no dose adjustments allowed during evaluation period.

From the selected studies, first-line probabilities on seizure freedom, failure due to side effects, and failure due to insufficient seizure reduction were calculated. All analyses were performed on a per protocol basis. Individual probabilities were based on weighted probabilities from the different studies based on their study size.

Studies reporting effectiveness of these drugs as second-line therapy were selected from available full-published studies evaluated in two earlier review articles [8,9]. The inclusion criteria were:

- titration and taper schedules in accordance with present guidelines;
- combination period of 8 to 12 weeks;
- monotherapy phase of 8 to 12 weeks.

From the selected studies, second-line probabilities on seizure freedom, failure due to side effects, and failure due to insufficient seizure reduction were calculated.

Collection of Data on Cost

From a societal viewpoint, three sectors can be identified in which epilepsy-related costs may occur: health-care sector, patient and family sector, and others [10]. To estimate the cost of epilepsy care in the first sector, data were obtained from the medical records of patients. Data on costs in the two latter sectors were collected using patient questionnaires. In this questionnaire, information was collected retrospectively over a period of 3 months and prospectively the same data were collected for 6 months following the inclusion date. Three months is a recommended recall period for retrospective data collection [11]. Adult epilepsy patients visiting the outpatient department of neurology of the University Medical Centre Nijmegen and the University Hospital Maastricht could participate. The treating physicians classified each patient into one of the three outcome groups based on seizure frequency. Patients were classified as complete success (seizure-free), partial success (more than 50% reduction in seizure frequency), or failure (less then 50% seizure reduction).

The daily maintenance doses defined in the decision model are based on the average doses achieved in the trials considered, that is, 600 mg for CBZ, 150 mg for LTG, and 1000 mg for VPA. For LTG used in combination with CBZ, the daily dose was set at 300 mg.

Cost Valuation

The assignment of unit cost to the various elements of epilepsy care is based on an instruction document for economic evaluation in Dutch health care by Oostenbrink et al. [12]. This document provides guideline prices relevant for The Netherlands for various items, such as outpatient clinic visits and hospitalization. When there is no guideline price for an item, these items were valued by using official tariff lists for allowable reimbursement rates.

Table 1 mentions these cost units and their prices. All figures were updated to January 2002 according to the rate of inflation. Inflation was measured by the

Table 1 Unit cost per item

Cost item	Cost measure	Unit cost (€)	Source
Health-care sector			
GP services	Cost per visit	16.7	Guideline price
Physician services	Cost per visit	46.1	Guideline price
Hospital services			
Neurologic ward	Cost per admission day	304.3	Guideline price
Ambulance	Cost per trip	265.2	Guideline price
Diagnostics			
Laboratory	Cost per procedure	4.4	Tariff*
Imaging (EEG, CT, MRI)	Cost per procedure	95.6	Tariff†
Drug therapy	Cost per month		Tariff
CBZ 600 mg		9.7	
LTG 150 mg		69.6	
VPA 1000 mg		15.9	
Patient and family sector			
Unpaid care	Cost per hour	8.9	Guideline price
Other sectors			
Absence of work	Cost per day	106.5	Guideline price‡

*Weighted composition of tariffs from different laboratory investigations.
†Weighted composition of tariffs from different imaging tests.
‡Weighted composition of different ages.
CBZ, carbamazepine; CT, computed tomography; EEG, electroencephalogram; GP, general practitioner; LTG, lamotrigine; MRI, magnetic resonance imaging; VPA, valproate.

Table 2 Studies incorporated into first-line strategies of the decision tree model

Model	AED	Patients (n)	Doses (mg/day)	Starting doses (mg)	Titration	Complete success (%)	Failure due to ADR (%)	Failure due to incomplete control (%)	Reference
A	CBZ	101	600	200	200 mg/2 weeks	63	12	25	Reunanen et al. (2)
	CBZ	45	Based on plasma levels	Not mentioned	Not mentioned	67	27	6	Kälviäinen et al. (13)
	VPA	97	Flexible	300	No fixed scheme	59	11	30	Christe et al. (14)
	LTG	98	100	25	25 mg/2 weeks	60	5	35	Reunanen et al. (2)
	LTG	106	200	25	25 mg/2 weeks	63	5	32	Reunanen et al. (2)
B	CBZ	103	Flexible	200	200 mg/week	48	34	18	Brodie et al. (1)
	LTG	107	Flexible	50	50 mg/week	48	19	33	Brodie et al. (1)
C	CBZ	141	Flexible	200	First: 200 mg/week Then: 200 mg/2 weeks	47	17	36	Richens et al. (17)
	VPA	140	Flexible	400	400 mg/week	44	6	50	Richens et al. (17)

