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Cost-effectiveness of add-on lamotrigine therapy in clinical practice

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Abstract

Objective: This retrospective study addresses the cost-effectiveness of add-on therapy with lamotrigine in clinical practice.
Methods: Two years' observational data of 165 patients were used. Seizure frequency, adverse effects and direct medical costs were recorded for the year before and the year after the start of lamotrigine add-on therapy. Therapy effectiveness was measured by: (1) reduction in seizure frequency and (2) retention time. The incremental cost-effectiveness ratio expressed the direct medical cost per patient treated effectively with lamotrigine.
Results: The cost of medication was €492 (95% CI: €399–583) higher after the start of lamotrigine therapy. The extra cost of lamotrigine therapy (€622) was partly offset by a reduction of the cost of co-medication (−€130; 95% CI: −€210 to −€50). Overall, the total medical cost was €453 higher in the first year of lamotrigine therapy than in the year before the start of lamotrigine. Lamotrigine was effective in 47% of all the patients, making the resultant incremental cost-effectiveness ratio €954 per year.
Discussion: Add-on therapy of lamotrigine for patients with uncontrolled epilepsy offers improved health outcomes. Lamotrigine therapy is associated with increased cost (€453) and an annual incremental cost-effectiveness ratio of €954. These data, together

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with utility data published in the literature, support the notion that lamotrigine should be considered as an add-on therapy in for patients with refractory epilepsy.

Keywords: Lamotrigine; Cost-effectiveness; Observational; Retrospective

1. Introduction

Antiepileptic drugs (AEDs) have traditionally been the cornerstone of clinical epilepsy management. Approximately 30% of epilepsy patients respond poorly to the conventional AEDs, either because of a lack of efficacy or because of intolerable side effects. New AEDs have broadened the treatment options of patients with uncontrolled epilepsy, and possibly a larger proportion of patients may be rendered seizure free with the help of these drugs. Jacoby et al. (1998) found that cost of illness for patients with refractory epilepsy was up to eight times more than for those with controlled epilepsy. van Hout et al. (1997) also found that higher seizure frequencies are associated with higher cost of illness as well as with reduced quality of life. Estimates of the direct medical costs of refractory epilepsy found in medical literature vary roughly from €850 to €4250 per year (Griffiths et al., 1999; Kotsopoulos et al., 2001, 2003; Murray et al., 1996; van Hout et al., 1997). It is as yet unclear whether the new AEDs, with their higher acquisition costs than the conventional AEDs, may actually reduce other direct medical costs (outpatient visits, hospital admissions, diagnostic investigations and cetera) or indirect costs (care for family during disease exacerbation, productivity and cetera).

Because of the tension between budget constraints and the growing treatment possibilities, health economic evaluations are becoming more important in the field of epilepsy. However, it is questionable whether the effectiveness and cost-effectiveness of a drug as established in clinical trials is similar to its effectiveness and cost-effectiveness in clinical practice, as these trials are carried out according to strict protocols and in selected patient populations. The effectiveness and cost-effectiveness therefore also needs to be assessed in observational studies (Black, 1996).

In this retrospective multicenter study, the cost-effectiveness of lamotrigine add-on therapy was established. This was done by comparing costs and seizure frequency during the year after start of LTG treatment with the seizure frequency and costs in the year before LTG was started.

2. Methods

2.1. Setting and data collection

The cost-effectiveness analysis was performed alongside a detailed observational study on the effectiveness of LTG (Knoester et al., 2005a). The study population consisted of 165 adult patients (≥18 years) who received add-on LTG therapy because of uncontrolled epilepsy and/or intolerable adverse effects on conventional AEDs or vigabatrin. These were patients under the care of neurologists in different medical centres: 32 general hospitals, 3 academic hospitals and 2 tertiary epilepsy centres.

