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Safety Review of Adult Clinical Trial Experience with Lamotrigine

John Messenheimer,[1] *E. Lynette Mullens,*[2] *Luigi Giorgi*[2] and *Frances Young*[1]

1 Glaxo Wellcome Research Institute, Research Triangle Park, North Carolina, USA
2 Glaxo Wellcome Research and Development, Greenford, Middlesex, UK

Contents

Summary

To date approximately 4000 adults >12 years of age have been treated with lamotrigine in Glaxo Wellcome sponsored clinical trials. Review of the data from these trials shows lamotrigine to be effective and well tolerated in both add-on and monotherapy treatment. Safety of lamotrigine was comparable to that of other anticonvulsants in add-on controlled clinical trials. In addition, fewer than half the number of patients in monotherapy studies who were taking lamotrigine discontinued treatment because of adverse events compared to those taking carbamazepine and phenytoin. Most of the reported adverse events seen in lamotrigine treated patients in all studies were judged by the investigator to be mild or moderate in severity; few of the adverse events resulted in the withdrawal of patients from studies. Analysis of vital signs and clinical laboratory data have revealed no undesirable effect of lamotrigine on major systems of the body.

The most concerning adverse event has been rash. In clinical trials, this has most often been limited to a simple morbilliform rash which is not associated

with evidence of systemic involvement. The incidence of Stevens-Johnson syndrome (SJS) in clinical trials is approximately 1 in 1000. Rash associated with lamotrigine has typically occurred within the first 8 weeks of treatment. Data from clinical trials clearly point to exceeding currently recommended dosage guidelines of lamotrigine and co-administration of valproic acid (valproate sodium) as risk factors for rash. Early in 1997, Glaxo Wellcome strengthened existing warnings in the product label regarding the risk of rash and reinforced the importance of adherence to administration guidelines in an effort to reduce the incidence of rash.

Lamotrigine is a novel anticonvulsant which is thought to act in part via a use-dependent blockade of voltage-sensitive sodium channels to stabilise the neuronal membrane.[1,2] This results in the inhibition of the excessive release of excitatory amino acids, such as glutamate, during epileptic activity. Lamotrigine acts selectively on neurones displaying sustained repetitive discharges associated with epileptiform activity and has no effect on normal neuronal activity.[1] It is likely that additional mechanisms of action contribute to the broad spectrum of efficacy of lamotrigine which extends to typical absence seizures, myoclonic seizures and the generalised seizures of Lennox-Gastaut syndrome.[3-6]

First approved in Ireland in 1990, lamotrigine has been approved in over 70 countries throughout the world for use as add-on therapy in adults and children >12 years of age for refractory partial and generalised seizures. 15 countries have approved lamotrigine in monotherapy in adult patients and 6 have approved paediatric monotherapy use. Add-on therapy in paediatric patients has been approved in 28 countries and 10 countries have approved use in the treatment of Lennox-Gastaut syndrome. Up to June 30, 1997, it was estimated that approximately 950 000 patients, ranging in age from <2 years to over 65 years, would have been treated with lamotrigine. This figure includes 4657 patients and healthy volunteers from completed clinical trials.

Clinical trials have demonstrated the efficacy of lamotrigine against a wide range of seizure types in both adults and paediatrics in partial and generalised seizures, including the major seizures of Lennox-Gastaut syndrome.[4-18] In adult monotherapy trials, lamotrigine has been shown to be at least as effective as carbamazepine or phenytoin monotherapy and to be significantly better tolerated.[19-21]

This report presents a review of the safety data from all completed adult clinical trials enrolling patients with epilepsy that were centrally coordinated and managed by Glaxo Wellcome. Safety in paediatric patients enrolled in clinical trials will be the focus of a subsequent publication.

1. Clinical Trials

To date, a total of 107 clinical trials involving 3985 adults >12 years of age, conducted throughout the world, have been completed in which lamotrigine has been administered either as monotherapy or has been added to an existing anticonvulsant regimen. Table I shows each category of clinical trial and the number of patients enrolled. Studies in which anticonvulsant drugs have been withdrawn from polypharmacy regimens to result in monotherapy have been categorised as add-on. This manuscript summarises the safety data from the 68 completed safety and efficacy add-on and monotherapy studies, that involved 3514 patients with epilepsy >12 years of age. Clinical pharmacology studies are not included as the exposure to the drug was felt to be insufficient to render patients at reasonable risk of experiencing a drug-related adverse event.

In addition to adverse event reporting, the safety assessments in many of the clinical trials have included the routine measurement of vital signs, clinical chemistry and haematological parameters as well as urinalysis and electrocardiograms (ECG). These assessments have consistently failed to re-

Table I. Lamotrigine exposures in clinical trials

Study category	No. of clinical trials	No. of patients
All clinical trials	108	4657
All adults (>12 years)	107	3985
Adult clinical pharmacology	38	447[a]
Adult epilepsy monotherapy	5	443
Adult epilepsy add-on	63	3071[a]
primary controlled	13	962
primary uncontrolled	36	1948
continuation studies	14	161
Migraine	1	39

a 15 patients who were originally enrolled in clinical pharmacology studies were later enrolled in add-on studies and have been counted in both places.

veal any clinically significant changes in these parameters. These findings have been previously reviewed[22,23] and are not reviewed further in this paper.

Adverse event data were collected in all trials by asking patients at each visit if they had experienced any adverse events since the previous study visit, regardless of whether they believed the cause to be the study drug or not. All patient responses were recorded on the case report forms along with information on the intensity and seriousness of the adverse event and investigator's opinion of attribution. Intensity was derived from the investigator's medical judgement as to whether the event was mild, moderate, or severe. Serious adverse events were defined as anything that: (i) happened during the course of the study that was fatal, life threatening, permanently or significantly disabling; (ii) required or prolonged hospitalisation or; (iii) was a congenital anomaly in the offspring of a patient who received drug, a malignancy, an overdose of the trial medication, or an event which jeopardised the patient or required intervention to prevent one of the previously listed outcomes.

Adverse events reported in clinical trials may not be directly attributable to the drug being studied as such reports include any undesirable medical event regardless of attribution to study drug. Increased reporting of adverse events is typical of add-on trials in which it is necessary to minimise changes in the dosages of all background anticonvulsants and the study medication. Therefore, the incidence of adverse events reported from clinical trials do not always reflect rates in routine clinical use.

Data are summarised by lamotrigine treatment mode (monotherapy or add-on therapy) and by the type of averse event: treatment emergent, those leading to discontinuation of the study drug, or those defined as serious. The occurrence of rash is discussed in greater detail in section 7.

