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Patterns of lamotrigine use in daily clinical practice during the first 5 years after introduction in the Netherlands

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SUMMARY

Objective: Follow-up data on the long-term effectiveness (efficacy and tolerability) of lamotrigine are limited. A useful though crude measure for effectiveness in daily clinical practice is the treatment retention rate determined from drug dispensing data. This study describes the baseline characteristics, the usage patterns and the retention rate of this antiepileptic drug (AED) in a population-based cohort of lamotrigine users in the Netherlands during the first 5 years after its registration in 1995. Data from this cohort are compared with those from the initial randomized clinical trials (RCTs) in patients with refractory epilepsy.
Methods: This retrospective cohort study used dispensing data from community pharmacies. Baseline characteristics and usage patterns were evaluated for first time users of lamotrigine in this study. Usage patterns were characterized as continued, add-on or discontinued use during the patient observation time window. Cox regression analysis was used to explore possible relationships between baseline characteristics and specific usage patterns defined. The baseline characteristics and discontinuation rates in this cohort study were compared with RCT data reported in medical literature.

Results: A total of 3598 lamotrigine users were identified. The mean age of the population was 39 years and 54% were female. On average, patients used two other AEDs at the start of lamotrigine therapy and approximately 6% of the patients had no history of prior AED use. The discontinuation rate was 25% after 1 year, and approximately 32% at the end of the 5-year study. Addition of another drug or discontinuation was seen in more than half of the population 3 years after the start of therapy. Concurrent use of valproic acid was associated with a better retention rate. Absence of AED history, use of antidepressants, or use of migraine abortive drugs resulted in an increased likelihood of discontinuing lamotrigine. The population from RCTs differed from the study cohort with respect to age, concurrent use of AEDs and length of follow-up.
Conclusion: Data from RCTs cannot easily be extrapolated to daily clinical practice. In this large, observational study, lamotrigine therapy failed in a considerable number of patients, although the mean retention rate was better than previously reported by others. Population-based linkage of health care records can be used to further clarify the effectiveness of lamotrigine.

Keywords: daily practice, effectiveness, lamotrigine, pharmacoepidemiology, prescription patterns, retention time

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INTRODUCTION

Lamotrigine was introduced in the Netherlands in 1995, based on data from clinical trials regarding its

efficacy, tolerability and safety. In add-on trials involving patients with intractable epilepsy, lamotrigine reduced seizure frequency by more than 50% in approximately 30% of patients (1–3). However, clinical trials do not mirror daily practice, as in trials the effects of the drug are examined (a) for a limited period of time, (b) under well-controlled conditions and (c) in a homogeneous, though highly selected, group of patients (4, 5). This may affect the generalizability of findings from clinical trials with regard to efficacy, tolerability and safety to daily clinical practice and pleas for observational research within the setting of daily clinical practice.

A useful though crude measure of effectiveness in large observational studies is the retention time using drug-dispensing data. Effectiveness is an outcome measure, which encompasses both efficacy and tolerability (6). This study focused on the retention time on lamotrigine and on patterns of the drug's use in the Dutch community. By using dispensing data, we identified lamotrigine users during the first 5 years after its introduction. The objective of the present study is to describe baseline characteristics, and compare these characteristics with those from the initial clinical trials of lamotrigine in patients with refractory epilepsy.

METHODS

Data collection and source population

There is a high level of agreement between automated pharmacy data and self-reported drug use, especially for drugs used chronically (7, 8). Analysing computerized records of prescriptions actually filled, thus makes it possible to collect information on drug use for a large number of patients (9, 10).

This retrospective cohort study used prescription data from community pharmacies in the Netherlands. A total of 1428 (90%) pharmacies out of 1586 Dutch pharmacies in January 2001 received a request for anonymous data of all patients to whom lamotrigine was dispensed during the observation period. The selected pharmacies used one of the three major pharmacy computer systems in the Netherlands. These pharmacies serve an open population of approximately 13 million persons.

For each patient who filled at least one lamotrigine prescription during January 1996 to December 2000, a complete prescription drug dispensing history, covering the period 1996–2000, was collected by means of computerized data extraction methods. Each dispensed drug led to one electronic record containing patient information (unique though anonymous identification number, gender, date of birth and residential postal code) and information about the prescribed medicine (drug identification number, dispensing date, number of units dispensed and the prescribed daily dose). The software program Microsoft Access was used for database management, internal quality control and validation procedures. The resulting research database consisted of 6544 patients and 660 097 prescriptions.

