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Effectiveness of lamotrigine in clinical practice: Results of a retrospective population-based study

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Abstract

Objective: Evaluation of the effectiveness of lamotrigine in a population-based cohort of epilepsy patients.
Methods: Medical charts of 360 patients treated in 37 centres in The Netherlands were reviewed. Effectiveness of lamotrigine therapy was assessed during the first year of use, with patients serving as their own controls. Effectiveness was measured by reduction in seizure frequency and retention time.
Results: Effectiveness could only be assessed in 165 patients; assessment in remaining patients was not possible due to various reasons, such as insufficient medical chart information. Lamotrigine was effective in 40% of patients who had been prescribed lamotrigine because of insufficient seizure control ($n = 112$), and 14% of these 112 patients became seizure free. Duration of epilepsy, baseline seizure frequency, valproate use, drug load and number of antiepileptic drugs (AED) used were related to effectiveness of lamotrigine. In this group, 36% continued lamotrigine (LTG) throughout the first year without experiencing a >50% seizure reduction. Lamotrigine was effective in 63% of patients who received the drug because of poor tolerability of other antiepileptic drugs ($n = 53$).

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Discussion: Lamotrigine is an effective drug in clinical practice. Use of retention time measures only may not correctly reflect the efficacy of antiepileptic drugs.

Keywords: Lamotrigine; Seizure frequency; Retention time; Valproate
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1. Introduction

During the last 15 years, six new antiepileptic drugs (AEDs) (gabapentin, lamotrigine (LTG), levetiracetam, oxcarbazepine, topiramate and vigabatrin) have become available for clinical practice in The Netherlands. This was a welcome development, as no new antiepileptic drugs had been introduced during the two preceding decades. In order to be licensed, these new drugs had to demonstrate efficacy as add-on drugs in patients with refractory epilepsy in placebo-controlled clinical trials. However, in daily practice, these drugs are used in broader groups of patients and under less-controlled and less-monitored conditions. The effectiveness in daily practice may differ from the effectiveness found in clinical trials. Therefore, the actual merit of these new drugs remains to be ascertained in daily practice (French, 2002; Martin et al., 2003; Wieringa et al., 2003).

One of these new antiepileptic drugs, lamotrigine, has been evaluated in clinical trials in a variety of patient groups, including patients with newly diagnosed epilepsy (Brodie et al., 1995; Matsuo et al., 1993; Messenheimer et al., 1994; Motte et al., 1997; Nieto-Barrera et al., 2001). In addition, the effectiveness of LTG in clinical practice was evaluated in a number of observational studies, with retention time as the end point (Collins et al., 2000; Datta and Crawford, 2000; Lhatoo et al., 2000; Walker et al., 1996; Wong et al., 1999). Retention time is the period during which patients continue using the drug, and is considered to be a useful indicator of effectiveness because it reflects seizure control as well as tolerability (Baker et al., 1998). However, retention time is only a crude indicator, as the actual changes in seizure frequency and side effects are not known. In addition, patients in these retention time studies often were participants of previous clinical trials (Walker et al., 1996).

The aim of this study was to assess the effectiveness of LTG in a population-based cohort of epilepsy patients and to assess its tolerability in this population.

2. Methods

2.1. Setting and data collection

In a previous study, we identified a large number of LTG users through pharmacy dispensing records (Knoester et al., 2004). For privacy reasons, these patients were approached through their pharmacists for permission to review their medical chart (Knoester et al., 2005). Of the 968 patients who gave consent for chart review, a sample of 368 patients was selected for the actual review. This sample was representative for the group of 968 concerning hospital type, geographical area, number of AEDs used and lamotrigine retention rate. The medical records were reviewed by a physician specialised in the field of epilepsy (C.D.). Data were collected from 32 general hospitals, 3 academic hospitals and 2 tertiary epilepsy centres. The period studied for each patient spanned from the year before the start date of LTG (year −1) to the first year after start of LTG (year +1). Recorded data covered the following domains:

- Demographics: age, gender.
- Epilepsy characteristics: epilepsy type, duration of epilepsy.
- Medication: AEDs used, duration of use, dosage regimen and drug load. Drug load is the ratio between the prescribed daily dosage (PDD) and the defined daily dosage (DDD, as defined by the World Health Organisation (Deckers et al., 1997)). For example, when a patient uses 600 mg of carbamazepine, this represents a drug load of 0.6, as the DDD for carbamazepine is 1000 mg. When several drugs are used, the drugs loads per drug are summed to arrive at the total drug load for that patient.
- Seizure frequency in year −1 and in year +1.
- Tolerability: all adverse effects registered in the medical chart for year −1 and year +1.
- Reason for initiation of LTG therapy.

A patient was excluded from the study if the information obtained proved that:

- there was no or an uncertain diagnosis of epilepsy, based on clinical history, seizure description and/or EEG registration;
- the patient was younger than 18 at the start date of LTG (index date);
- LTG was the first AED to be prescribed;
- the index date was before 1 August 1997, the reimbursement date of LTG (i.e. as of that day, LTG was reimbursed by health insurance companies);
- chart data for at least 1 year before and after the index date were not available;
- seizure frequency had been documented for less than 75% of the evaluated period.
- Psychogenic pseudo-epileptic seizures were thought to be present.
- Non-compliance was considered to be present.

2.2. Outcome

The primary outcome was the effectiveness of LTG in daily clinical practice. Data of all eligible patients were analysed, with an intent-to-treat approach. 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.

Patients were classified as seizure free if treatment with LTG led to the absence of any type of seizures for the 12 months following the start of the LTG therapy.

2.3. Data analysis

Continuous variables were compared with the use of the Students' *t*-test, categorical variables with the Chi-square test. The relationship between patient characteristics and LTG effectiveness was assessed with multiple logistic regression analysis, and expressed as odds ratios (OR) with 95% CI.

3. Results

3.1. Patients

The medical charts and clinical notes of 360 selected outpatients were reviewed in 37 different medical centres (32 general hospitals, 3 university hospitals, 2 tertiary epilepsy centres). This chart review led to the exclusion of more than half of these patients: 94 patients were excluded because of insufficient data on seizure frequency, 42 because charts were unavailable or because the comprised time period was too short, 27 patients had an unconfirmed diagnosis of epilepsy and 27 were excluded because LTG had been initiated before the reimbursement date. Furthermore, the chart data of three patients with progressive brain tumours and two non-compliant patients were excluded. Thus, the final study population consisted of 165 patients. The study population and the population of excluded patients had similar baseline characteristics, no significant differences were found between eligible and ineligible patients in the distribution of age, gender, hospital type, duration of illness, pre-LTG treatment history or LTG retention time (data not shown).

The baseline demographic and clinical characteristics of the study population per hospital type are shown in Table 1. In most cases (81%), LTG was started after previous use of two or more other AEDs. Significant differences were found in the distribution of patient characteristics between the three different hospital types (Table 1).

3.2. Initiation of LTG therapy

The baseline demographic and clinical characteristics of the study population per indication are shown in Table 2. The reasons to start with LTG were insufficient seizure control (68%) and AED intolerance (32%).