Data of LTG users were recorded retrospectively from their medical records. Data were collected for the period of one year before (year −1) and one year after (year +1) the day of start of LTG treatment in a mirror-image design. Recorded data covered the following domains:

- Demographics: age and gender.
- Epilepsy characteristics: epilepsy type and duration of epilepsy.
- Reason for initiation of LTG therapy.
- Seizure frequency in year −1 and in year +1.
- Tolerability: all adverse effects registered in the medical chart for year −1 and year +1.
- Use of resource items during the study period was directly recorded in a specifically designed database. Recorded items included hospital services (outpatient department visits, emergency room visits and hospital admissions), diagnostic investigations (radiology, EEG and laboratory) and antiepileptic medication as specified in Table 1. Type and dosage of medication used, as well as date of drug

Table 1
Unit costs in 2004 (€)

Cost item	Cost measure	Unit cost (€)	Source of unit cost
Hospital services			
Outpatient			
Outpatient consult	Per visit	62.1	Guideline price
Telephonic consult	Per call	31.1	Guideline price
Inpatient			
Hospital visit	Per admission day	316.1	Guideline price
Intensive care visit	Per admission day	1294	Guideline price
Diagnostic procedures			
Imaging procedures			
CT scan	Per procedure	160.3	CVZ tariff
EEG	Per procedure	87.7	CVZ tariff
EEG, 24 h	Per procedure	740.7	CVZ tariff
MRI scan	Per procedure	211.9	CVZ tariff
Laboratory procedures			
Clinical chemistry	Per procedure	5.5–15.2	CVZ tariff
Drug monitoring	Per procedure	12.8–21.5	CVZ tariff
Medication[a]			
Carbamazepine (1000 mg)	Per month	10.20	CVZ tariff
Phenytoin (300 mg)	Per month	2.3	CVZ tariff
Vigabatrin (2000 mg)	Per month	80.2	CVZ tariff
Valproate (1500 mg)	Per month	17.2	CVZ tariff
Lamotrigine (300 mg)	Per month	110.6	CVZ tariff

[a] Monthly total cost for daily defined dose based on most frequently used oral dosage form (only the most frequently used AEDs in this study are listed). CVZ: Dutch Health Care Insurance Board.

changes and reason for drug changes were recorded. Resources related to patient and family sector (e.g. transportation and paid care) or to other sectors (e.g. time loss from work/usual activity) could not be collected from the medical charts.

2.2. Cost valuation

In the analysis, epilepsy related direct medical costs were calculated by multiplying resource items of each patient with unit costs for those items. The assignment of unit costs to the various elements of epilepsy care is based on guideline prices for economic evaluation in Dutch health care (Oostenbrink et al., 2002, 2003a). When no guideline price for an item was available, tariffs were used as shadow prices and in our study this applied to drug cost, laboratory tests and imaging procedures (Table 1). All prices were updated to the rate of inflation by the Consumer Price Index (Statistics Netherlands, http://www.cbs.nl) to 2004 and expressed in Euro (€; exchange rate for currency conversion in November 2004—1€: US$ 1.3). Non-parametric bootstrap analysis was used to analyse differences in costs between year −1 and year +1. Healthcare costs have a right skewed distribution and normal distribution assumptions are not valid. Non-parametric bootstrap analysis can be used to provide accurate estimates of the uncertainty of the ICER. The bootstrap method estimates the sampling distribution of a statistic through a large number of simulations, based on sampling with replacement from the original data. Confidence can then be constructed using this empirical estimate of the sampling distribution (Briggs et al., 1997). For this study, 1000 bootstrap replications were generated with the same size as the original data. Confidence limits were obtained by selecting the 2.5th and 97.5th percentiles of the bootstrapped replications.

2.3. Effectiveness

In this mirror-image analysis, patients served as their own control group in the LTG effectiveness

assessment. Criteria for effectiveness during the first year of treatment depended on the reason for initiation:

1. If LTG had been prescribed for inadequate seizure control with other AEDs: LTG therapy was considered effective if a reduction in mean seizure frequency of at least 50% in year +1 compared to the mean seizure frequency in year −1 was established and LTG use continued for a full 12 months in year +1 without the addition of another AED.
2. If LTG was prescribed because of adverse effects of other AEDs: LTG therapy was considered effective if there had been no clinically relevant increase in mean seizure frequency in year +1 compared to the seizure frequency in year −1 (defined as a maximum increase of less than 50%) and LTG use continued for 12 months in year +1 without the addition of another AED.