Study population

For the present study only those patients were included who received lamotrigine for the first time. The date of first prescription of lamotrigine was defined as the index date. To ascertain first time use, patients were required to have at least 365 days of prescription history for any medicine before the index date (180 days for children under 2 years of age). Patients who were not regular visitors of the pharmacy, defined by a time gap of more than 180 days between two successive prescriptions for whatever medication, were excluded from the analysis. Patients with a follow-up time (i.e. observation period between index date and the last ever registered prescription) of <180 days were also excluded. Application of these exclusion criteria resulted in a study population of 3598 patients with 468 859 prescription records as shown in Table 1.

Data analysis

Baseline characteristics Baseline characteristics of the study population that were examined included gender, age at index date and certain concomitantly used medication. For co-medication we focused on the prescription of other antiepileptic drugs (AEDs), psychotropic drugs (antidepressants, antipsychotics, benzodiazepines, lithium salts) and migraine abortive drugs.

Lamotrigine patterns of use and retention rate For each prescription, the theoretical duration of use was

Table 1. Application of inclusion criteria to the initial patient population

Inclusion criteria	Number of patients excluded	Remaining study population
Initial population	–	6544
A minimum of 1-year drug history before index date[a]	1786	4758
<180 days between two successive prescriptions	728	4030
A minimum of 180 days of follow up after index date	432	3598
Final study population	–	3598 (55%)

[a]For children under 2 years of age an period of 180 days of drug history was required.

calculated using information on dispensing date, amount supplied and dosage regimen. The observation window for each patient was defined as the time between the date of the first prescription and the theoretical end date of the last prescription registered. Lamotrigine retention time was calculated as the sum of the theoretical duration of consecutive lamotrigine prescriptions. Patterns of use (continuation, add-on and discontinuation) were defined for cohort members, based on observation window and lamotrigine retention time (as shown in Fig. 1). Continuation of lamotrigine therapy was defined for patients with less than 180 days between the theoretical end date of lamotrigine and the end of the observation window. Add-on was defined if another AED was added to lamotrigine, without discontinuation of lamotrigine therapy. Discontinuation of lamotrigine therapy was defined for patients for whom more than 180 days elapsed between the theoretical end date of the last lamotrigine prescription refill and the end of the observation window. The baseline characteristics were explored in order to identify a possible association with the specific usage pattern defined using Cox proportional hazard modelling. The strength of these associations was expressed by hazard ratios with 95% CI. Hazard ratios can be interpreted as relative risks (RR) in this analysis. In a subsequent analysis, we stratified patients into those who filled just one prescription and those who filled more than one lamotrigine prescription.

Comparison with reported clinical trials We compared the data from our study with those from randomized clinical trials (RCTs) published in the medical literature, that examined the efficacy of lamotrigine in patients with refractory epilepsy. Data from unpublished RCTs or from trials that enrolled <25 patients in the lamotrigine treatment group were summarised from a meta-analysis performed by Marson *et al.* (3). Baseline characteristics and discontinuation rates were compared between trial population and population-based cohort.

RESULTS

Baseline characteristics

A total of 1056 pharmacies (74% response) responded to our request to retrieve prescription data of all patients to whom lamotrigine was dispensed. The responding pharmacies covered both

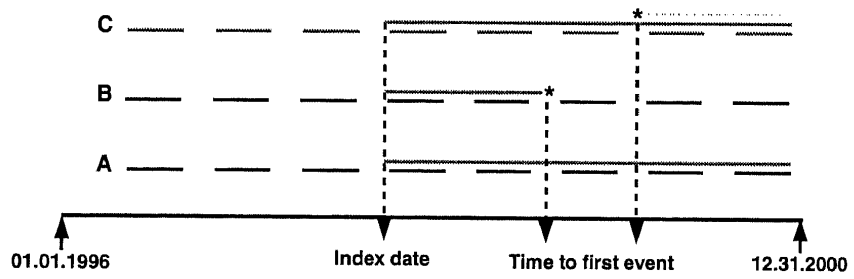

Fig. 1. Patterns of lamotrigine use. Information from all prescriptions (observation window, dashed line) and lamotrigine prescriptions (concrete line) was used to measure lamotrigine retention and to define patterns of use. A: continuation of lamotrigine, B: discontinuation of lamotrigine (more than 180 days between end date of lamotrigine and end of observation window) and C: add-on of another AED (dotted line) after the start of lamotrigine. Time to first event (either discontinuation, add-on or end of analysis) was used in statistical analyses.