Table 1
Demographic and clinical baseline characteristics per hospital type

	General hospital	Academic hospital	Epilepsy centre	All hospitals
All Patients	93	25	47	165
Male	37 (39.8)	13 (52.0)	22 (46.8)	72 (43.6)
Female	56 (60.2)	12 (48.0)	25 (53.2)	93 (56.4)
Age	47.7 ± 15.1	42.5 ± 16.7	40.1 ± 12.8[a]	44.9 ± 15.0
Epilepsy type				
Partial	85 (91.4)	21 (84.0)	41 (87.2)	147 (89.1)
Generalised	7 (7.5)	4 (16.0)	6 (12.8)	17 (10.3)
Unclassified	1 (1.1)			1 (0.6)
Duration of epilepsy (years)	14.4 ± 13.6	21.4 ± 19.3[b]	22.9 ± 14.6[a]	17.9 ± 15.3
Baseline monthly seizure frequency	2.1 ± 4.9	4.2 ± 6.4)	4.9 ± 6.5[a]	3.2 ± 5.7
Number of previous AEDs trials				
One	29 (31.2)	1 (4.0)[a]	2 (4.3)[a]	32 (19.4)
Two	19 (20.4)	7 (28.0)[a]	11 (23.4)[a]	37 (22.4)
Three	20 (21.5)	4 (16.0)[a]	9 (19.1)[a]	33 (20.0)
Four or more	25 (26.9)	13 (52.0)	25 (53.2)[a]	63 (38.2)
Concurrently used AEDs				
Carbamazepine	33 (35.5)	11 (44.0)	30 (63.8)[a]	74 (44.8)
Phenobarbital	5 (5.4)	0 (0)	5 (10.6)	10 (6.1)
Phenytoin	13 (14.0)	6 (24.0)	5 (10.6)	24 (14.5)
Sodium valproate	41 (44.1)	8 (32.0)[a]	26 (55.3)[a]	75 (45.5)
Vigabatrin	18 (19.4)	11 (44.0)[a]	7 (14.9)	36 (21.8)
Drug load	1.1 ± 0.9	1.6 ± 1.0	1.8 ± 1.1[a]	1.4 ± 1.0
Reasons for starting LTG				
Lack of efficacy	43 (46.2)	10 (40.0)	37 (78.7)[b]	90 (54.5)
Adverse events	40 (43.0)	8 (32.0)	5 (10.6)[b]	53 (32.1)
Both	10 (10.8)	7 (28.0)	5 (10.6)[b]	22 (13.3)

Values are numbers of patients with percentages in parentheses, or mean values with standard deviations (with a ± sign).
[a] Statistically significant ($p \leq 0.05$) differences compared to patients from hospital types.
[b] Statistically significant ($p \leq 0.05$) differences for patients from tertiary centres when compared to patients from other hospital types.

In the first group, adverse effects were a concurrent problem in 13% (of the total patient group). There were significantly more women than men in the AED intolerance group (Table 2). Also, duration of epilepsy before LTG initiation was significantly shorter and mean seizure frequency significantly lower in this group than in the first. Finally, patients in the AED intolerance group had used less AEDs before start of LTG and their drug load was approximately half of that of the seizure-control group.

3.3. Treatment effectiveness

In the total group of patients, LTG was effective, according to our criteria, in 78 out of 165 patients (47%) (Table 3). Effectiveness of LTG therapy was significantly lower in patients that had insufficient seizure control (40.2%) compared to patients who were prescribed LTG because of adverse effects on other AEDs (62.2%). In the former group, 16 patients became seizure free. In this group, 40 patients continued lamotrigine without experiencing a ≥50% seizure reduction. In the latter group, the previously non-tolerated drug was sometimes continued at a lower dose and sometimes withdrawn concurrently to the introduction of lamotrigine. Conversion to LTG monotherapy was significantly lower in the seizure-control group: 8 and 37.7%, respectively. The spectrum of adverse effects mentioned in the medical charts differed in the years before and after start of LTG (Table 4).

Table 2
Demographic and clinical baseline characteristics per indication group

	Seizure control	AED intolerance
All Patients	112	53
Male	53 (47.3)	19 (35.8)
Female[a]	59 (52.7)	34 (64.2)
Age	44.3 (14.9)	45.5 (15.3)
Epilepsy type		
Partial	100 (89.3)	47 (88.7)
Generalised	12 (10.7)	5 (9.4)
Unclassified		1 (1.9)
Duration of epilepsy (year)*[a]	20.4 (15.9)	12.6 (12.4)
Baseline monthly seizure frequency*[a]	4.4 (6.4)	0.5 (1.4)
Number of previous AEDs[a]		
One	19 (17.0)	13 (24.5)
Two	21 (18.8)	16 (30.2)
Three	23 (20.5)	10 (18.9)
Four or more	49 (43.8)	14 (26.4)
Concurrent AEDs		
Carbamazepine[a]	58 (51.8)	16 (30.2)
Phenobarbital	9 (8.09)	1 (1.9)
Phenytoin	17 (15.2)	7 (13.2)
Sodium valproate	56 (50.0)	19 (35.8)
Vigabatrin	23 (20.5)	13 (24.5)
Drug load*[a]	1.7 (1.1)	0.8 (0.8)

Values are number of patients with percentages in parentheses, except '*': mean (S.D.).
[a] Statistically significant differences ($p \leq 0.05$) between the two indication groups.

