Safety and Tolerability of Lamotrigine: Results From 12 Placebo-Controlled Clinical Trials and Clinical Implications

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Abstract: The mechanism of action of lamotrigine depends on voltage-sensitive sodium channels by which the neuronal membrane is stabilized and the release of excitatory neurotransmitters, such as glutamate and aspartate, is inhibited. Lamotrigine is indicated for maintenance treatment of bipolar I disorder to delay the time to the occurrence of mood episodes for those treated for acute mood episodes with standard therapy. There are significant gaps between clinical practices and research settings; data from controlled clinical trials of lamotrigine provide essential information about safety in bipolar populations because they result from large samples of patients with a specific disease and include comparisons with placebo or other comparators with randomized designs. In addition, lamotrigine's safety and tolerability data differ slightly in relation to disease entities, age ranges of the patients taking lamotrigine, and treatment conditions. For example, the incidence of serious rashes, including Stevens-Johnson syndrome, is approximately 0.8% (8/1000) in pediatric patients (2–16 years of age) receiving lamotrigine as adjunctive therapy for epilepsy and 0.3% (3/1000) in adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% (0.8/1000) in adult patients receiving lamotrigine as initial monotherapy and 0.13% (1.3/1000) in adult patients receiving lamotrigine as adjunctive therapy.

Hence, in this study, we focus on the data regarding the safety and tolerability of lamotrigine in the treatment of bipolar disorder gathered from 12 placebo-controlled trials, regardless of publication status, that were sponsored by GlaxoSmithKline. We also inform clinicians of practical issues in safety and tolerability in the use of lamotrigine in the treatment of bipolar disorders.

Key Words: lamotrigine, safety, tolerability

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Lamotrigine is a widely prescribed anticonvulsant that has demonstrated efficacy in a variety of neuropsychiatric disorders. Lamotrigine is currently indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, and mixed episodes) in patients treated for acute mood episodes with standard therapy in psychiatric treatment.

The safety and tolerability of lamotrigine monotherapy (100–400 mg/d) in bipolar disorder were established in two 18-month double-blind placebo-controlled trials.[1,2] Adverse events (AEs) occurred in at least 5% of patients and were numerically more common during the dose-escalation phase of lamotrigine in clinical trials, when patients may have been receiving concomitant medications, compared with the monotherapy phase. The AEs were headache, rash, dizziness, diarrhea, abnormal dreams, and pruritus. During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months' duration, 13% of 227 patients who received lamotrigine (100–400 mg/d), 16% of 190 patients who received a placebo and 23% of 166 patients who received lithium discontinued therapy because of AEs. The AEs that most commonly led to discontinuation of lamotrigine were rash and mania/hypomania/mixed mood AEs.

Lamotrigine seems comparable to placebo treatment in terms of safety and tolerability based on currently available findings.[1,2] However, there are significant gaps between clinical practices and research settings. Data from controlled clinical trials of lamotrigine provide mandatory information about safety and tolerability in bipolar populations because they result from large samples of patients with a specific disease and include comparisons with placebo or other comparators within randomized designs.

This review therefore summarizes and focuses on the currently available data regarding safety and tolerability issues in the practical use of lamotrigine for the treatment of bipolar disorders to inform clinicians of proper use and careful advertence in prescribing lamotrigine for patients with bipolar disorders in clinical practice. All of the data were gathered from the clinical trial registry Web site provided by the manufacturer of lamotrigine, GlaxoSmithKline. GlaxoSmithKline has reviewed the data acquisition for scientific accuracy.

OVERALL SAFETY AND TOLERABILITY IN CLINICAL TRIALS

In this study, data on the safety and tolerability data of lamotrigine were gathered from 12 placebo-controlled trials of patients with bipolar disorder[1–12] (Table 1). Eight of them compared lamotrigine with placebo as acute therapy for 3 to 10 weeks (studies 1–6, 8, and 12), and the other 4 studies examined it as maintenance therapy for 26 to 76 weeks (studies 7 and 9–11). Lamotrigine was administered as monotherapy in 10 placebo-controlled studies, whereas 1 study evaluated lamotrigine as an add-on therapy to lithium, and one included lamotrigine as both a monotherapy and an add-on therapy. Four of the studies included lithium as an active comparison treatment, and the remainder included only a placebo as a comparison treatment. Six enrolled patients during depressive episodes, whereas 3 of them enrolled patients during manic episodes (including both mania and hypomania). One study enrolled rapid cyclers, and one enrolled