large and small pharmacies and both low and highly urbanised areas. In all, 3598 new users of lamotrigine were identified during the observation period. These patients could be followed for a mean observation window of 4·6 years per patient. The corresponding baseline characteristics are shown in Table 2. The mean age of the population was 39 years, and 54% was female. There were 218 (6·1%) patients not using other AEDs on the index date. A significant trend towards an increased incidence of patients without an AED-history was observed from 1996 to 2000. On average, patients used two other AEDs on the index date (range 0–8); carbamazepine and valproic acid were by far the most frequently concomitantly used other AEDs.

Benzodiazepines (excluding clobazam, clonazepam and diazepam) were the most prevalent concomitantly used psychotropic drugs in the year prior to the index date (26%), followed by antidepressants (10%), migraine abortive therapy (3%) and lithium (1·5%).

Table 2. Baseline characteristics of study population (n = 3598)

Characteristics	Number of patients (%)
Demographics	
Age, years [mean (SD)]	[38·5 (19·9)]
0–17	642 (17·9)
18–34	873 (24·2)
35–49	1000 (27·8)
50–64	690 (19·2)
≥65	393 (10·9)
Female gender	1954 (54·3)
Index year	
1997	605 (16·8)
1998	1035 (28·8)
1999	1168 (32·5)
2000	790 (21·9)
Number of previous AED trials (prior and concurrent)	
None	218 (6·1)
1	856 (23·8)
2	1263 (35·1)
≥3	1261 (34·0)
Concomitant use of other AEDs	
Carbamazepine	1510 (42·0)
Valproate	1424 (39·6)
Phenytoin	566 (15·7)
Vigabatrin	534 (14·8)
Concomitant use of other medication	
Antidepressants	352 (9·8)
Antipsychotics	243 (6·8)
Benzodiazepines[a]	925 (25·7)
Lithium salts	53 (1·5)
Migraine abortive drugs	118 (3·3)
Observation window, in years [mean (SD)]	[4·6 (0·8)]

[a]Others than clobazam, clonazepam or diazepam.
AED, antiepileptic drug.

Retention rates and patterns of use

The mean time from the initiation of lamotrigine therapy to a change in lamotrigine therapy (discontinuation or add-on) or completion of the observation period was 1·3 years (range 17 days–4·2 years). One year following the initiation of lamotrigine therapy approximately 25% of the study population had discontinued therapy, the discontinuation rate at 3 years was 32% (Fig. 2). Addition of another AED increased linearly by approximately 10%/year for the first 3 years after initiation of lamotrigine. Clobazam, topiramate and gabapentin were most frequently used as add-on AED.

In total, there was a change in therapy (either discontinuation or add-on) in approximately 52% of the study population after 3 years of follow-up.

Usage patterns of lamotrigine treatment stratified according to various baseline characteristics are shown in Table 3. Males were as likely to continue treatment as females. Patients aged 65 years

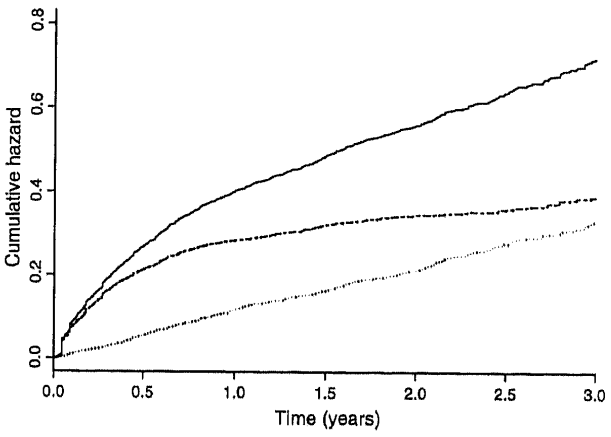

Fig. 2. Cumulative hazard rates: patterns of discontinuation or add-on. Cumulative hazard rates for occurrence of add-on pattern of use (lower, dotted line); discontinuation pattern of use (middle, dashed line) and both patterns of use combined (upper, solid line).