Model B incorporates the studies of models A and B; model C incorporates the studies of models A and C; model D (not shown) incorporates all studies.
ADR, adverse drug reaction; AED, antiepileptic drug; CBZ, carbamazepine; LTG, lamotrigine; VPA, valproate.

Consumer Price Index published by Statistics Netherlands (http://www.cbs.nl). All costs were expressed in euro (€).

Cost-Effectiveness Analysis

The analysis of the decision tree model results in probabilities of a theoretical patient to end up in one of three outcome groups, that is, complete success, partial success, or failure, the so-called path probabilities. Based on these path probabilities, the expected cost of each of the six strategies was determined. General principles of cost-effectiveness analysis were applied to these results [10]. First, it was determined whether certain strategies were dominated by other strategies. A dominated strategy is more costly, but less effective than another strategy. For nondominated strategies, the cost-effectiveness analysis combines the expected costs with the probability of complete success, that is, the incremental cost-effectiveness ratio (ICER). Beginning with the least costly strategy, nondominated alternatives were compared with calculate incremental ratios. The ICER is calculated as:

$$\frac{(\text{mean annual cost per patient})_{\text{strategy 2}} - (\text{mean annual cost per patient})_{\text{strategy 1}}}{(\text{complete success})_{\text{strategy 2}} - (\text{complete success})_{\text{strategy 1}}}$$

Sensitivity Analysis

Second-order uncertainty of the cost-effectiveness estimates of the six strategies was investigated by Monte Carlo simulation techniques. Distributions were defined for the probabilities and costs used in the model (complete success, incomplete seizure reduction, unacceptable side effects). As probabilities are supposed to have a value between 0 and 1, beta distributions were fitted for all these parameters. For costs gamma distributions (zero to infinity) were defined. For defining the gamma distributions, the observed mean and variance of the total costs in our patient data were used. The probabilities of complete success and acceptable seizure for the different drug regimens were treated as independent binomial distributions using the total patient numbers and the proportion of success as shown in Table 2. Of course, the patient outcome measure complete success was dichotomous and therefore, in contrast to the probability of success, was not part of the probabilistic sensitivity analysis. All six strategies were evaluated in the simulation that was performed with 1000 iterations. As a result of the iterations, for every cost and effectiveness pair of a strategy, net benefits were calculated for a range of levels of ceiling cost-effectiveness ratios. For each iteration, a strategy is considered optimal in case of the highest net benefit and the proportion of the iterations being optimal is determined for each strategy. Subsequently, cost-effectiveness acceptability curves were drawn for each of the six strategies.

Additional models were designed that, next to the studies in the initial model, incorporated studies that did not meet the inclusion criteria used for our initial model (which will be called model A from here on). This was done to check for bias introduced by our inclusion criteria. These additional models will be called models B–D.

Results

Decision Tree Analysis

A literature search yielded 14 first-line monotherapy trials. Only three of these 14 studies met our inclusion criteria [2,13,14]. The probabilities for the various outcome groups derived from these studies are presented in Table 2. The other studies were excluded for various reasons. Two studies also concerned patients that did not have newly diagnosed epilepsy [6,15]. One study only considered patients older than 65 years of age [3]. Titration schedules used in two studies were no longer in agreement with present guidelines [1,4]. The evaluation period was too short in one study [16]. In

Table 3 Probabilities of second-line drug strategies

Second-line strategy*	Patients (n)	Complete success (%)	Partial success (%)	Failure (%)	Comments	Reference
CBZ–VPA and VPA–CBZ	95	8	23	69	Assumption: VPA → CBZ as CBZ → VPA	Brodie and Mumford (22)
CBZ–LTG and LTG–CBZ	63	22	21	57	Assumption: CBZ → LTG as LTG → CBZ	Jozwiak and Terczynski (23)
VPA–LTG and LTG–VPA	63	32	32	34	Assumption: VPA → LTG as LTG → VPA	Jozwiak and Terczynski (23)
Second AED after failure of first AED due to side effects	98	34		66	General assumption	Kwan and Brodie (24)

*CBZ-VPA: path probabilities of VPA as second-line drug after failure of CBZ as first-line drug (see Fig. 1).
AED, antiepileptic drug; CBZ, carbamazepine; LTG, lamotrigine; VPA, valproate.

five studies the number of patients becoming seizure-free at the end of the evaluation phase was not mentioned [17–21].