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TABLE 1. Summary of 12 Placebo-Controlled Clinical Trials With Lamotrigine in Bipolar Disorder

Study No./ID	Study Population (Episode)	Treatment Group	Randomized (n)	Safety (n)	LTG Administration	Design
Study 1: SCA30905[3]	Bipolar I or II disorder (depressive)	LTG 200 mg/d	64	64	Add-on therapy	8-wk randomized phase
		Placebo	60	60		8-wk open label antidepressant add-on phase
						52-wk open-label continuation phase
Study 2: SCA30924[4]	Bipolar I disorder (depressive)	LTG 200 mg/d	131	127	Monotherapy	8-wk randomized phase
		Placebo	128	122		
Study 3: SCA40910[5]	Bipolar I disorder (depressive)	LTG 200 mg/d	133	129	Monotherapy	8-wk randomized phase
		Placebo	124	118		26-wk open-label continuation phase
Study 4: SCA100223[6]	Bipolar II disorder (depressive)	LTG 200 mg/d	111	109	Monotherapy	8-wk randomized phase
		Placebo	110	109		
Study 5: SCAA2008[7]	Bipolar I disorder (manic/mixed)	LTG 50 mg/d	85	84	Monotherapy	3-wk randomized phase
		Li 0.8–1.3 mEq/L	36	36		
		Placebo	95	95		
Study 6: SCAA2010[8]	Bipolar I or II disorder (depressive)	LTG 100–400 mg/d	103	103	Monotherapy	10-wk randomized phase
		Placebo	103	101		
Study 7: SCAA2012[9]	Bipolar I or II disorder (rapid cycling)	LTG 100–500 mg/d	93	92	Monotherapy	4- to 8-wk tapering and titration phase
		Placebo	89	88		26-wk randomized phase
Study 8: SCAB2001[10]	Bipolar I or II disorder (depressive)	LTG 50/d	66	66	Monotherapy	6-wk randomized phase
		LTG 200 mg/d	63	63		
		Placebo	66	65		
Study 9: SCAB2003[2]	Bipolar I disorder (depressive)	LTG 50 mg/d	50	50	Monotherapy	8- to 16-wk tapering and titration phase; 76-wk randomized phase
		LTG 200 mg/d	124	122		
		LTG 400 mg/d	47	47		
		Li 0.8–1.1 mEq/L	121	120		
		Placebo	121	121		
Study 10: SCAB2005[11]	Bipolar I or II disorder (rapid cycling)	LTG 50–500 mg/d	68	68	Monotherap y or add-on therapy	32-wk randomized phase
		Placebo	69	69		
Study 11: SCAB2006[1]	Bipolar I disorder (manic/hypomanic)	LTG 100–400 mg/d	59	58	Monotherapy	8- to 16-week tapering and titration phase; 76-wk randomized phase
		Li 0.8–1.1 mEq/L	46	46		
		Placebo	70	69		
Study 12: SCAB2009[12]	Bipolar I disorder (manic)	LTG 200 mg/d	74	74	Monotherapy	6-wk randomized phase
		Li 0.8–1.3 mEq/L	78	78		
		Placebo	77	77		

Li indicates lithium; LTG, lamotrigine.

patients with both manic and depressive episodes. In the 4 flexible-dose studies, lamotrigine was used at dose range of 50 to 500 mg/d, and 5 of 6 single-dose studies used a lamotrigine dose of 200 mg/d. Lamotrigine multidose studies included doses of 50, 200, and 400 mg/d, but separate safety data for lamotrigine 400 mg/d were not provided (the data of 47 patients receiving lamotrigine 400 mg/d were combined with those of patients receiving lamotrigine 200 mg/d). In the long-term monotherapy studies, an open-label phase to increase the lamotrigine dose and taper out any previous psychotropic medication preceded the randomized-trial phase (studies 7, 9, and 11). Two long-term trials for depressive episodes consisted of 8-week randomized-trial phases both before and after an open-label continuation phase (studies 1 and 3). In this study, the data used for analysis were limited to the results of randomized-trial phases.