2. Demography and Baseline Characteristics

Overall, patients involved in the clinical trials were evenly split between male and female (53% and 47%, respectively) with the mean ages being 28.6 and 29.3 years, respectively (standard deviation 14.4 and 14.3 years). Of the 3071 adult patients with epilepsy exposed to lamotrigine in add-on trials, approximately 30% were taking more than 1 concomitant anticonvulsant and had been diagnosed with epilepsy for a median duration of 20 years. Monotherapy patients had experienced epilepsy for a median duration of 1 year.

Clinical trial patients who received lamotrigine had a variety of seizure types. Overall, of the refractory patients treated in the adult add-on trials, 12.7% had primary generalised tonic clonic seizures, 78.9% had complex partial seizures, 39.1% had secondarily generalised seizures and 28.9% had simple partial seizures. Aetiology of the seizure disorder in the newly diagnosed monotherapy group of adult patients who received lamotrigine was largely cryptogenic (82%) with the remaining 18% being symptomatic. The treatment refractory epilepsy in patients who received add-on therapy with lamotrigine was split more evenly between idiopathic (58.7%) and symptomatic (40.4%). The epilepsy in the remaining patients was either cryptogenic (0.3%) or unspecified (0.6%). Of the newly diagnosed adult patients treated in monotherapy trials, 47.6% had primary generalised tonic-clonic seizures, 29.3% had complex partial seizures, 29.8% had secondarily generalised seizures and 22.8% had simple partial seizures.

Table II. Dosage schedules for lamotrigine

Concomitant medication	Dosage for weeks 1 & 2	Dosage for weeks 3 & 4	Usual maintenance dosage
Lamotrigine dosages for adults and children over 12 years of age			
Valproic acid (valproate sodium) [or any anticonvulsant with unknown pharmacokinetic interaction with lamotrigine), with or without other anticonvulsants]	12.5 mg/day (given as 25mg on alternate days)	25mg (once a day)	100-200 mg/day (once a day or given in 2 divided doses) To achieve maintenance, the daily dosage may be increased by 25-50mg every 1 to 2 weeks
Enzyme-inducing anticonvulsants with or without other anticonvulsants (except valproic acid)	50 mg/day (once a day)	100 mg/day (given in 2 divided doses)	200-400 mg/day (given in 2 divided doses) To achieve maintenance, the daily dosage may be increased by a maximum of 100mg every 1-2 weeks
Lamotrigine dosages for children aged 2-12 years old			
Valproic acid (valproate sodium) [or any anticonvulsant with unknown pharmacokinetic interaction with lamotrigine), with or without other anticonvulsants]	0.2 mg/kg (if the calculated daily dose is 2.5 to 5mg, then 5mg may be taken on alternate days for the first 2 weeks. If the calculated daily dose is less than 2.5mg, then lamotrigine should not be administered)	0.5 mg/kg (once a day)	1-5 mg/kg (once a day or in 2 divided doses) To achieve maintenance, the daily doses may be increased by 0.5-1 mg/kg every 1-2 weeks to a maximum of 200 mg/day
Enzyme-inducing anticonvulsants with or without other anticonvulsants (except valproic acid)	2 mg/kg (given in 2 divided doses)	5 mg/kg (given in 2 divided doses)	5-15 mg/kg (given in 2 divided doses) To achieve maintenance, the daily doses may be increased by 2-3 mg/kg every 1-2 weeks to a maximum of 400 mg/day

3. Treatment Duration and Dosage

3.1 Exposure to Drug

The randomised, placebo-controlled, add-on trials provided up to 24 weeks of exposure to lamotrigine, the randomised monotherapy trials provided 48 weeks of lamotrigine exposure, the trials in which an anticonvulsant was withdrawn to achieve monotherapy with lamotrigine provided up to 48 weeks of drug exposure and the open-label, long term safety, add-on trials provided up to 336 weeks of exposure to lamotrigine.

338 patients received lamotrigine treatment as monotherapy and 1699 patients received treatment with lamotrigine as add-on therapy to other anticonvulsants for up to 48 weeks. An additional 81 monotherapy patients and 682 add-on patients received treatment with lamotrigine for up to 96 weeks. At the time of writing, data were available on patients who had been treated with lamotrigine as monotherapy for up to 192 weeks and as add-on therapy for up to 336 weeks. The total experience of lamotrigine in the monotherapy randomised trials, along with their continuation trials represents 314 patient-years of exposure, while the total experience with the drug in add-on therapy represents 3538 patient-years of exposure. The majority of the patients included in this analysis, who were treated with lamotrigine as monotherapy, received maintenance dosages of 100 to <300 mg/day. Most patients with refractory epilepsy who were treated with add-on lamotrigine received dosages between 100 and 500 mg/day. 29% of add-on patients were treated with dosages of 500 mg/day or more. It should be noted that most of these trials did not incorporate the manufacturer's currently recommended dosage escalation schedule as this was implemented after the completion of the trials. The currently recommended dosage schedules for lamotrigine are given in table II.

4. Safety of Lamotrigine as Add-On Therapy

4.1 Treatment-Emergent Adverse Events

Add-on lamotrigine therapy was very well tolerated in clinical trials involving 3071 adult exposures (>12 years of age) to lamotrigine worldwide. Of 9334 recorded adverse events in this group, 8771 (94%) were mild to moderate in intensity. In general, these adverse events were usually observed within the first 6 weeks of therapy and, in most patients, resolved without the need for dosage adjustment or discontinuation. With the exception of rash, almost all reported adverse events were CNS complaints typical of anticonvulsants that resolved promptly upon dosage adjustment or upon discontinuation of the drug. Of 9334 reported adverse events in these studies, 3456 (37%) were judged by the investigator to be reasonably attributable to study drug.

The treatment-emergent adverse-events most frequently reported in the 12 primary controlled add-on studies, (n = 593 placebo treated patients; n = 962 lamotrigine treated patients) and not seen at a similar frequency in placebo-treated patients (lamotrigine incidence at least 3% greater than placebo), included dizziness, diplopia, ataxia, blurred vision, nausea, somnolence, rash, headache, vomiting, abnormal coordination, rhinitis, tremor and insomnia. The incidence of these adverse events, most of which were transient and infrequent, should be compared with the very low incidence with which these adverse events led to discontinuation of lamotrigine during the primary studies (table III).

A recent meta-analysis[24] of randomised placebo controlled trials with lamotrigine revealed the following odds ratios (incidence with lamotrigine **:** incidence with placebo) and 95% confidence intervals for specific adverse events:

- ataxia 2.98 (1.86 to 4.77)
- diplopia 3.39 (2.05 to 5.61)
- dizziness 2.38 (1.63 to 3.48)
- nausea 1.70 (1.08 to 2.68).