3.4. Logistic regression analysis

Logistic regression analysis showed that several characteristics were significantly associated with effectiveness in the seizure-control group. Both length of duration of epilepsy (OR 0.96, 95% CI: 0.94–0.99) and baseline seizure frequency (OR 0.91, 95% CI: 0.84–0.97) were inversely related to LTG effectiveness. Baseline drug load was also related to successful LTG response, higher drug loads were related to failure of therapy (drugload_{1-2}: OR 0.45, 95% CI: 0.23–0.92; $\text{drugload}_{\geq 2}$: OR 0.29, 95% CI: 0.10–0.83). The number of AEDs used before the start of LTG was significantly correlated to the successful outcome of LTG therapy, the success rate in patients that used one AED previously being at least three-fold higher than in patients who used two or more AEDs previously.

Table 3
Clinical outcome of lamotrigine therapy in the study population

	Seizure control ($n = 112$)	AED intolerance ($n = 53$)
LTG treatment outcome		
Ineffective[a]	67 (59.8)	20 (37.8)
Effective[a]	45 (40.2)	33 (62.2)
Seizure free	16 (14.3)	n.a.
Reasons for failure of LTG		
Inadequate seizure control[a]	50 (83.6)	7 (35.0)
Adverse events[a]	17 (16.4)	13 (65.0)
Discontinuation in first year	27 (24.1)	11 (20.7)
Due to rash	10 (8.9)	2 (3.8)
Retention time of LTG (days)	313 ± 106	312 ± 113
Conversion to LTG monotherapy[a]	9 (8.0)	20 (37.7)
LTG dosage (mg/day)	206 ± 128	194 ± 128
Range (mg/day)	12.5–600	12.5–500

Values are numbers of patients with percentages in parentheses, or mean values with standard deviations (with a $\pm$ symbol). n.a: not analysed.
[a] Statistically significant differences ($p \leq 0.05$) between the two indication groups.

Effectiveness of LTG therapy was more likely in patients who had used sodium valproate concurrently (OR 0.42, 95% CI: 0.17–0.96). Effectiveness of LTG was less likely in patients using phenytoin (OR 0.20, 95% CI: 0.05–0.81). There was no association in this group between treatment outcome and gender, age, epilepsy type, or use of carbamazepine, phenobabital or vigabatrin.

The impact of the number of previously used AEDs on the effectiveness of LTG in this group is illustrated

Table 4
Most frequently reported side effects

Adverse events	Year −1 (%)	Year +1 (%)
Concentration loss	15.2	7.9
Weight gain	14.8	2.4
Mood disorder	9.7	11.5
Diplopia/blurred vision	9.7	10.3
Sleepiness	9.1	4.8
Dizziness	9.1	13.3
Tiredness	7.9	Not mentioned
Tremor	7.9	7.3
Gastrointestinal complaints	6.1	9.7
Hair loss	5.5	1.2
Skin disorders (acne; rash)	3.6	14.5
Headache	3.0	9.1

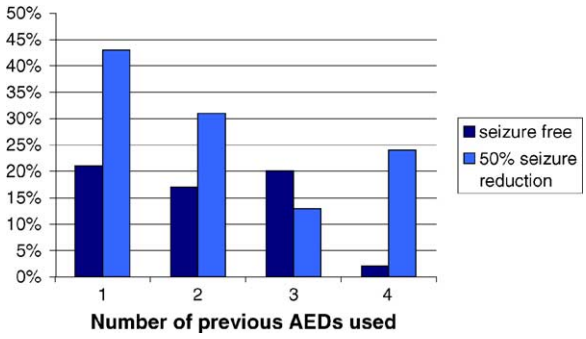

Fig. 1. Efficacy of lamotrigine related to the number of AEDs previously used.

in Fig. 1. Effectiveness of LTG after failure of one AED was 74%, including 21% seizure-free patients. The effectiveness of LTG after four previously used AEDs was 26%, and a total of 2% became seizure free. There were no differences in effectiveness between patients with localization-related epilepsy and patients with generalized epilepsy.