The observed AEs, which were reported in at least 5% of patients in any treatment group in the 12 controlled clinical trials with lamotrigine, are listed in Table 2. The AE profile of lamotrigine was generally comparable to that of placebo. The most common AEs reported by the lamotrigine groups were headache (24.4%), nausea (12.8%), and any rash (8.2%), and these percentages were similar to those for patients receiving placebo (22.8%, 13.8%, and 6.7%, respectively). No AEs had greater than 5% frequency in the lamotrigine-treated groups, and no AE occurred at least twice as frequently in the lamotrigine-treated groups as in the placebo groups. When compared with patients treated with lithium, patients administered lamotrigine had a relatively higher incidence of headache (24.4% vs 13.6%) and any rash (8.2% vs 2.5%) and a lower incidence of somnolence (4.8% vs 9.6%) and tremor (3.5% vs 11.4%). The proportion of patients withdrawn from study due to AEs was comparable between patients receiving lamotrigine and placebo (11.7% vs 9.2%, respectively) but higher in patients with lithium (19.3%).

TABLE 2. Percentage of AE Incidence Across 12 Controlled Clinical Trials*

AE	Placebo (n = 1094)	Lamotrigine (n = 1256)	Lithium (n = 280)
Headache	22.8	24.4	13.6
Nausea	13.8	12.8	16.1
Any rash	6.7	8.2	2.5
Infection	9.0	8.0	7.9
Dizziness	7.7	7.0	6.8
Insomnia	6.3	7.1	6.1
Somnolence	4.8	7.0	9.6
Dry mouth	4.3	6.3	—
Diarrhea	8.4	6.2	13.9
Pain	5.0	6.1	1.8
Back pain	4.2	5.7	2.5
Influenza	4.9	5.8	5.7
Tremor	3.4	3.9	11.4
Vomiting	3.5	3.5	5.4

*Occurrence at incidence of greater than 5% in any treatment group.

Table 3 provides the AE data for the controlled clinical trials with lamotrigine as monotherapy (studies 2–9, 11, and 12) or as adjunctive therapy with lithium (study 1). The data of the lamotrigine group in study 10 were excluded because no separate data were provided about lamotrigine monotherapy and concomitant use of lamotrigine with other psychotropic agents. Compared with lamotrigine monotherapy, adjunctive therapy with lithium had a higher incidence of fatigue (17.2% vs 0.6%), tremor (12.5% vs 2.5%), influenza (10.9% vs 4.0%), skin problems other than rash (7.8% vs 0 %), and abdominal pain (6.3% vs 1.2%). Except for influenza, these AEs also were at least twice as frequent in patients receiving lamotrigine adjunctive therapy with lithium compared with those receiving placebo. A comparison of the proportion of patients withdrawn from study because of AEs revealed that treatment with lamotrigine adjunctive therapy with lithium was associated with a relatively lower incidence of withdrawal (6.3%) compared with placebo and lamotrigine monotherapy (9.2% and 11.7%, respectively).

The AEs in controlled clinical trials of short-term therapy (≤10 weeks, studies 1–6, 8, and 12) and of long-term maintenance treatment (≥26 weeks, studies 7 and 9–11) are shown in Table 4. Compared with short-term treatment with lamotrigine, maintenance treatment showed a higher incidence of infection (12.4% vs 5.7%), back pain (9.2% vs 2.5%), tremor (6.9% vs 1.2%), and influenza (6.2 % vs 2.4%). The incidence of any rash was lower in maintenance therapy than in short-term therapy (2.3% vs 9.1%). However, these incidence rates were comparable to those found with placebo in maintenance-treatment trials.

The incidence of AEs under a differential dose of lamotrigine, such as 50 mg/d (studies 5, 8, and 9), 200 mg/d (studies 1–4, 8, 9, and 12), or a flexible dose (50–500 mg/d; studies 6, 7, 10, and 11) are shown in Table 5. The 504 patients in the lamotrigine 200 mg/d group included 47 patients treated with lamotrigine 400 mg/d because only combined results were provided (study 9). Overall AEs in the lamotrigine 200 mg/d group were comparable to those in the lamotrigine 50 mg/d group. The proportion of patients withdrawn from study because of AEs also was comparable between patients with lamotrigine 50 mg/d and lamotrigine 200 mg/d (13.0% vs 11.3%, respectively). There was no evidence of an association between AEs and lamotrigine dose when comparing lamotrigine 50 and 200 mg/d. However, flexible-dose studies showed a trend of higher incidence rates in some AEs, including nausea, dizziness, somnolence, pain, infection, and tremor, compared with rates under lamotrigine 200 mg/d. Considering that the data are not sufficient with respect to lamotrigine dose above 200 mg/d in fixed-dose trials and that a relatively higher dose could be used in flexible-dose studies compared with fixed-dose trials (3 used up to 400 mg/d, and 1 was up to 500 mg/d), more data are needed to clarify association between AEs and lamotrigine dose.