The fact that these confidence intervals do not include zero implies statistical significance, however the overall odds ratio for discontinuation for any reason was 1.19 (95% confidence interval 0.79 to 1.79) leading the authors of the meta-analysis to conclude that there was not sufficient evidence to

Table III. Number and percentage of patients reporting adverse effects and withdrawing from treatment due to adverse events in primary studies

Adverse event	Placebo add-on [n = 593]		Lamotrigine add-on controlled studies [n = 962]		Leading to withdrawal in lamotrigine controlled studies [n = 962]		Lamotrigine add-on open studies (weeks 1-12) [n = 1948]	
	%	n	%	n	%	n	%	n
Dizziness	15	87	35	338	2	19	7	142
Headache	21	125	26	251	1	12	6	116
Diplopia	6	38	25	236	<1	6	6	112
Nausea	9	55	19	179	1	11	4	80
Ataxia	6	34	20	188	<1	7	5	96
Somnolence	7	44	13	121	0		5	100
Blurred vision	4	25	14	130	<1	7	2	34
All rash[a]	5	30	10	99	2	21	6	120
Vomiting	5	27	10	96	<1	6	3	55
Abnormal coordination	2	9	6	57	<1	2	<1	12
Rhinitis	8	45	11	107	0		0	
Tremor	1	8	5	46	<1	1	1	23
Insomnia	3	15	6	56	<1	3	1	26

a The term 'all rash' includes the terms angioedema, erythema, rash, rash macular/papular, rash petechia, rash purpura, rash pustular, rash vesicular, Stevens-Johnson syndrome and urticaria.

conclude that patients taking lamotrigine were more likely to discontinue the medication than patients taking placebo.[24] As illustrated in table III and as expected from differences in study design, the incidence of most adverse events was much lower in open studies, in which dosage adjustments were possible, than in controlled studies in which such adjustments were very restricted.

4.2 Adverse Events Leading to Discontinuation of Treatment

Adverse events leading to patient withdrawal from controlled primary studies occurred in 77 of 962 (8%) patients receiving add-on lamotrigine and in 17 of 593 (3%) patients receiving placebo. The most common adverse events associated with drug discontinuation in lamotrigine recipients were dizziness, rash, headache and nausea. Dizziness and rash each accounted for 2% of study withdrawals, while nausea and headache each accounted for 1%. All other reported adverse events each accounted for less than 1% of withdrawals (table III).

In the controlled add-on studies, a higher percentage of patients on lamotrigine with concomitant carbamazepine reported diplopia, nausea, dizziness, blurred vision and headache than did patients on lamotrigine in combination with any other anticonvulsant. Rash and tremor were reported by a higher percentage of patients receiving concomitant valproic acid (valproate sodium) and percentage wise asthenia was most frequently reported in the group receiving phenytoin concomitantly with lamotrigine. Withdrawal rates because of adverse events were low for all anticonvulsant combinations studied with the exception of the combination of lamotrigine and valproic acid, where rash led to a 6% rate of withdrawal (table IV).

5. Safety of Lamotrigine as Monotherapy

To date, 3 randomised, controlled monotherapy trials (and 2 monotherapy continuation trials), with a total of 443 adult epilepsy patients exposed to lamotrigine have been completed. These Glaxo Wellcome sponsored trials were conducted as multicentre studies throughout Europe and Australia. Data from these trials provide important comparator data regarding efficacy and adverse events. In these randomised parallel comparative trials, lamotrigine monotherapy was initiated in newly diagnosed and untreated patients with partial seizures (with or without secondary generalisation) or primary tonic-clonic seizures using standard first-line monotherapy agents, carbamaz-

Table IV. Influence of concomitant anticonvulsant therapy on reporting of adverse effects (AEs) and withdrawing from treatment (WD) due to adverse effects

Adverse event	Lamotrigine + valproic acid (valproate sodium) [n = 546]		Lamotrigine + carbamazepine (without valproic acid) [n = 1549]		Lamotrigine + phenytoin (without valproic acid) [n = 608]	
	AEs reported (%)	WD (%)	AEs reported (%)	WD (%)	AEs reported (%)	WD (%)
Dizziness	12	<1	26	2	14	1
Headache	10	1	18	1	14	1
Diplopia	12	<1	20	<1	9	<1
Ataxia	10	1	14	<1	13	<1
Somnolence	10	<1	10	<1	11	<1
Nausea	8	1	12	1	8	<1
Asthenia	8	<1	8	<1	11	<1
All rash[a]	12	6	8	2	4	1
Vomiting	8	<1	7	<1	3	<1
Blurred vision	3	<1	9	<1	4	<1
Tremor	5	<1	3	<1	3	0

a The term 'all rash' includes the terms angioedema, erythema, rash, rash macular/papular, rash petechia, rash purpura, rash pustular, rash vesicular, Stevens-Johnson syndrome and urticaria.

Table V. Randomised lamotrigine (LTG) monotherapy trials in newly diagnosed patients with epilepsy

Reference	Design	Comparator	Number of patients taking LTG	Number of patients taking comparator	Treatment duration (wks)
Brodie et al.[19]	Double-blind parallel	CBZ	131	129	48
Steiner et al.[21]	Double-blind parallel	PHT	86	95	48
Reunanen et al.[20]	Open parallel	CBZ	226	117	30

Abbreviations: CBZ = carbamazepine; PHT = phenytoin.

epine[19,20] and phenytoin,[21] respectively, as active comparator drugs (table V). Two of these trials were double-blind and of similar design, each using one of the comparators.[19,21] The third trial was an open randomised comparison of lamotrigine with carbamazepine.[20] The latter trial also permitted entry of patients with untreated recurrent epilepsy. Patient populations in each of the 3 studies had similar demographics and medical histories which allowed pooling of the safety data in order to compare relatively large numbers of patients receiving lamotrigine, carbamazepine or phenytoin monotherapy. The double-blind studies used 4-week dosage titrations of the study drug subsequently permitting investigators blinded to study drug to make dosage adjustments on the basis of coded serum concentration information.

Maximum duration of treatment in each of these trials was 48 weeks; however, patients on lamotrigine were allowed to receive an additional 144 weeks of open-label treatment by enrolling in 1 of 2 open continuation trials designed to assess long term tolerability of the drug. Of the 443 patients treated with lamotrigine, 119 patients who completed the double-blind studies entered open continuation studies with 24% of them receiving lamotrigine monotherapy for between ≥48 to <96 weeks and 5% receiving lamotrigine monotherapy for between ≥96 to <144 weeks.

These studies showed that lamotrigine was well tolerated as monotherapy. This was particularly true in regard to adverse experiences related to the CNS. In the 3 primary studies combined, somnolence, asthenia, dizziness and ataxia all occurred less frequently in patients taking lamotrigine than in patients taking either carbamazepine or phenytoin. Rash was slightly more common in the patients randomised to receive carbamazepine and headache and insomnia were reported to be slightly more frequently in patients taking lamotrigine. The majority of rashes associated with any anticonvulsant were mild and resolved quickly upon discontinuation of the study drug. All adverse experiences reported by patients with ≥5% occurrence are listed in table VI. Overall, the withdrawal rate for patients treated with lamotrigine was 9.5%, compared to 19.1% for carbamazepine treated patients and 18.9% for those treated with phenytoin (table VI).