This outcome endpoint encompasses the efficacy endpoint used in randomised clinical trials of AEDs (seizure reduction of at least 50%) and the effectiveness endpoint used in observational studies (retention time). The Student's *t*-test was used to analyse differences in effectiveness.

2.4. Cost-effectiveness analysis

The prespecified incremental cost-effectiveness ratio (ICER) was used to calculate the direct medical costs per patient effectively treated with LTG. The ICER is calculated as follows:

$$\frac{(\text{mean annual cost per patient})_{\text{year}+1} - (\text{mean annual cost per patient})_{\text{year}-1}}{(\%\ \text{effectively treated patients})_{\text{year}+1}}$$

The health outcomes and resource utilisation were recorded for the two-year period and analysed by intention-to-treat. Healthcare costs have a right skewed distribution and normal distribution assumptions are not valid. Non-parametric bootstrap analysis was used to estimate the uncertainty of the ICER by defining the 2.5th and 97.5th percentiles of a 1000 bootstrapped replications (Briggs, 2004).

3. Results

3.1. Demographics

The study population of 165 patients included 93 women, the mean age at start of LTG therapy was 45 years (Table 2). The mean duration of epilepsy before start of LTG was 18 years. In most cases (81%), LTG was started after previous use of two or more other AEDs. The reasons to start with LTG were insufficient seizure control (68%) and AED intolerance (32%). In the first group, adverse effects were a concurrent problem in 13% (of the total patient group).

3.2. Effectiveness

In the total group of patients, LTG was effective in 78 of 165 patients (47%) (Knoester et al., 2005a). Effectiveness of LTG therapy was 40.2% in the group receiving LTG because of insufficient seizure control on other AEDs. In this group, 14% of patients became seizure free. In the AED intolerance group, LTG was effective in 62.3% of patients. In this group, 14 patients (26%) were seizure free before the addition of LTG and 13 patients (25%) remained so after its addition.

3.3. Costs

Direct medical costs were €1266 in year −1 and €1719 in year +1, a significant difference of €453 (95% CI: €21–885; Table 3). Costs for hospital services or diagnostic procedures were similar for year +1 compared to year −1. Costs for medication were significantly higher in year +1 compared to year −1, the cost difference was €492 (95% CI: €399–583). The extra costs of LTG therapy (€622) were partly offset by a reduction of costs of co-medication in year +1 (−€130; 95% CI: −€210 to €50). The costs for carbamazepine, oxcarbazepine, valproic acid and vigabatrin were significantly lower in year +1 compared to year −1 and contributed most to the reduction in costs for co-medication in year +1. Direct medical costs in year +1 of patients treated effectively with LTG were not significantly different compared to year −1 (cost difference €84; 95% CI: −€215 to €383; Fig. 1). The intensive care costs in year −1 were caused by one patient being admitted to intensive care for 15 days. Despite the relatively small number of patients, a significant cost

Table 2
Demographic and clinical baseline characteristics per indication group

	Seizure control	AED intolerance	Total
All patients	112	53	165
Male	53 (47.3)	19 (35.8)	72 (43.6)
Female†	59 (52.7)	34 (64.2)	93 (56.4)
Age (years)	44.3 ± 14.9	45.5 ± 15.3	44.9 ± 15.0
Hospital type†			
General hospital	53 (57.0)	40 (43.0)	93 (56.4)
Academic hospital	17 (68.0)	8 (32.0)	25 (15.1)
Tertiary epilepsy centre	42 (89.4)	5 (10.6)	47 (28.5)
Epilepsy type			
Partial	100 (89.3)	47 (88.7)	147 (89.1)
Generalised	12 (10.7)	5 (9.4)	17 (10.3)
Unclassified		1 (1.9)	1 (0.6)
Duration of epilepsy (years)†	20.4 ± 15.9	12.6 ± 12.4	17.9 ± 15.3
Baseline monthly seizure frequency†	4.4 ± 6.4	0.5 ± 1.4	3.2 ± 5.7
Number of previous AEDs†			
One	19 (17.0)	13 (24.5)	32 (19.4)
Two	21 (18.8)	16 (30.2)	37 (22.4)
Three	23 (20.5)	10 (18.9)	33 (20.0)
Four or more	49 (43.8)	14 (26.4)	63 (38.2)
Concurrent AEDs			
Carbamazepine†	58 (51.8)	16 (30.2)	74 (44.8)
Phenytoin	17 (15.2)	7 (13.2)	24 (14.5)
Sodium valproate	56 (50.0)	19 (35.8)	75 (45.5)
Vigabatrin	23 (20.5)	13 (24.5)	36 (21.8)