TABLE 3. Percentage of AE Incidence in Each Treatment Groups Including Concomitant Use of Lamotrigine With Lithium, Lamotrigine Monotherapy, and Placebo Across 12 Controlled Clinical Trials*

AE	Placebo (n = 1094)	Lamotrigine (With Lithium, n = 64)	Lamotrigine (Monotherapy, n = 1124)
Headache	22.8	21.9	25.0
Fatigue	3.9	17.2	0.6
Nausea	13.8	15.6	15.2
Tremor	3.4	12.5	2.5
Influenza	5.8	10.9	4.0
Insomnia	6.3	9.4	6.8
Skin problem	0.1	7.8	—
Abdominal pain	0.5	6.3	1.2
Infection	9.0	—	7.9
Dizziness	7.0	1.6	7.6
Somnolence	4.8	—	7.5
Diarrhea	8.4	—	6.5
Any rash	6.7	4.7	6.3
Dry mouth	4.3	—	5.2
Pain	5.0	—	4.8

*Occurrence at incidence of greater than 5% in any treatment group.

TABLE 4. Percentage of AE Incidence in Short-Term Acute Treatment Trials and Long-Term Maintenance Treatment Trials*

	Placebo†		Lamotrigine	
AE	Overall (n = 1094)	Maintenance Treatment (n = 347)	Acute Treatment (n = 755)	Maintenance Treatment (n = 437)
Headache	22.8	19.3	26.2	22.2
Nausea	13.8	14.4	11.4	16.9
Any rash	6.7	4.0	9.1	2.3
Dry mouth	4.3	—	7.7	—
Dizziness	7.0	7.8	7.2	9.4
Insomnia	6.3	5.8	6.8	6.9
Diarrhea	8.4	8.1	6.5	6.4
Somnolence	4.8	6.9	6.2	9.4
Infection	9.0	13.3	5.7	12.4
Pain	5.0	5.5	5.2	5.5
Back pain	4.2	5.5	2.5	9.2
Influenza	5.8	7.5	2.4	6.2
Tremor	3.4	7.2	1.2	6.9

*Occurrence at incidence of greater than 5% in any treatment group.
†Data from 12 controlled clinical trials.

TABLE 5. Percentage of AE Incidence in Each Treatment Dose of Lamotrigine Across 12 Controlled Clinical Trials*

AE	Placebo (n = 1094)	Lamotrigine† 50 mg/d (n = 200)	Lamotrigine† 200 mg/d (n = 503)	Lamotrigine‡ 50–500 mg/d (n = 321)
Headache	22.8	27.5	20.5	29.9
Nausea	13.8	14.0	10.7	18.7
Any rash	6.7	8.0	4.9	8.4
Dizziness	7.0	7.5	5.1	12.8
Somnolence	4.8	7.0	5.1	11.5
Pain	5.0	5.5	1.3	11.2
Back pain	4.2	5.5	4.6	5.9
Infection	9.0	5.0	5.8	13.7
Diarrhea	8.4	4.5	6.5	6.5
Insomnia	6.3	4.0	7.9	7.5
Tremor	3.4	3.5	3.3	5.6
Dry mouth	4.3	3.0	5.2	3.7

*Occurrence at incidence of greater than 5% in any treatment group.

†Data from fixed dose trials.

‡Data from flexible dose trials.

As a whole, nonfatal serious AEs were observed in 6.6% of the lamotrigine treatment group, 7.2% of the placebo group, and 8.2% of the lithium treatment group. Among 1256 patients receiving lamotrigine treatment, 31 patients (2.5%) experienced one of the manias (manic, hypomanic, or mixed episode), and 14 patients (1.1%) experienced a depressive episode during treatment periods. Among 1094 patients with placebo and 280 patients with lithium treatment, 2.2% and 2.5% showed manic relapses, and 1.2% and 1.8% showed recurrent depression, respectively.