Table 3. Determinants of lamotrigine discontinuation or failure

Covariant	Discontinuation (n = 951) RR [95% CI][a]	Add-on (n = 534) RR [95% CI][a]	Overall (n = 1485) RR [95% CI][a]
Age			
0–17 years	0·92 [0·72–1·21]	1·26 [0·95–1·68]	1·03 [0·86–1·25]
18–34 years	1·00 [reference]	1·00 [reference]	1·00 [reference]
35–49 years	0·98 [0·81–1·17]	0·81 [0·64–1·02]	0·91 [0·79–1·05]
50–64 years	1·20 [0·99–1·45]	0·77 [0·60–1·08]	1·01 [0·86–1·18]
≥65 years	1·35 [1·08–1·68]	0·79 [0·56–1·13]	1·13 [0·94–1·36]
Gender			
Male	1·00 [reference]	1·00 [reference]	1·00 [reference]
Female	1·09 [0·96–1·24]	0·89 [0·75–1·05]	1·01 [0·91–1·12]
Index year			
1997	1·00 [reference]	1·00 [reference]	1·00 [reference]
1998	1·30 [0·98–1·59]	1·49 [0·36–6·10]	1·21 [0·89–1·36]
1999	1·27 [0·96–1·56]	1·21 [0·59–2·45]	1·19 [0·91–1·39]
2000	0·93 [0·74–1·17]	1·18 [0·77–1·81]	1·11 [0·92–1·33]
Previous number of AED trials			
None	1·00 [reference]	1·00 [reference]	1·00 [reference]
≥1	0·61 [0·48–0·78]	0·75 [0·61–0·94]	0·71 [0·58–0·89]
Concomitant AEDs[b]			
Carbamazepine	0·85 [0·71–1·10]	1·07 [0·75–1·51]	1·06 [0·81–1·38]
Valproate	1·17 [0·77–1·78]	0·51 [0·29–0·90]	0·73 [0·63–0·84]
Phenytoin	0·77 [0·63–1·04]	1·08 [0·85–1·37]	1·02 [0·83–1·26]
Vigabatrin	0·81 [0·61–1·08]	1·15 [0·82–1·61]	0·95 [0·76–1·18]
Prior use of comedication[b]			
Antidepressants	1·85 [1·54–2·23]	1·23 [0·87–2·31]	1·60 [1·35–1·88]
Antipsychotics	1·12 [0·89–1·43]	0·79 [0·54–2·31]	1·03 [0·85–1·26]
Benzodiazepines	1·17 [1·01–1·34]	1·24 [0·81–1·42]	1·24 [0·94–1·40]
Lithiumsalts	0·77 [0·48–1·23]	0·73 [0·27–2·04]	0·82 [0·54–1·24]
Migraine abortive drugs	1·39 [1·03–1·88]	1·43 [0·89–2·31]	1·39 [1·08–1·79]

[a]Relative risk [RR] vs. continued use.
[b]Presence vs. absence (reference).
AED, antiepileptic drug.

or above discontinued treatment at an earlier phase (RR 1·35; 95% CI 1·08–1·68). Addition of another AED after the start of lamotrigine treatment was less likely for patients that used valproic acid concomitantly (RR 0·51; 95% CI 0·29–0·90).

Prior use of migraine abortive drugs lead to a more rapid onset in discontinuation of lamotrigine (RR 1·39; 95% CI 1·35–1·88). Patients on antidepressants prior to the start of lamotrigine were more likely to have a change in lamotrigine therapy (RR 1·60; 95% CI 1·35–1·88).

Overall, patients with a history of earlier AED treatment were more likely to continue lamotrigine treatment compared with patients who had no background of AED-treatment prior to using lamotrigine (RR 0·71; 95% CI 0·58–0·89). Stratification by the number of filled lamotrigine prescriptions (one vs. more than one prescription) showed that 7% of all patients (n = 257) discontinued lamotrigine therapy after filling just one prescription. Patients without a history of AEDs were more prone for rapid discontinuation, 47 patients (22%) discontinued therapy after filling one prescription, compared with 6% (n = 210) in the group with a history of AEDs.