Values are number of patients with percentages in parentheses, or mean values with standard deviations (with a '±' symbol).
† Statistically significant differences ($p \leq 0.05$) between the two indication groups.

difference compared to year −1 was seen in patients with a lack of effectiveness from LTG (cost difference €803; 95% CI: €278–1329); this was related to relatively high costs of hospital services (mean costs €1017) and medication (€926) for these patients in year +1, as shown in Fig. 1.

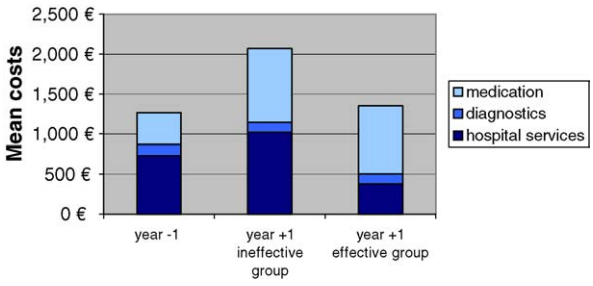

Fig. 1. Impact of treatment outcome on costs.

3.4. Cost-effectiveness analysis

By definition, patients were not treated effectively in the year −1 period. The ICER therefore can be calculated as follows: (€1719 − €1266.3)/(0.47–0) = €954. So, per patient €453 extra was needed to increase effectiveness of epilepsy treatment by 47%, indicating an investment of €954 per successfully treated patient. In Fig. 2, the distribution of bootstrap replicates is displayed graphically in a cost-effectiveness plane. Overall, 6% of the bootstrap replicates were found in the quadrant that indicated that LTG therapy is more effective at lower costs, while 94% of replicates indicated that LTG therapy is more effective but against higher costs. The ICER for patients that started LTG because of insufficient seizure control was €849, and the ICER for patients that started LTG because of adverse effects on other AED(s) was €1094.

Table 3
The mean healthcare costs per patient and year in 2004 (€)

	Year before LTG	Year with LTG	Difference	95% CI
Hospital services				
Outpatient	247.6	256.5	8.9	−12.5 to 30.2
Outpatient consult	233.5	235.8	2.3	−17.1 to 21.9
Telephonic consult	14.2	20.7	6.5	0.4–12.6
Inpatient	481.6	449.7	−31.9	−445.0 to 381.2
Hospital visit	358.8	449.7	90.9	−284.7 to 466.6
Intensive care visit	122.8	0	−122.8	−297.9 to 52.2
Subtotal	729.3	706.2	−23.1	−438.7 to 392.6
Diagnostic procedures				
Imaging procedures	97.6	80.3	−17.3	−71.7 to 37.0
CT scan	20.3	8.1	−12.2	−20.0 to −4.4
EEG	53.2	65.6	12.3	−39.4 to 64.0
MRI scan	24.1	6.7	−17.4	−26.6 to −8.3
Laboratory procedures	42.5	44.0	1.5	−7.1 to 10.2
Clinical chemistry	25.1	25.8	0.7	−5.2 to 6.6
Drug monitoring	17.4	18.2	0.8	−3.3 to 5.0
Subtotal	140.1	124.3	−15.8	−71.0 to 39.4
Medication				
AED co-medication	396.9	266.8	−130.1	−210.2 to −49.9
Lamotrigine	0	621.7	621.7	573.0–670.3
Subtotal	396.9	888.5	491.6	399.9–583.3
Total	1266.3	1719.0	452.7	20.9–884.6