Two second-line studies met our inclusion criteria [22,23]. No data were found on probabilities for second-line VPA or CBZ after failure of LTG. An assumption was made that these latter probabilities were the same as for second-line LTG after failure of VPA or CBZ. No drug-specific data were found on the probability of a second drug leading to complete success after failure of a first drug due to side effects. A general probability for this scenario was derived from the observational study by Kwan et al. [24]. The probabilities for second-line treatments are shown in Table 3.

Collection of Data on Cost

Self-reported data on cost were collected from a total of 71 patients: 30 patients (21 men; mean age 49 ± 19 years) were in the complete success outcome group, 27 patients (13 men; mean age 43 ± 18 years) in the partial success outcome group, and 14 patients (7 men; mean age 54 ± 20 years) in the failure outcome group. Average monthly costs per patient, with the exception of drug costs, are presented in Table 4. Overall, an inverse relation between cost consumption per item and outcome groups was demonstrated. Patients in the complete success group appeared to incur the lowest costs (€35.8/month) in contrast to patients in the failure outcome group (€130.4/month). The items "hospital services" and "unpaid care" contributed most to the costs. Lost productivity due to absence of work was negligible.

Cost-Effectiveness Analysis

The results of the cost-effectiveness analysis are presented in Table 5 and ranked in ascending order of expected costs. The probability of obtaining complete success varied from 64% (VPA–CBZ strategy) to 74% (LTG–VPA strategy). The treatment strategy with the lowest cost, the reference treatment, was CBZ–VPA with expected annual costs per patient for the first year of treatment of €975 (probability complete success is 68.4%). The treatment strategy LTG–CBZ took up the highest costs, €2036 annually. The LTG–CBZ strategy and also the strategies VPA–LTG and VPA–CBZ were dominated strategies (more expensive and less effective). Two treatment alternatives, CBZ–LTG and LTG–VPA, were nondominated strategies. The ICER of CBZ–LTG relative to the CBZ–VPA strategy is €6079 per additional complete success patient. That of LTG–VPA relative to CBZ–LTG is €40,422 per additional complete success patient.

Sensitivity Analysis

Figure 2 shows the cost-effectiveness acceptability curves of the different strategies and illustrates that

Table 4 Average breakdown of costs per patient group in euro per month (and ranges)

Cost item	Complete success	Partial success	Failure
Health-care sector			
GP services	0 (0–0)	0.5 (0–10.7)	4.9 (0–46.2)
Physician services	8.5 (0.1–35.3)	8.3 (0–46.2)	13.1 (0.1–73.6)
Hospital services	0 (0–0)	17.6 (0–625.5)	54.6 (0–727.6)
Diagnostics (laboratory & imaging)	24.5 (0.2–161.8)	33.8 (0–302.2)	41.0 (0.2–330.0)
Patient and family sector			
Unpaid care	2.8 (0–64.5)	67.4 (0–3642.7)	16.8 (0–413.6)
Others			
Absence of work	—	—	—
Subtotal*	35.8	127.6	130.4

*The cost of drug therapy is strategy-specific and therefore not shown in this table.
GP, general practitioner.

Table 5 Cost-effectiveness analysis

Strategy (model A)	Expected 1-year cost per patient (€)	Expected complete success	ICER*
CBZ–VPA	975	0.684	Reference
VPA–CBZ	1,111	0.635	(Dominated)
CBZ–LTG†	1,230	0.726	6,079
VPA–LTG	1,255	0.722	(Dominated)
LTG–VPA‡	1,861	0.742	40,422
LTG–CBZ	2,036	0.706	(Dominated)

*The ICER is calculated relative to the next less costly nondominated strategy.
†Calculation ICER CBZ–LTG: (1230–975)/(0.726–0.684).
‡Calculation ICER LTG–VPA: (1861–1230)/(0.742–0.726).
CBZ, carbamazepine; ICER, incremental cost-effectiveness ratio; LTG, lamotrigine; VPA, valproate.