Each of the most frequently reported adverse events listed in table VII led to withdrawal of a greater percentage of patients taking carbamazepine or phenytoin than taking lamotrigine with the exception of insomnia which caused a very slightly higher rate of withdrawal in the lamotrigine group than in either of the others. Only rash resulted in the withdrawal of more than 5% of the patients from any single treatment arm of the trials. 8.9% of patients taking carbamazepine withdrew from the study because of rash, while 6.1% of patients

Table VI. Overall withdrawal rates due to adverse events

Anticonvulsant therapy	Patients withdrawing due to adverse events (%)
LTG monotherapy	9.5
CBZ monotherapy	19.1
PHT monotherapy	18.9
Placebo add-on	6.9
LTG + VPA	12.2
LTG + non EI-AED without VPA	12.2
LTG + any EI-AED without VPA	10.2
LTG + any add-on	10.8

Abbreviations: CBZ = carbamazepine; EI-AED = enzyme-inducing anticonvulsant; LTG = lamotrigine; PHT = phenytoin; VPA = valproic acid (valproate sodium).

Table VII. Adverse events (AEs) reported and leading to withdrawal (WD) from treatment in monotherapy patients

AE	Lamotrigine alone (n = 443)		Carbamazepine alone (n = 246)		Phenytoin alone (n = 95)	
	AEs reported (%)	WD (%)	AEs reported (%)	WD (%)	AEs reported (%)	WD (%)
Somnolence	8	0.2	20	2.4	28	4.2
Asthenia	16	1.1	24	3.7	29	3.2
Dizziness	8	0.5	14	1.6	12	0
Ataxia	<1	0	6	2.0	12	2.1
Insomnia	6	0.5	2	0.4	3	0
Headache	20	1.1	17	1.6	19	2.1
All rash[a]	12	6.1	14	8.9	9	5.3
Nausea	10	0.7	10	2	4	0
Tremor	2	0	<1	0	8	1.1
Lung disorder	1	0	2	0	6	0

a The term 'all rash' includes the terms angioedema, erythema, rash, rash macular/papular, rash petechia, rash purpura, rash pustular, rash vesicular, Stevens-Johnson syndrome and urticaria.

taking lamotrigine and 5.3% of patients taking phenytoin discontinued for this reason. The only patient who developed a rash associated with hospitalisation was taking carbamazepine.

In the lamotrigine treated patients, most of the adverse events were judged to be mild (58%), or moderate (35%) and cause was felt in many cases not to be reasonably attributable to drug (40%) or unknown (28%). This compared favourably to the comparator groups where 55% of reported adverse events in both the carbamazepine and phenytoin groups were judged to be mild, 38% and 29%, respectively, were judged to be moderate and 50% and 55%, respectively, were felt by the investigators to be reasonably attributable to drug. Only 28% and 27% of adverse events in carbamazepine and phenytoin groups, respectively, were judged to be not reasonably attributable to study drug.

6. Serious Adverse Events – All Trials

Serious adverse events, as stated in section 1 were defined as anything that: (i) happened during the course of the study that was fatal, life threatening, permanently or significantly disabling; (ii) required or prolonged hospitalisation; or (iii) was a congenital anomaly in the offspring of a patient who received drug, a malignancy, an overdose of the trial medication, or an event which jeopardised the patient or required intervention to prevent one of the previously listed outcomes. Tables VIII and IX list the most frequently reported adverse events from all trials that met the definition of serious or life-threatening. Serious adverse events were entered on a serious adverse event case report form page and reported directly to the company as soon as the investigator had knowledge of them. All serious adverse events have been reported to regulatory authorities.

Rash was the single most frequently reported serious adverse event in both add-on and monotherapy trials and is discussed in greater detail in section 7. Rash was reported as a serious adverse event in 78 of 3071 patients receiving add-on therapy; in 42 patients attribution to study drug was determined by the investigator to be reasonable and

Table VIII. Adverse events rated as serious by investigators in add-on trials (n = 3071)

Adverse events	All events		Reasonable or unknown relationship to study drug	
	n	%	n	%
Rash	42	1	36	1
Increased seizures	31	1	20	<1
Injury/accident	28	<1	7	<1
Seizures	21	<1	10	<1
Dizziness	19	<1	16	<1
Ataxia	15	<1	10	<1
Diplopia	15	<1	12	<1
Depression	12	<1	6	<1

in 36 attribution was determined by the investigator as unknown. Rash was reported as serious in the monotherapy trials by 2 of the 443 patients. Neither case required hospitalisation.

Table VIII lists all serious adverse events reported in the clinical trials by more than 10 patients and table IX lists all serious adverse events reported by more than 2 monotherapy patients. In the placebo-controlled trials, only rash, seizures and dizziness had a higher incidence in lamotrigine treated patients (1% each), than in placebo treated patients (<1% each).

Table IX. Adverse events rated as serious by investigators in monotherapy trials (n = 443)

Adverse event	All events		Reasonable or unknown relationship	
	n	%	n	%
All rash	2	<1	2	<1
Headache	2	<1	1	<1
Haematemesis	2	<1	2	<1
Brain tumour	4	<1	0	0
Vomiting	2	<1	1	<1

7. Rash in Adult Clinical Trials

A range of cutaneous reactions have been reported with lamotrigine. Most often these have taken the form of a simple morbilliform rash which is not associated with evidence of systemic involvement. More severe cutaneous reactions, some reported as Stevens-Johnson syndrome (SJS), have occurred less frequently in clinical trials. Although toxic epidermal necrolysis and severe forms of hypersensitivity, some associated with multiorgan failure, have been reported with lamotrigine use in post marketing reports,[25] these severe reactions have not been observed in approximately 4000 adult patients in clinical trials which are the focus of this report.

The following rash incidence figures are derived from pooling data from all adult clinical trial patients. The starting dosages and dosage escalation schedules of lamotrigine varied considerably across studies. This is a reflection of the time period in which these studies were carried out, during which there was increasing recognition of the effect of lamotrigine dosage and of use of concomitant valproic acid, on the incidence of rash. In light of the variable dosage schedules used in these clinical trials, the rates of rash presented here are higher than the rates expected in association with the currently recommended dosage guidelines.

Of the adult (>12 years old) patients who have received lamotrigine in clinical trials as monotherapy or add-on therapy, 33 or 0.9% have experienced cutaneous reactions defined by investigators as severe. Rash leading to hospitalisation was reported by 11 patients, giving an incidence of 0.3%. Within this same group of patients there were 4 reports of SJS, giving an incidence of 0.1%. These rates are similar to previous reports based on lamotrigine clinical trial experience.