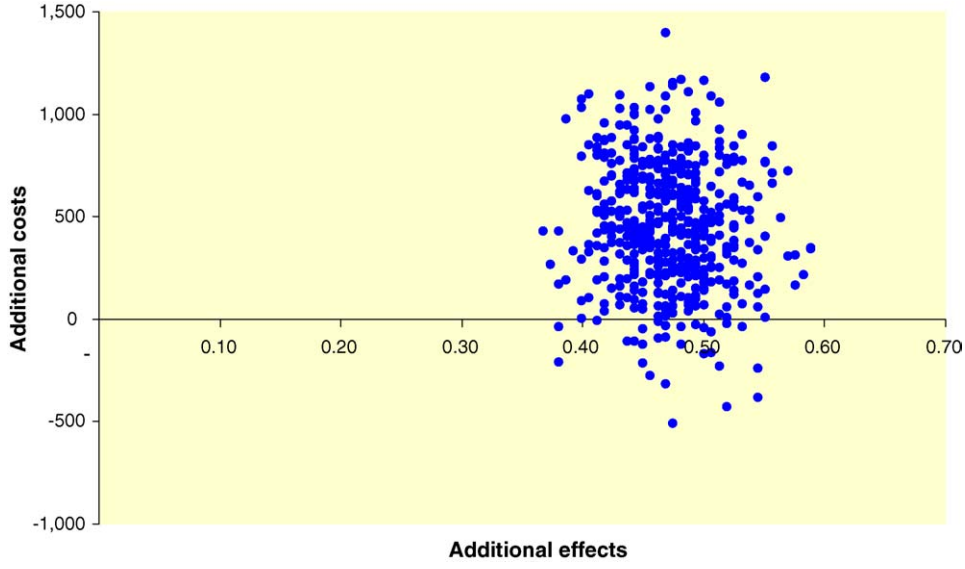

Fig. 2. Bootstrap replicates of incremental cost-effectiveness ratio. One thousand bootstrap replicates of ICER showing the joint distribution of costs and health outcomes in the cost-effectiveness plane. On the *x*-axis the difference in effectiveness between year +1 and year −1, on the *y*-axis the difference in average annual costs.

4. Discussion

This observational study determined the cost-effectiveness of LTG treatment with patients as their own controls. In the first year of LTG treatment, an overall effectiveness rate of 47% was found. LTG treatment was associated with extra annual direct medical costs of €452.8 on average. The largest cost difference was found in drug costs, as the extra costs for LTG (€622) were only partly offset by a reduction in costs for other AEDs (−€130; 21% reduction). It has been argued that despite the high acquisition costs, LTG may offer financial savings because of its fewer side effects and increased tolerability (Chadwick, 1998; Heaney et al., 1998). We could not confirm overall savings for the total cohort. For patients that were treated effectively with LTG there was no significant cost difference between year +1 and year −1, as savings in hospital services (−€350) offset most of the rise in drug costs (€452). In patients where LTG was not effective, financial savings were absent in year +1 and a significant cost difference compared to year −1 was found.

The direct medical costs found in this study fell within the aforementioned range of €850–4250 per year for patients with uncontrolled epilepsy (Griffiths et al., 1999; Kotsopoulos et al., 2001, 2003; Murray et al., 1996; van Hout et al., 1997). This study showed that the ICER associated with the add-on use of LTG was €954 per year. The economic question, based on the cost-effectiveness analysis, is whether €954 annually for an extra patient treated effectively is good value for money. Previous studies regarding the cost-effectiveness of add-on LTG were based on decision analytic models (Hughes and Cockerell, 1996; Markowitz et al., 1998; Messori et al., 1998; O'Neill et al., 1995). Their validity was questioned as their input depended on extrapolation of trial data and estimations of expert panels (Heaney and Begley, 2002).