CBZ–VPA has the highest probability of being most cost-effective in the lower range of the ceiling ratio. In the higher range of the ceiling ratio, second-line LTG options have the highest probability to be the most cost-effective. The first-line strategies with LTG as a first-line drug are clearly shown not to be cost-effective, despite a high cost-effectiveness threshold of €25,000 per effectively treated patient. Probabilistic sensitivity analysis confirms these findings to be robust.

In a subsequent analysis, the impact of the inclusion criteria used (to select studies reporting first-line path probabilities) on the outcomes of the cost-effectiveness model was evaluated. Three additional models were designed that, next to the studies in the initial model, incorporated studies that did not meet the inclusion criteria used for model A (see Table 2). In model B, a study by Brodie et al. was added to the studies in model A [1]. This study was not included into model A because titration schedules for both CBZ and LTG were not conform present guidelines [25]. Table 6 shows that incorporation of this study leaves the reference strategy CBZ–VPA unchanged, and that the strategies CBZ–LTG and LTG–VPA become dominated strategies (where as in model A they were nondominated strategies). Model C consists of the studies included in model A plus a study by Richens et al. [17]. This study was left out of model A for two reasons. The starting dosage of VPA was rather low compared with present guidelines, and this resulted in a prolonged period before the eventual effect of this drug could be expected. Furthermore, the number of patients becoming seizure-free was not clearly mentioned in this study and had to be estimated from a Kaplan–Meier graph. Table 6 shows that incorporation of this study leaves the reference strategy unchanged and that the ICER of the LTG–VPA strategy becomes 8021 (whereas in model A the ICER was 40,422). In model D, both the Brodie et al. and the Richens et al. studies were added to the studies in model A. Consequently, all first-line path probabilities changed compared with model A. Table 6 shows that the strategy with the least costs was CBZ–VPA and that the strategies CBZ–LTG and LTG–VPA were more