Data regarding comparable rates of serious cutaneous reactions with other anticonvulsants are very limited. Most reports have come from spontaneous reports or case-control studies which are not able to provide accurate estimates of risks. Recently a large record linkage study using prescription records and hospitalisation files for the Province of Saskatchewan, Canada has been reported.[26] This cohort study was able to provide more accurate estimates of the risk of cutaneous reactions associated with the older anticonvulsants than previous studies. The overall risk for serious cutaneous reactions leading to hospitalisation for new carbamazepine users was 0.62 per 1000 (95% confidence intervals 0.25 to 1.41). The overall risk for serious cutaneous reactions leading to hospitalisation for new phenytoin users was 0.9 per 1000 (95% confidence intervals 0.42 to 1.85). For both drugs, hypersensitivity reactions rather than SJS accounted for the majority of the reactions. Nevertheless it can be seen that the incidence of hospitalisation with a cutaneous reaction to phenytoin or carbamazepine in this study is similar to that observed in lamotrigine clinical trials in adults.

Rash with lamotrigine typically occurs within the first 8 weeks of treatment as illustrated in figure 1.

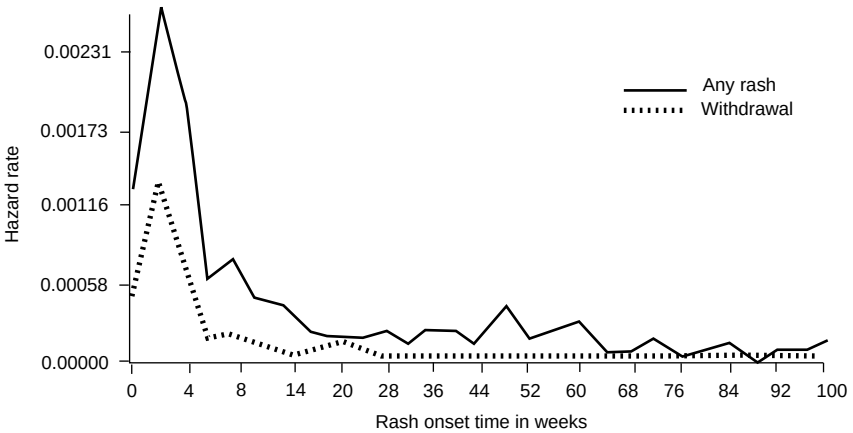

Fig. 1. Hazard plot for rash leading to withdrawal from adult add-on therapy and monotherapy clinical trial data.

8. Possible Risk Factors for Serious Rash

8.1 Effect of Concomitant Anticonvulsant Therapy on the Incidence of Rash in Adults

By defining adults by age as >16 years (n = 3387), an additional analysis of the lamotrigine safety database has been completed investigating the incidence of rash events on the basis of concomitant anticonvulsant administration and lamotrigine dosage. The rates of rash attributed to lamotrigine use with different background anticonvulsants are listed in table X.

8.2 All Rash

The highest incidence of the category 'all rash' occurred when lamotrigine was combined with valproic acid in the absence of other anticonvulsants (19.5%) while the lowest incidence occurred when lamotrigine was used with enzyme-inducing anticonvulsants (6.7%) [figure 2]. The rates for lamotrigine with enzyme-inducers and lamotrigine with valproic acid and enzyme-inducers were not statistically significantly different. The rate for lamotrigine with valproic acid (19.5%) is significantly ($p = 0.004$) different than the rate of lamotrigine with valproic acid and an enzyme inducer.

8.3 Rash Leading to Treatment Discontinuation

The highest incidence of rash leading to treatment discontinuation occurred in patients receiving treatment with lamotrigine and valproic acid alone (12.2%) while the lowest rate occurred in patients receiving lamotrigine and an enzyme-inducing anticonvulsant (2.0%) or lamotrigine and valproic acid and an enzyme-inducing anticonvulsant (3.3%) [figure 2]. The difference between the rate with lamotrigine and valproic acid alone and lamotrigine and valproic acid and an enzyme-inducing anticonvulsant was statistically significant ($p = 0.002$).

8.4 Rash Associated with Hospitalisation

Rash associated with hospitalisation in patients older than 16 years, occurred most often (2.0% of 205 patients) when lamotrigine was combined with valproic acid alone and least often when lamotrigine was used in monotherapy (0% of 420) [figure 2]. When lamotrigine was combined with enzyme-inducing anticonvulsants (n = 2240) the rate of rash leading to hospitalisation was 0.1%. When lamotrigine was combined with valproic acid and enzyme-inducing anticonvulsants (n = 303) the incidence of rash associated with hospitalisation was 0.7%.

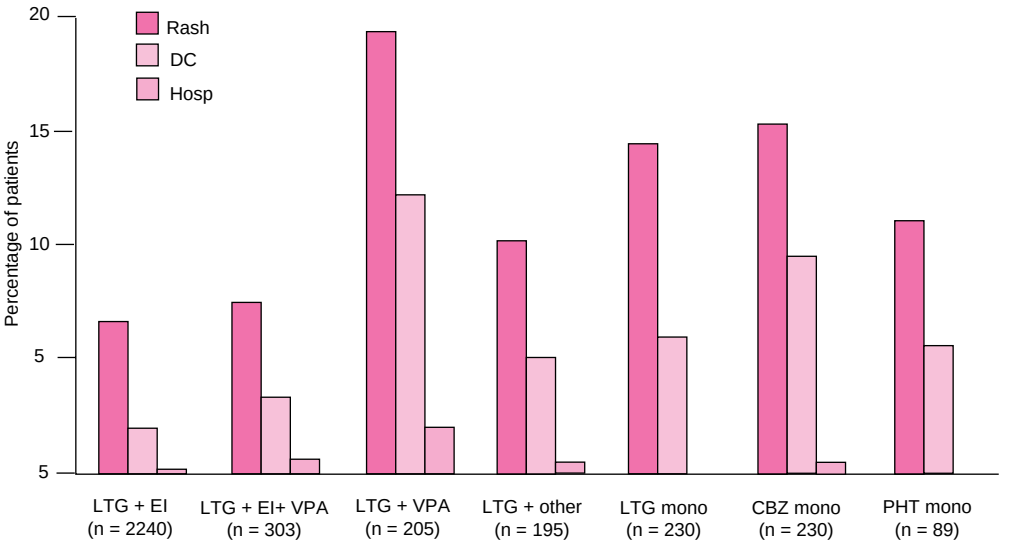

Fig. 2. Percentage of adult patients with rash, rash leading to treatment discontinuation (DC) or rash associated with hospitalisation (Hosp) for various anticonvulsant therapy groups. *Abbreviations:* CBZ = carbamazepine; EI = enzyme-inducing anticonvulsant; LTG = lamotrigine; mono = monotherapy; other = anticonvulsants which are neither inducers or inhibitors of the metabolism of lamotrigine; PHT = phenytoin; VPA = valproic acid (valproate sodium).