Health economic decisions are often based on cost–utility analyses rather than cost-effectiveness analyses. The utility is a measurement of the patient's global functioning and one of the instruments used to measure utility is the quality adjusted life year (QALY) method. In a cost–utility analysis using QALY's, one determines the cost of improving utility by one QALY. The advantage of a cost–utility analysis is that its results are more universal than a disease-specific cost-effectiveness analysis. Quantitative thresholds for cost per quality adjusted life year gained have been proposed upon review of economic evaluations (Laupacis et al., 1992; Drummond et al., 1997). If cost per QALY are under the threshold of about €20,000, it is accepted that strong evidence exists for adoption of the new therapy. The available data form the medical records did not allow us to measure QALY's. Messori et al. (1998) used a time trade-off method to value health states of patients with epilepsy. Using this data, a patient treated effectively (i.e. 50% reduction in seizure frequency) gained at least an increase in utility of 0.13. Forbes et al. (2003) used the EuroQol-5D Health State instrument, and they found for a 50% reduction in seizure frequency a mean gain in health could reasonably be valued as 0.17 utility extra. Assuming that an utility of 0.15 may indeed be gained by effective add-on therapy, together with the extra costs of treatment with LTG of €452.8 found in this study, would result in an incremental cost utility ratio well below €20,000. This supports the notion that lamotrigine should be considered as an add-on therapy inpatients with refractory epilepsy.

The observational design used in this study has both strong points and weaknesses. A strong point of the design is that utilisation data from clinical practice are collected and analysed; health economic data based on clinical trials reflect cost of the protocol rather than how individual patients are doing (Oostenbrink et al., 2004). In an earlier study, we demonstrated that the baseline characteristics of our cohort differs from those reported from clinical trials, with respect to age, concurrent use of specific AEDs, and length of follow-up (Knoester et al., 2004). This may be explained by the use of lamotrigine in a broader population of epilepsy patients compared to patients included in add-on LTG regulatory trials, including patients with less severe epilepsy. A majority of patients in our cohort had chronic epilepsy and had used three or more AEDs without becoming seizure free (and thus resemble patients in regulatory trials), but about 40% of our cohort had previously only used one or two AEDs. Furthermore, about 30% of our cohort started with lamotrigine because of intolerable side effects on their previous treatment, such as the development of visual field defects while using vigabatrin, rather than because of inadequate seizure control. The observational design furthermore enabled us to continue the collection of data from patients that were not treated effectively with LTG for the full

study period and the economic evaluation followed the intention-to-treat principle. Missing data because of patient withdrawal from a clinical trial before reaching the scheduled end date cause a well-known problem in the data analysis (Oostenbrink et al., 2003b).

With regards to weaknesses, the non-blinded and non-controlled design firstly allowed for selection bias and confounding variables (Knoester et al., 2005b). We used a mirror-image design (patients serving as their own control) instead of a control group, a study design previously used to evaluate the cost-effectiveness of clozapine, a new antipsychotic drug (Hayhurst et al., 2002). One may expect that physicians started LTG at the peak of disease activity, i.e. at the time of unacceptable seizure frequency or intolerable side effects. This may result in a higher utilisation of hospital services or diagnostic procedures in year −1. The course of epilepsy is variable, and improvements could have occurred without any special intervention (i.e. regression to the mean), and as a resultant lower utilisation of health care may have occurred in year +1. One may, however, claim that recording 12 months before and after the start of LTG is sufficiently long to rule out regression to the mean. Furthermore, 14% of patients receiving LTG because of insufficient seizure control on other AEDs became seizure free after addition of LTG and more than 50% reduction in seizure frequency is noted; this is not to be expected from regression to the mean. Finally, in patients with difficult-to-treat epilepsy in the placebo arm of add-on trials, a reduction in seizure frequency of 50% or more is attained in 20% of patients or less (Matsuo et al., 1993; Shorvon et al., 2000; US Gabapentin Study Group No. 5, 1993), which is considerably lower than the effectiveness we found in the seizure control group. Another weakness, inherent to the retrospective character of the study, is that only direct medical costs could be measured. In a prospective study, indirect costs such as transportation to the hospital and care for patient and family during disease exacerbation could have been determined as well as non-medical costs such as loss of productivity (Kotsopoulos et al., 2003). Given the effectiveness of LTG in 47% of patients in year +1, it is likely that these costs were lower for year +1 compared with year −1. There is evidence that increasing the effectiveness of epilepsy treatment is the most important contributor to a change in quality of life and a reduction in costs (Baker et al., 1997; van Hout et al., 1997).

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