In the AED intolerance group, no individual characteristics were found to be significantly related to the treatment outcome.

4. Discussion

This study aimed at assessing the effectiveness of LTG in clinical practice. The results add to the present knowledge concerning the efficacy and tolerability of LTG.

4.1. Seizure control (efficacy)

A higher success rate of LTG therapy was found in this study than in previous add-on trials. In the first year of treatment, LTG therapy was effective in 40% of the patients with refractory epilepsy. In the initial regulatory trials, with a maximum follow-up of 24 weeks, the percentage of patients experiencing a $\geq$50% reduction was lower (Matsuo et al., 1993; Messenheimer et al., 1994). This difference in efficacy may be due to a broader study population in our sample, i.e. more patients who had tried only one or two AEDs prior to LTG. Seizure reduction of 50% or more is broadly accepted as the recognisable threshold of effect in add-on trials, and there is evidence that reducing a patient's seizure frequency is the most important contributor to a change in quality of life (Marson and Chadwick, 2001). However, the relevance of reducing seizures by 50% may not be obvious to individual patients. Seizure freedom is a much more relevant and easier to interpret efficacy parameter. In the seizure-control group of this study, seizure freedom was attained in 14% after addition of LTG. In patients that had previously used four or more other AEDs, addition of LTG only rendered 2% seizure free, which is comparable to the 5% seizure-free rates reported in regulatory trials. However, 15–20% of patients who had previously used one, two or three other AEDs, became seizure free in this group (Fig. 1). These data on the efficacy of LTG compare favourably with the observational data reported by Kwan and Brodie (2000). These authors reported seizure freedom with any drug or combination of drugs in only 4% when patients did not become seizure free on their first or second antiepileptic drug.

Our study confirms the general finding that an early response to drug therapy or a low seizure frequency confirms a favourable prognosis (Kwan and Brodie, 2001). The combination of LTG and valproate seems to exhibit a favourable pharmacodynamic interaction in patients with refractory epilepsy, an observation that has been made previously (Brodie and Yuen, 1997; Pisani et al., 1999).

4.2. AED intolerance (tolerability)

LTG therapy was effective in 60% of the patients who started taking the drug because of adverse events with other AEDs. In previous observational studies on the effectiveness of LTG, only patients with inadequate seizure control were evaluated (Faught et al., 2004; Trenite et al., 2001; Walker et al., 1996; Wong et al., 2001). In clinical practice, physicians also prescribe LTG because the drug is known to have a more favourable side-effect profile than conventional AEDs (Brodie et al., 1995; Nieto-Barrera et al., 2001; Steiner et al., 1999). Due to LTG's mild side-effect profile, the drug is an effective alternative for cases of AED intolerance. In the present study, adverse effects necessitated withdrawal of LTG therapy in 22% of the patients, with rash as the most common cause for discontinuation (7%). This is actually higher than in the clinical trails; pooled trial data showed a discontinuation rate of LTG therapy of 10%, rash being reported the most

frequently (3.8%) as the reason for discontinuation (Richens, 1994). Seven of the 53 patients prescribed LTG because of adverse effects on previous drug or combination of drugs, experienced a significant worsening of seizure control. However, 33 of the patients in this group responded well to LTG, which implies that LTG was able to maintain seizure control in these patients.