Although concomitant valproic acid appears to be a risk factor for rash with lamotrigine, it should be noted that these data are not sufficient to differentiate an effect of lamotrigine dosage independently from that of valproic acid alone.

9. Effect of First Week Dosage

Dosage regimen as a risk factor for rash was investigated by comparing the rates of rash stratified by mean lamotrigine dosages in the first week of treatment. Table XI lists the incidence with varying mean mg/day dosages over the first week of treatment. The currently recommended dosages are shaded.

The lowest incidence of the category 'all rash' occurred with lamotrigine as adjunctive therapy with enzyme-inducers given at the currently recommended starting dosage (4.9% of 225 patients).

Table X. Rash rates with different background anticonvulsants

Anticonvulsant group	Total no. of patients	All rash (%)	Rash leading to DC (%)	Rash associated with hosp (%)
LTG + EI	2240	6.7	2.0	0.1
LTG + EI + VPA	303	7.6	3.3	0.7
LTG + VPA only	205	19.5	12.2	2.0
LTG + other	195	10.3	5.1	0.5
LTG mono	420	14.5	6.0	0
CBZ mono	230	15.7	9.6	0.4
PHT mono	89	11.2	5.6	0

Abbreviations: CBZ = carbamazepine; DC = treatment discontinuation; EI = enzyme-inducing anticonvulsants; hosp = hospitalisation; LTG = lamotrigine; Other = anticonvulsants which are neither inducers or inhibitors of the metabolism of lamotrigine; PHT = phenytoin; VPA = valproic acid (valproate sodium).

The highest rate of the category 'all rash' occurred when lamotrigine was given with valproic acid alone (20.0% of 80 patients) when it was given at dosages higher than the current recommendations. When lamotrigine was given with valproic acid alone, the rate of 'all rash' when lamotrigine was given at the recommended starting dosage was also higher at 14% than in other categories (n = 50) [see table XI].

Rash leading to discontinuation of treatment occurred in fewer patients at the current recommended dosages for all anticonvulsant combinations, although some categories had small numbers of patients. In patients taking enzyme-inducers with valproic acid, 0.9% of 106 patients receiving dosages higher than the current recommendations discontinued treatment because of rash, which is lower than in other categories of patients receiving dosages higher than the current recommendations. This group also had a low rate of 'all rash' (6.6%), comparable to that seen with enzyme-inducers plus lamotrigine alone and no cases of rash leading to hospitalisation. This suggests a protective effect with respect to rash when enzyme-inducers are used with valproic acid and lamotrigine. The highest rate of rash leading to treatment discontinuation occurred with lamotrigine plus valproic acid alone (13.8% of 80 patients) at lamotrigine dosages higher than the current recommendations. Lamotrigine monotherapy was also associated with a high rate of rash leading to treatment discontinuation when dosages higher than the current recommendations were used (9.0 to 12%).

The lowest incidence of rash associated with hospitalisation (0%) occurred in several groups: most notably lamotrigine monotherapy and lamotrigine plus enzyme-inducer anticonvulsants, in both cases when lamotrigine was given at the currently recommended dosage. The highest rate (4.0% of 50 patients with lamotrigine and valproic acid alone) occurred despite use of the recommended dosage of lamotrigine.

These data suggest that lamotrigine added to valproic acid alone may be a risk factor for rash, but the significance of a contribution because of use of inappropriate lamotrigine dosages in these patients cannot be excluded. It appears that combining lamotrigine, valproic acid and enzyme-inducers significantly reduces the risk of rash associated with valproic acid combined alone with lamotrigine.

9.1 Logistic Regression

The effect of dosage on the incidence of rash has also been investigated by regression analysis of clinical trial data. The results of this analysis are presented in figure 3 in which the relationship between lamotrigine dosage is related to rash incidence.

The effect of exceeding the currently recommended starting dosages is clearly that of increasing the risk of rash and rash leading to treatment discontinuation. Because of the small numbers, the effect of dosage on rash leading to hospitalisation is less clear. The effect of lamotrigine starting dosage within the lamotrigine plus valproic acid group is not clear. For the lamotrigine plus valproic acid only group there are not more than 80 patients in any of the dosage groups which may obscure an effect of dosage.

The effects of lamotrigine starting dosage and dosage escalation are best evaluated in monotherapy studies in which the potential confounding effects of concomitant anticonvulsants are not present. It is difficult to separate the effects of a high starting dosage from the effects of dosage escalation since the onset of rash is typically delayed for 2 to 4 weeks. Figures 4 and 5 summarise the relationship between starting dosage and dosage escalation with the rate of lamotrigine discontinuation because of rash for all monotherapy studies involving treatment-naive patients with epilepsy.

In summary, the incidence of nonserious rash and possibly also that of serious rash, though this is less clear, can be significantly influenced by the dosage of lamotrigine and the presence or absence of valproic acid. These data from clinical trials indicate that use of dosages within the current recommendations in the absence of valproic acid is associated with rates of rash that are consistent with or

Table XI. Incidence of rash by mean dosage during week 1 of lamotrigine treatment

Mean dosage (mg/day) week 1	Total no. of patients	All rash (%)	Rash leading to DC (%)	Rash associated with hospitalisation (%)
Lamotrigine + EI without VPA				
0 to <16	5			
16 to <31	60			
31 to <62.5[a]	225	4.9	1.3	0
62.5 to 125	1237	10.6	2.3	0.1
>125	698	9.6	2.4	0.1
Lamotrigine + VPA + EI				
0 to <16[a]	5			
16 to <31	5			
31 to <62.5	106	6.6	0.9	0
62.5 to 125	172	8.7	4.1	1.2
>125	7			
Lamotrigine + VPA only				
0 to <16[a]	50	14.0	8.0	4.0
16 to <31	80	20.0	13.8	1.3
31 to <62.5	55	12.7	5.5	1.8
62.5 to 125	18			
>125				
Lamotrigine + other				
0 to <16[a]	2			
16 to <31	30			
31 to <62.5	20			
62.5 to 125	97	15.5	7.2	0
>125	17			
Lamotrigine monotherapy				
0 to <16				
16 to <31[a]	213	6.1	1.9	0
31 to <62.5	122	25.4	9.0	0
62.5 to 125	83	20.5	12.0	0
>125	2			

a Current recommended dosages.

Abbreviations: DC = treatment discontinuation; EI = enzyme-inducing anticonvulsant; other = anticonvulsants which are neither inducers or inhibitors of the metabolism of lamotrigine; VPA = valproic acid (valproate sodium).

below those associated with other commonly used anticonvulsants.