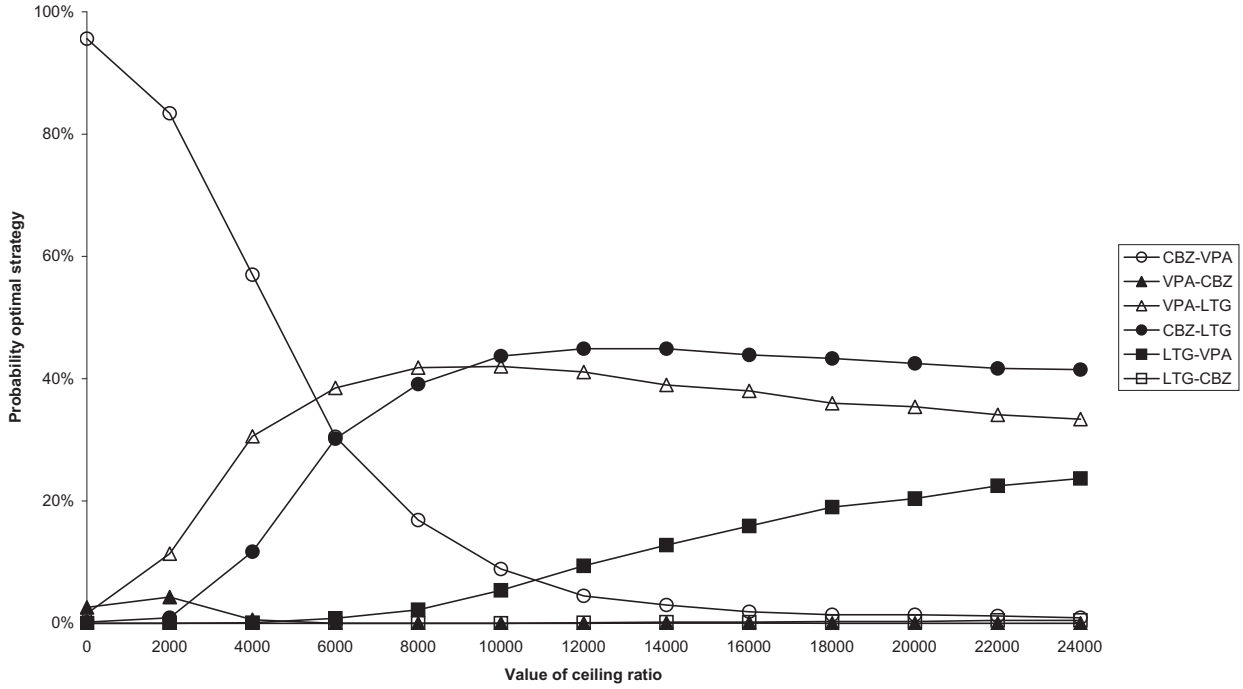

Figure 2 Cost-effectiveness acceptability curves for the decision regarding the most efficient strategy for antiepileptic drug treatment in newly diagnosed epilepsy patients. CBZ, carbamazepine; LTG, lamotrigine; VPA, valproate.

Table 6 Sensitivity of cost-effectiveness outcome for studies incorporated into the model

	Model A			Model B			Model C			Model D		
Strategy	Cost (€)	Effect	ICER	Cost (€)	Effect	ICER	Cost (€)	Effect	ICER	Cost (€)	Effect	ICER
CBZ–VPA	975	0.684	Reference	1,038	0.658	Reference	1,050	0.640	Reference	1,126	0.585	Reference
VPA–CBZ	1,111	0.635	(Dominated)	1,102	0.648	(Dominated)	1,270	0.508	(Dominated)	1,271	0.508	(Dominated)
CBZ–LTG	1,230	0.726	6,079	1,297	0.686	(Dominated)	1,332	0.677	7,485	1,449	0.627	(Extended dominated)
VPA–LTG	1,255	0.722	(Dominated)	1,255	0.723	3,348	1,473	0.621	(Dominated)	1,473	0.621	(Dominated)
LTG–VPA	1,861	0.742	40,422	1,891	0.703	(Dominated)	1,855	0.743	8,021	1,891	0.703	11,354
LTG–CBZ	2,036	0.706	(Dominated)	2,057	0.667	(Dominated)	2,012	0.710	(Dominated)	2,057	0.667	(Dominated)

"Effect" refers to probability of complete success group at the end of the first year of treatment.
CBZ, carbamazepine; ICER, incremental cost-effectiveness ratio; LTG, lamotrigine; VPA, valproate.

effective compared with this reference strategy. Nevertheless, the strategy CBZ–LTG is extended dominated by LTG–VPA and the ICER of the LTG–VPA strategy becomes 11,354.

Discussion

Ideally, an economic evaluation consists of a real-life study in which both clinical and cost data are assessed [10,26]. Such a study is not available for AEDs and therefore we used existing published literature for estimates of effectiveness and a patient questionnaire for estimates on cost items. As there is no randomized trial directly comparing CBZ, VPA, and LTG, a decision model was used for an indirect comparison of a number of original, controlled trials. To strengthen these comparisons, stringent inclusion criteria to the eligible trials were applied. This resulted in a limited number of included trials. For the probabilities of second-line treatment we had to rely on several assumptions, since only two studies satisfied our predefined inclusion criteria. In our opinion, it is justified to assume that the effectiveness of CBZ and VPA as second-line treatments following LTG is equal to that of LTG used as a second-line treatment following CBZ or VPA. The efficacy of a drug is determined not only by its pharmacodynamic properties, but also by the stage of treatment at which it is given and by which drugs were given earlier. The observational study by Kwan and Brodie showed that more than 50% of patients become seizure-free on the first drug, whereas the chances of becoming seizure-free on the second or third drug rapidly decline thereafter [24]. The LTG substitution study by Jozwiak and Terczynski showed that the efficacy of LTG was higher in patients that had not become seizure-free on VPA, than in patients that had not become seizure-free on CBZ [23]. Because of these factors, one would expect the total number of patients responding to the treatment strategy A, possibly followed by B, to be equal as the total number of patients responding to the treatment strategy B, possibly followed by A. This has actually been demonstrated by two crossover studies in the literature [27,28].