The methods of patient recruitment and reviewing charts in different medical centres employed for this study are quite laborious, certainly compared with the aforementioned retention time studies. They do, however, have important advantages. First, our methods produce more information than retrospective studies that focus only on retention time, as the actual seizure frequency reduction per patient and the percentage of seizure-free patients are determined. We found that 36% stayed on LTG for longer than 12 months, despite their not experiencing a >50% seizure reduction. In the observational studies focusing only on retention time, more patients discontinued lamotrigine than in our study, but the study period in these studies was longer. Second, the employed methods result in studying a cross-section of patients visiting different hospital types. The retention time studies mostly concerned patients from tertiary referral epilepsy clinics, which represent less than one-third of the epilepsy population as a whole (French, 2002). As Table 2 shows, patients attending tertiary clinics have a high number of previous AED trials, are on high drug loads and have higher seizure frequencies. These are factors that have a negative impact on the success of AED treatment.

The results of the present study must also be considered within the context of several limitations. First, this study only included patients who had given consent to their community pharmacist. This may have led to biased enrolment towards patients in which LTG was effective (Knoester et al., 2005). Second, this was a retrospective cohort study. The resultant data acquisition was non-blinded and drug selection was non-random. Third, we used a mirror-image design (patients serving as their own control group) instead of an independent control group. Physicians start LTG at the peak of disease activity: either an unacceptable seizure frequency or intolerable side effects. The course of epilepsy is variable, and improvements could have occurred without any special intervention (i.e. regression to the mean). One may nevertheless claim that monitoring 12 months before and after the start of LTG is sufficiently long to rule out regression to the mean as sole reason for LTG effectiveness. Fourth, the data for this study were collected with the use of medical chart notes. These notes are primarily kept to aid in the treatment of individual patients, and not for outcome research. Therefore, seizure counts are not always recorded into the notes, and in these cases retrospective baselines could not be obtained, and these patients had to be excluded. Nevertheless, eligible and ineligible patients seemed comparable with respect to baseline characteristics.

Despite these limitations, this study allowed us to assess the effectiveness of LTG in a population-based setting. The data for the present study came from diverse regions of the country and from diverse medical centres. As such, the results are likely to be representative. Therefore, the study should be considered as complementary to the initial randomised add-on trials and subsequent post-marketing studies addressing the efficacy of LTG in selected patients. It can be concluded from the present study that LTG is an effective treatment option and a useful alternative for patients with varying needs, including those with inadequate seizure control and intolerable side effects.

References

Baker, G.A., Camfield, C., Camfield, P., Cramer, J.A., Elger, C.E., Johnson, A.L., Martins, D.S., Meinardi, H., Munari, C., Perucca, E., Thorbecke, R., 1998. Commission on Outcome Measurement in Epilepsy, 1994–1997: final report. Epilepsia 39, 213–231.

Brodie, M.J., Richens, A., Yuen, A.W., 1995. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet 345, 476–479.

Brodie, M.J., Yuen, A.W., 1997. Lamotrigine substitution study: evidence for synergism with sodium valproate. 105 Study Group. Epilepsy Res. 26, 423–432.

Collins, T.L., Petroff, O.A., Mattson, R.H., 2000. A comparison of four new antiepileptic medications. Seizure 9, 291–293.

Datta, P.K., Crawford, P.M., 2000. Refractory epilepsy: treatment with new antiepileptic drugs. Seizure 9, 51–57.

Deckers, C.L.P., Hekster, Y.A., Keyser, A., Meinardi, H., Renier, W.O., 1997. Drug load in clinical trials: a neglected factor. Clin. Pharm. Ther. 62, 592–595.

Faught, E., Matsuo, F.U., Schachter, S., Messenheimer, J., Womble, G.P., 2004. Long term tolerability of lamotrigine: data from a 6-year continuation study. Epilepsy Behav. 5, 31–36.

French, J.A., 2002. Post-marketing surveillance of new antiepileptic drugs: the tribulations of trials. Epilepsia 43, 951–955.

Knoester, P.D., Belitser, S.V., Deckers, C.L.P., Keyser, A., Renier, W.O., Egberts, A.C.G., Hekster, Y.A., 2004. Patterns of lamotrigine use in daily clinical practice during the the first five years after introduction in The Netherlands. J. Clin. Pharm. Ther. 29, 131–138.