Higher rates of rash are seen with concomitant valproic acid use even when the correct lamotrigine dosage is used. Therefore, concomitant use of valproic acid appears to be a risk factor for rash as well as lamotrigine dosage. The effect of valproic acid on the risk of rash is significantly diminished if an enzyme-inducing anticonvulsant is also being taken. The differences in rash incidence between lamotrigine plus enzyme-inducers and lamotrigine plus valproic acid plus enzyme-inducers is not statistically significant for any of the rash categories.

10. Discussion

Lamotrigine has shown an excellent tolerability profile in adult clinical trials, both as add-on and monotherapy. Safety of add-on lamotrigine was comparable to that of other anticonvulsants in controlled clinical trials. During open trials, where physicians were allowed to make changes to concomitant anticonvulsant therapy, as in clinical

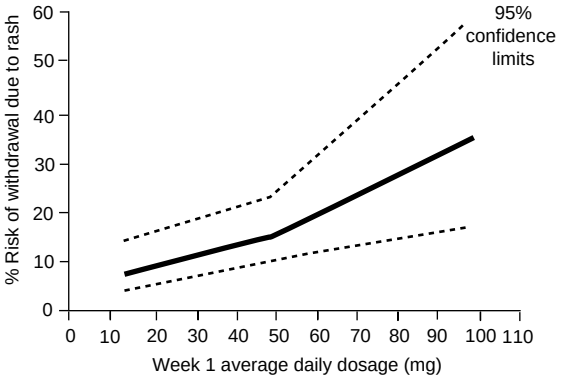

Fig. 3. Relationship between probability of withdrawal caused by rash and lamotrigine dosage during the first week of therapy in patients taking concomitant valproic acid (valproate sodium) ± a noninducer.

practice, the safety profile for lamotrigine was comparable to that seen with placebo in the controlled add-on trials. Lamotrigine has also been shown to be well tolerated in monotherapy. Less than half the number of patients on lamotrigine withdrew from treatment in clinical studies because of adverse events compared to those receiving carbamazepine and phenytoin. Additionally, lamotrigine patients had fewer complaints of somnolence, asthenia, dizziness and ataxia. Most of the adverse events in lamotrigine treated patients in all studies have been judged by the investigator to have been mild or moderate in severity. Few adverse events have resulted in the withdrawal of patients from studies.

Of concern are the cutaneous reactions that have been reported with the use of lamotrigine. Though very serious reactions including toxic epidermal necrolysis and hypersensitivity reactions associated with multiorgan failure have been reported in association with the drug in post marketing reports, none have occurred in clinical trials. Reactions have most often been limited to simple morbilliform rash not associated with evidence of systemic involvement in the approximately 4000 patients who have experienced over 3800 patient-years of exposure to the drug through adult clinical trials. There have been reports of Stevens-Johnson syndrome in a small number (0.1%) of these clinical trial patients. Rash with lamotrigine typically occurs within the first 8 weeks of treatment.

Inspection of the logistic regression plots leads to the question of whether using lower lamotrigine starting dosages than are currently recommended would significantly lower the rash rate further. However, extrapolation of the regression lines to a zero dose does not result in a significant reduction in the rates of rash noted at the currently recommended starting dosages. It should be noted, however, that these logistic regressions are based on a small number of patients who have received lamotrigine at the recommended dosages. For this reason it remains possible that additional data would indicate a significant reduction in rash for these lower dosages. The logistic regressions should be viewed with caution as they are approximations based on available data that, in some cases, provide very few patients at critical dosage points. For example, only 2% of patients taking lamotrigine, valproic acid and an enzyme-inducing anticonvulsant have received currently recommended lamotrigine dosages over the first 4 weeks.

Although the addition of lamotrigine to valproic acid monotherapy carries the highest risk for rash, this combination may also provide significant ben-

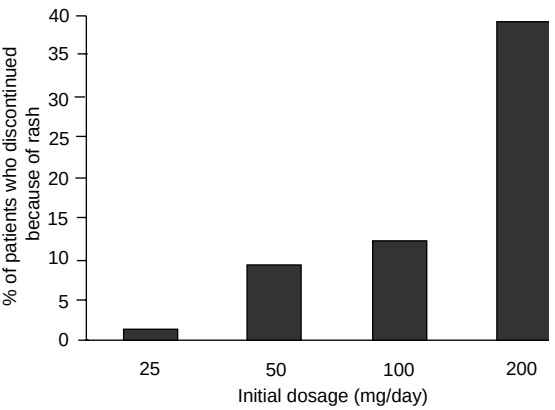

Fig. 4. Relationship between initial lamotrigine dosage and rash leading to treatment discontinuation in treatment-naive adult monotherapy patients. Note: the recommended starting dosage for lamotrigine monotherapy is 25 mg/day.

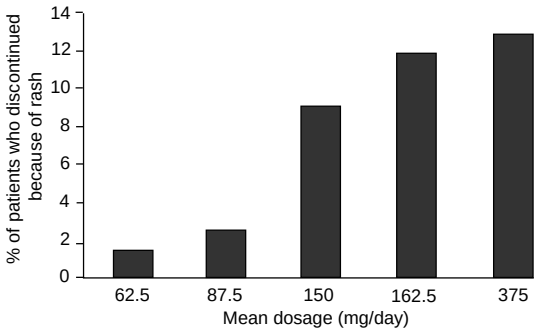

Fig. 5. Relationship between mean lamotrigine dosage over the first 5 weeks of treatment and rash leading to treatment discontinuation in treatment-naive adult patients receiving lamotrigine monotherapy. Note: the mean lamotrigine dosage for the first 5 weeks of monotherapy treatment for a patient treated according to current recommendations is 50 mg/day.

efit for some patients. Brodie[28] recently reported results of a study in which patients were converted from monotherapy with phenytoin, carbamazepine or valproic acid to lamotrigine monotherapy. Patients who had lamotrigine added to valproic acid monotherapy in the add-on phase of this study experienced an 83% reduction in baseline seizure frequency while those on carbamazepine and phenytoin experienced much lower reductions (43 and 34%, respectively) with the addition of lamotrigine. The reason for this enhanced response with the combination of lamotrigine and valproic acid does not appear to be caused by a pharmacokinetic interaction. This difference was maintained even during the phase of the study in which valproic acid, phenytoin and carbamazepine were withdrawn to achieve monotherapy with lamotrigine at which time the serum concentrations of lamotrigine did not differ significantly for all 3 groups (4.1 mg/L for valproic acid group, 4.9 mg/L for carbamazepine group, 5.2 mg/L for phenytoin group).