All models in our study show that CBZ–VPA is the reference treatment and that there are more effective treatments, but at considerable costs per extra patient treated effectively. Assessing levels of uncertainty is important in cost-effectiveness analysis because of the assumptions made about the relation between the intervention and the outcome [29]. This is, however, rather complicated because the outcome in a cost-effectiveness analysis is a ratio of two different outcomes (costs and effects), rather than an estimate of a single outcome (say, adequate seizure reduction). Sensitivity analysis, preferably probabilistic, is an accepted

method to evaluate whether the result is robust to changes in the different parameters involved. This study shows that it is also important to use transparent inclusion criteria for data used to build the decision tree model. In our opinion, Model A is the most appropriate model because the titration schedules used in these studies are up to date and because the results of these studies were presented clearly. Nevertheless, the inclusion criteria used were of influence on the outcome, especially on the ICER, as the differences between models A–D show. A limitation of our model is the fact that the probabilities of complete success and acceptable seizure were treated as independent binomial distributions. By employing a Dirichlet distribution, these probabilities could have been made conditionally dependent, but a major influence on our conclusions is not expected.

In this study, we used a cost questionnaire to obtain data on cost consumption. The validity of a cost questionnaire such as ours was assessed previously [30]. This comprehensive questionnaire allows collecting patient-based costs of epilepsy, as is widely recommended for cost-effectiveness studies [31]. Another approach to estimate cost items is the use of an expert panel (Delphi panel), as has been used in previous economic studies in epilepsy [32,33]. Such a panel estimates the costs incurred by patients. We believe that patient-based cost collecting is at least as adequate, and gives additional valid data. The costs are assumed to be equal within each of the three outcome categories, except for drug costs. It seems reasonable that the frequency of visits to the outpatient department and of investigations is dependent on the response to treatment, rather than on the drug with which this outcome is realized. It also is likely that the utility within an outcome category is related to that category, rather than to the drug used.

We found that cost of treatment of patients with newly diagnosed epilepsy was lowest for the conventional strategy CBZ–VPA. The LTG–VPA strategy, with first-line use of LTG, was more effective but against considerably higher cost per individual seizure-free patient in model A. The cost-effectiveness of LTG monotherapy was compared with CBZ monotherapy in one cost minimization study and with CBZ, phenytoin, and VPA monotherapy in a second cost minimization study [32,33]. The first study was based on only one comparative monotherapy trial, while the second study was based on eight different monotherapy studies. In cost minimization studies, the efficacy of the respective treatments is assumed to be equal; the only outcome is treatment cost per initial strategy and the costs considered are drug costs, costs of resources employed in the management of adverse events, and costs associated with therapeutic switching. Both cost minimization studies showed that LTG is considerably more expensive for newly diagnosed patients in health service costs incurred. There are several differences between our study and these two cost minimization studies: 1) efficacy is not assumed to be equal in our study; 2) we determined costs per additionally effectively treated patient in comparison with the reference treatment; 3) we used stringent inclusion criteria to yield a sample of comparable studies; 4) our sensitivity analysis evaluated the effects of including further studies instead of evaluating best-case and worst-case scenarios of included studies; and 5) we used a patient questionnaire instead of a Delphi panel. Despite differences in methodology between the approaches, the findings are overall rather similar for model A.

Our model supports the use of conventional AEDs as first-line options for patients with newly diagnosed epilepsy. LTG second-line therapy is likely to be the most cost-effective option in case society is willing to pay more than €6000 for an additional successfully treated patient. Our findings agree with the technology appraisal guidance "newer drugs for epilepsy in adults" from the National Institute for Clinical Excellence (NICE) from the UK [34]. In the NICE guidance, the newer AEDs like LTG are recommended for the management of epilepsy in people who have not benefited from treatment with the conventional AEDs, or for whom the older drugs are unsuitable because of contraindications, interactions, or the person is a woman of childbearing potential.

Our study also illustrates that with the data presently available, the outcome of decision analysis for drug treatment choice depends on the inclusion criteria used to select trials. Neurologists are counting on cost-effectiveness data to make rational choices [35]. Therefore, there is a need for prospective real-life studies comparing strategies of first- and second-line treatment and incorporating both cost and outcomes.

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