Knoester, P.D., Belitser, S.V., Deckers, C.L.P., Keyser, A., Renier, W.O., Egberts, A.C.G., Hekster, Y.A., 2005. Recruitment of a cohort of lamotrigine users through community pharmacists: differences between patients who gave informed consent and those who did not. Pharmacoepidemiol. Drug Saf. 14, 107–112.

Kwan, P., Brodie, M.J., 2000. Early identification of refractory epilepsy. N. Engl. J. Med. 342, 314–319.

Kwan, P., Brodie, M.J., 2001. Effectiveness of first antiepileptic drug. Epilepsia 42, 1255–1260.

Lhatoo, S.D., Wong, I.C., Polizzi, G., Sander, J.W., 2000. Long-term retention rates of lamotrigine, gabapentin, and topiramate in chronic epilepsy. Epilepsia 41, 1592–1596.

Marson, A.G., Chadwick, D.W., 2001. New drug treatments for epilepsy. J. Neurol. Neurosurg. Psychiatry 70, 143–148.

Martin, K., Begaud, B., Latry, P., Miremont-Salame, G., Fourrier, A., Moore, N., 2003. Differences between clinical trials and post-marketing use. Br. J. Clin. Pharmacol. 57, 86–92.

Matsuo, F., Bergen, D., Faught, E., Messenheimer, J.A., Dren, A.T., Rudd, G.D., Lineberry, C.G., 1993. Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. Neurology 43, 2284–2291.

Messenheimer, J., Ramsay, R.E., Willmore, L.J., Leroy, R.F., Zielinski, J.J., Mattson, R., Pellock, J.M., Valakas, A.M., Womble, G., Risner, M., 1994. Lamotrigine therapy for partial seizures: a multicenter, placebo- controlled, double-blind, cross-over trial. Epilepsia 35, 113–121.

Motte, J., Trevathan, E., Arvidsson, J.F., Barrera, M.N., Mullens, E.L., Manasco, P., 1997. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. Lamictal Lennox-Gastaut Study Group. N. Engl. J. Med. 337, 1807–1812.

Nieto-Barrera, M., Brozmanova, M., Capovilla, G., Christe, W., Pedersen, B., Kane, K., O'Neill, F., 2001. A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy. Epilepsy Res. 46, 145–155.

Pisani, F., Oteri, G., Russo, M.F., Di Perri, R., Perucca, E., Richens, A., 1999. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. Epilepsia 40, 1141–1146.

Richens, A., 1994. Safety of lamotrigine. Epilepsia 35 (Suppl. 5), 37–S40.

Steiner, T.J., Dellaportas, C.I., Findley, L.J., Gross, M., Gibberd, F.B., Perkin, G.D., Park, D.M., Abbott, R., 1999. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. Epilepsia 40, 601–607.

Trenite, D.G., Rentmeester, T.W., Scholtes, F.B., Gilissen, K.G., Arends, L.R., Schlosser, A., 2001. Peri-marketing surveillance of lamotrigine in The Netherlands: doctors' and patients' viewpoints. Pharm. World Sci. 23, 1–5.

Walker, M.C., Li, L.M., Sander, J.W., 1996. Long-term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. BMJ 313, 1184–1185.

Wieringa, N.F., Peschar, J.L., Denig, P., de Graeff, P.A., Vos, R., 2003. Connecting pre-marketing clinical research and medical practice. Int. J. Techn. Ass. Health Care 19, 202–219.

Wong, I.C., Chadwick, D.W., Fenwick, P.B., Mawer, G.E., Sander, J.W., 1999. The long-term use of gabapentin, lamotrigine, and vigabatrin in patients with chronic epilepsy. Epilepsia 40, 1439–1445.

Wong, I.C., Mawer, G.E., Sander, J.W., Lhatoo, S.D., 2001. A pharmacoepidemiologic study of factors influencing the outcome of treatment with lamotrigine in chronic epilepsy. Epilepsia 42, 1354–1358.