These clinical trial data from studies with higher starting dosages than currently recommended, clearly point to exceeding the manufacturer's currently recommended starting dosage of lamotrigine and co-administration of valproic acid alone or valproic acid with nonenzyme-inducing anticonvulsant as risk factors for rash. In a placebo controlled monotherapy study of lamotrigine as a therapy for migraine treatment,[27] not discussed so far, withdrawal because of rash was reduced to placebo levels when the starting dosage was changed halfway through enrollment from a fixed dose of 200 mg/day to a gradual escalation over a 4 week time period. Another study looking at add-on and switch to monotherapy had 2 protocol amendments to investigate the effect of slower dosage escalations upon the rate of withdrawal from treatment because of rash. In the group where lamotrigine was added to valproic acid therapy, the effect of reducing the starting lamotrigine dosage from 100 mg/day to 25 mg every alternate day, reduced the rate of discontinuation because of rash from 38% to 8%, which was statistically significant ($p = 0.006$).[28]

Because of the concern over the increased risk of rash formation, the manufacturer changed the package label in 1997 to include very strict dosage guidelines addressing both dose escalation and concomitant use with valproic acid.

Other than the cutaneous reactions with the drug, which are easily monitored and detected by patients themselves, there appears to be no undesirable effect of the drug on major systems of the body as indicated by analysis of vital signs and clinical laboratory data from monotherapy studies. The drug has no undesired affect on patient bodyweight as do some other anticonvulsants.

Lamotrigine has been shown to have efficacy in both partial and generalised seizures. It has a very good overall safety profile in adults. By carefully following the manufacturer's dosage guidelines, monitoring patients for rash during the first 8 weeks of treatment and discontinuing lamotrigine at the first sign of rash, the drug can be used as an effective therapy for control of a broad spectrum of seizure disorders in adults.

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References

1. Leach MJ, Lees G, Riddall DR. Lamotrigine: mechanisms of action. In: Levy RH, Mattson RH, Meldrum BS, et al., editors. Antiepileptic drugs. 4th ed. New York: Raven Press, 1995: 861-9
2. Xie X, Lancaster B, Peakman T, et al. Interaction of the antiepileptic drug lamotrigine with recombinant rat brain type IIA Na^+ channels and with native Na^+ channels in rat hippocampal neurones. Pflugers Arch-Eur J Physiol 1995; 430: 437-6
3. Hosford DA, Wang Y. Utility of lethargic (Ih/Ih) mouse model of absence seizures in predicting the effects of lamotrigine, vigabatrin, tiagabine, gabapentin, and topiramate against human absence seizures. Epilepsia 1997 Apr; 38 (4): 408-14
4. Motte J, Trevathan E, Arvidsson JFV, et al. Lamotrigine for generalized seizures associated with the Lennox-Gastaut Syndrome. N Engl J Med 1997; 337 (25): 1807-12
5. Buchanan N. The use of lamotrigine in juvenile myoclonic epilepsy. Seizure 1996; 5: 149-51
6. Uvebrant P, Bauzienne R. Intractable epilepsy in children. The efficacy of lamotrigine treatment, including non-seizure related benefits. Neuropediatrics 1994; 25: 284-9
7. Sander JWAS, Trevisol-Bittencourt PC, Hart YM, et al. The efficacy and long-term tolerability of lamotrigine in the treatment of severe epilepsy. Epilep Res 1990 Dec; 7: 226-9
8. Krejcova H, Salemanova Z, Tmavska Z, et al. The efficacy and long-term tolerability of lamotrigine in the treatment-resistant epilepsy [abstract]. J Neurol 1990; 237 Suppl 1: S32
9. Binnie CD, Debets RMC, Engelsman M, et al. Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy. Epilep Res 1989 Nov-Dec; 4: 222-9
10. Loisiau P, Yuen AWC, Duche B, et al. A randomised double-blind, placebo-controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures. Epilep Res 1990 Nov; 7: 136-45
11. Schapel GJ, Beran RG, Vajda FJE, et al. Double-blind, placebo-controlled crossover study of lamotrigine in treatment-resistant partial seizures. J Neurol Neurosurg Psychiatry 1993 May; 56: 448-53
12. Smith D, Baker G, Davies G. Outcomes of add-on treatment with lamotrigine in partial epilepsy. Epilepsia 1993 Mar-Apr; 34: 312-22
13. Messenheimer J, Ramsay RE, Willmore LJ, et al. Lamotrigine therapy for partial seizures: a multicenter placebo-controlled, double-blind, crossover trial. Epilepsia 1994 Jan-Feb; 35: 113-21
14. Binnie CD. The efficacy of lamotrigine. Rev Contemp Pharmacother 1994; 5: 115-22
15. Martin PJ, Miller PAH. Impact of lamotrigine on patients with refractory epilepsy: the Leicester experience. Seizure 1994; 3: 209-13
16. Timmings PL, Richens A. Lamotrigine in primary generalised epilepsy [letter]. Lancet 1992 May; 339: 1300-1
17. Vogt H, Lazareric G, Scalabrin JP, et al. Lamotrigine add-on therapy in 76 adult patients with refractory generalised epilepsies. Epilepsia 1994; 35 Suppl. 7: S71-2
18. Besag FMC, Wallace SJ, Dulac O, et al. Lamotrigine for the treatment of epilepsy in childhood. J Pediatr 1995; 127: 991-7
19. Brodie MJ, Richens A, Yuen AWC. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet 1995 Feb; 345: 476-9
20. Reunanen M, Dam M, Yuen AWC. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. Epilepsy Res 1996 Mar; 23: 149-55
21. Steiner TJ, Silveira C, Yuen AWC. Comparison of lamotrigine (Lamictal) and phenytoin monotherapy in newly-diagnosed epilepsy [abstract]. Epilepsia 1994; 35 Suppl. 7: S61
22. Goa KL, Ross SR, Chrisp P. Lamotrigine: a review of its pharmacological properties and clinical efficacy in epilepsy. Drugs 1993 Jul; 46: 152-76
23. Schachter SC, Leppik IE, Matsuo F, et al. Lamotrigine: a six month, placebo-controlled, safety and tolerance study. J Epilepsy 1995; 8: 201-9
24. Marson AG, Kadir ZA, Hutton JL, et al. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. Epilepsia 1997; 38 Suppl. 8: 859-80
25. Mackay FJ, Wilton LV, Pearce GL, et al. Safety of long-term lamotrigine in epilepsy. Epilepsia 1997; 38: 881-6
26. Tennis P, Stern RS. Risk of serious cutaneous disorders after the initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology 1997; 49: 542-6
27. Steiner TJ, Findley LJ, Yuen AWC. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalagia 1997; 17: 109-12
28. Brodie MJ, Yuen AWC, and the 105 study group. Lamotrigine substitution study: evidence for synergism with sodium valproate? Epilep Res 1997; 26: 423-32

Correspondence and reprints: Dr *John Messenheimer,* Neurosciences Clinical Research, Glaxo Wellcome Research Institute, Five Moore Drive, Research Triangle Park, NC 27709, USA.