Comparison with reported clinical trials

Study characteristics of patients in the add-on RCTs compared with those in the present study are

Table 4. Randomized clinical trials (RCTs) of add-on lamotrigine in patients with refractory epilepsy

Characteristics	Matsuo *et al.* (1)	Messenheimer *et al.* (2)	Marson *et al.* (3)[a]	Dutch cohort
Study design and demographics				
Design	RCT, parallel	RCT, crossover	Meta-analysis	Observational, cohort
Patient selection	chronic epilepsy	chronic epilepsy	chronic epilepsy	Population-based
Number of patients, *n* (LTG : placebo)	216 (143 : 73)	88 (46 : 42)	1000 (664 : 336)	3598 (3598 : 0)
Male : Female	67 : 149	41 : 47	486 : 514	1644 : 1954
Mean age (years) (range)	33 (18–63)	35 (18–64)	n.a. (15–67)	39 (0–99)
Duration of follow-up (weeks)	24	14	8–24	26–222
Concurrent AED therapy, *n* (%)				
None	0	0	0	218 (6)
1 AED	86 (40)	36 (41)	n.a.	856 (24)
2 AEDs	115 (53)	50 (57)	n.a.	1263 (35)
≥ 3 AEDs	15 (7)	2 (2)	n.a.	1261 (34)
CBZ	158 (73)	67 (76)	n.a	1510 (42)
PHT	76 (35)	40 (45)	n.a.	566 (16)
VPA	0[b]	0[b]	n.a.	1424 (40)
Overall discontinuation rate	13%	4%	19%	34%

[a]Meta-analysis including trials by Matsuo *et al.*, Messenheimer *et al.*, unpublished trials and trials with <25 patients in the lamotrigine treatment group.

[b]Concurrent use of valproic acid was an exclusion criterion in clinical trials.

LTG, lamotrigine; AED, antiepileptic drug; CBZ, carbamazepine; PHT, phenytoin; VPA, valproate; N.a., not analysed.

shown in Table 4. One thousand patients were included in the RCTs and the length of follow-up ranged from 8 weeks to 6 months.

Excluded from the RCTs were patients under 15 and above 67 years of age. These age categories comprised more than one-fourth of the present cohort of patients. Lamotrigine was used only as an add-on drug in these trials, whereas in the present study 6% of patients had no history of AEDs. Concurrent use of valproic acid was not allowed in the clinical trials, in the present study 40% of patients had concurrent use of valproate (VPA). The reported estimates of the discontinuation rates at the end of the trial periods ranged from 4 to 19%. In the present study the discontinuation rate was 10% at 8 weeks, 20% at 6 months and 25% at 12 months after initiation of lamotrigine.

DISCUSSION

The baseline characteristics of this Dutch population-based cohort differed from those reported from clinical trials, with respect to age, concurrent use of specific AEDs, and length of follow-up. This may be explained by the use of lamotrigine in a broader population of epilepsy patients, including those with less severe epilepsy, and newly diagnosed epileptics starting with lamotrigine because of intolerable side effects from their previous treatment rather than because of inadequate seizure control. As a consequence, data from efficacy studies may not reflect the outcome of lamotrigine therapy in daily practice.

Retention time as an indicator for effectiveness in general practice, reflects a drug's (1) efficacy, (2) tolerability/side effects and (3) ease of use (compliance) (9–11). Addition of another AED may reflect insufficient seizure control with lamotrigine. The rate of use of an additional AED may therefore reflect lack of efficacy. Tolerability or side effects are possibly reflected by the discontinuation rate (without previous addition of another AED). Attrition rate appeared to be highest in the first year (25%) and slowed in subsequent years. Approximately 7% of patients on lamotrigine filled just one prescription. The relatively high discontinuation rate in the first year of therapy possibly reflects the rather difficult administration of

lamotrigine at the start of therapy. The drug should be carefully titrated in order to overcome adverse events, particularly rash (12). Approximately 6% of the cohort population had not used AEDs previously. The discontinuation rate was significantly higher in this patient group. In this group of patients 22% stopped with lamotrigine therapy after filling just one prescription. Reported predictors of non-compliance are monotherapy, and uncomplicated epilepsy (13). Another possible explanation is the availability of an increasing number of AEDs for patients with newly diagnosed epilepsy, and physicians are possibly likely to change treatment sooner.

There are few published population-based follow-up studies of lamotrigine. Wong *et al.* reported on the long-term retention of add-on lamotrigine in patients with refractory epilepsy ($n = 1050$) and treated in tertiary referral epilepsy clinics in the United Kingdom (UK) (14). They estimated a retention rate for lamotrigine of 48% at 3 years after the start of therapy, compared with approximately 68% in our study. In the UK, new AEDs (gabapentin, lamotrigine, vigabatrin and topiramate) were available in the UK from the early 1990s onwards. In the Netherlands, registration of lamotrigine was in 1995, between that of vigabatrin in 1990, and gabapentin and topiramate in 1999. The retention rate on lamotrigine was higher in our study possibly because other alternatives were not available for patients with ongoing refractory epilepsy. Furthermore, the UK follow up studies focussed on a group of patients with difficult-to-manage epilepsy. The reason for lamotrigine initiation in this patient group is seizure control. It is possible that our study included a broader population with respect to disease severity and reasons for starting with lamotrigine. The retention rate of lamotrigine in patients switching from conventional AEDs because of intolerable side effects could be better than in those who start lamotrigine for better seizure control.

Another explanation for the observed differences may be an overestimation of the retention rate in our study. The date of discontinuation was defined as the date of the last recorded lamotrigine prescription plus the duration of that prescription. Moreover, the actual time of discontinuation of lamotrigine could not be measured, but was assumed if a minimum follow-up period of 180 days exceeded the last lamotrigine prescription. This approach may have resulted in an underestimation of the proportion of patients stopping lamotrigine therapy.

Limitations of this study, include absence of clinical information in the pharmacy-based data. No individual patient information was available on factors such as duration of disease, seizure classification and seizure frequency. These factors may also be associated with continuity of therapy, e.g. generalized epilepsy is associated with higher retention rates of lamotrigine compared with partial epilepsy (14). Also, it remains uncertain whether people continuing lamotrigine in the database, experience improved seizure control, long-term. Another limitation of using prescription data is that the use of lamotrigine is not exclusive to epilepsy treatment, but extends to the treatment of bipolar disorder, migraine, or neuralgic pain (15–17). Shackleton *et al.* estimated the prevalence and incidence of epilepsy using the PHARMO database, which contain the medication histories of approximately 300 000 individuals (18). They validated the use of AEDs by checking medical diagnoses of a proportion of identified AED users from general practitioners and hospital records. It appeared that certain AEDs are frequently used for other indications, as only half of the patients using carbamazepine monotherapy and 5% of patients using clonazepam monotherapy had epilepsy. However, epilepsy was present in 93% of patients using more than 1 AED. As 95% of the new lamotrigine users in our population were on polytherapy, it is very likely that the large majority of these individuals had epilepsy. Data from a survey of 1819 patients using lamotrigine, after failure of at least one AED, showed that off-label use was <6% (P.D. Knoester; not published).

The use of antidepressant drugs in patients with epilepsy deserves further attention because of the widespread conviction that these drugs facilitate seizures (19, 20). Moreover, lifetime prevalence of depression in epilepsy is higher than in the non-epilepsy population (21). Lamotrigine is an antiglutamatergic agent with activating effects (i.e. activation, weight loss) and has been postulated as an effective drug in treating epileptic patients with depressive co-morbidity (22). In this study, however, a higher failure rate of lamotrigine was observed, indicating that the position of lamotrigine

in the treatment of this subgroup of patients needs further attention. It is also possible that lamotrigine was used as an antidepressant or as a drug against neuropathic pain in this group of patients.

Despite its limitations, this study defines the usage patterns of lamotrigine in a large cohort of patients. Whereas treatment retention rate was better than reported previously, there was still a substantial proportion of patients who discontinued treatment. The observed use-patterns are likely to be reflected in populations other than the Dutch. Population-based linkage of pharmacy data with other clinical data would help in better defining the effectiveness of lamotrigine.

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