Among the serious AEs, 7 of 1256 patients treated with lamotrigine, 4 of 1094 patients treated with placebo, and 3 of 280 patients treated with lithium developed mania that was considered to be related to the treatment drugs. Five lamotrigine patients, 4 placebo patients, and no lithium patients developed depression considered to be related to the treatment. There were 2 cases of fatal SAE (2 suicides, one with lamotrigine and one with placebo) during the randomized phase, but neither was considered drug related.

The results of controlled clinical trials suggest that lamotrigine is generally well tolerated as both monotherapy and adjunctive therapy, and its adverse-effects profiles are comparable to those of placebo treatment. Long-term use and escalated doses up to 200 mg/d of lamotrigine also seem to be tolerable.

ADVERSE EVENTS OF SPECIAL INTEREST

Rash

Rash has been a common side effect of lamotrigine in the treatment of epilepsy and is experienced by approximately 10% of patients.[13,14] Rashes occurring with lamotrigine treatment include relatively mild forms of skin lesions, such as simple morbilliform rash, urticaria, and erythema multiforme, and more severe skin reactions, such as hypersensitivity syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[14] The distinction between a mild and a severe skin lesion is not clear, and the term *serious rash* is usually used to describe any rash associated with hospitalization or considered to be possible hypersensitivity syndrome or Stevens-Johnson syndrome.[14]

The underlying mechanism of hypersensitivity in skin is not completely understood. It has been hypothesized that lamotrigine produces active metabolites in the skin, which are able to activate the immune system, and hypersensitivity may be associated with the amount of lamotrigine or active metabolites in the skin.[15,16] In a rat model, at least 10% of lamotrigine given was found in the skin of rats 4 hours after a single dose injection.[17] Oxidation may represent a minor metabolic pathway of lamotrigine and may be associated with skin rash when glucuronidation is inhibited by combined use of valproate.[18] Until now, however, no reactive metabolite of lamotrigine associated with skin rash has been found.[19]

In the pooled prospective data including both placebo controlled trials and open trials for epilepsy, 0.3% of patients were hospitalized because of serious rash, and 0.1% of patients were reported as having possible Stevens-Johnson syndrome.[20] Rashes including both mild and serious form usually occurred within several weeks of initiation of lamotrigine treatment in the clinical trials of epilepsy.[20] Children had a higher risk of serious rash with up to a 3-fold incidence rate compared with adults.[14] The rate of dose escalation was associated with rash development. When doses of lamotrigine at 7 days were 25, 50, and 100 mg/d, the discontinuation rates because of rash were 2.2%, 9.2%, and 11.8%, respectively.[21] When used adjunctively with valproate, the incidence rates of discontinuation because of rash were 38% for lamotrigine at an initial dose of 100 mg/d and 8% for an initial dose of 25 mg/d.[22] As the tolerance to lamotrigine would be lost by 7 days after discontinuation, retitration would be needed in cases of interruption of several days.[23] Valproate increases the half-life and steady-state concentrations of lamotrigine via inhibition of the hepatic metabolism of lamotrigine.[24] Lamotrigine clearance with concomitant use of valproate was 39% of that of lamotrigine monotherapy.[25]

In the 12 controlled trials for bipolar disorder, the incidence of any rash was 8.2% of 1256 patients in the lamotrigine group, which was comparable to that of the placebo (6.7% of 1094 patients) (Table 2). In the long-term maintenance studies that had a randomization phase after a preliminary phase of dose titration, the incidence of rash was 2.3% of 437 patients during the randomization periods (Table 4). It was much lower than that found in an acute treatment study (9.1% of 775 patients) and that of placebo groups in randomization periods of maintenance studies (4.0% of 347 patients) (Table 4). In the controlled trials with fixed doses, the incidence of any rash was slightly higher in

patients with lamotrigine 50 mg/d (8.0% of 200 patients) compared with those of patients with lamotrigine 200 mg/d (4.9% of 503 patients) and patients with placebo (6.7% of 1094 patients).

In the 12 controlled trials using lamotrigine for bipolar disorder, serious rash did not occur in patients receiving lamotrigine, but 1 case occurred in the placebo group in a study looking at lamotrigine or placebo as add-on therapy to lithium (study 2). Across bipolar and other mood disorder studies overall, including both controlled and uncontrolled trials with lamotrigine, serious rash occurred in one of 1233 patients (0.08%) receiving lamotrigine monotherapy and in 2 of 1538 patients (0.13%) receiving lamotrigine adjunctive therapy.[26] All 3 cases of serious rash resolved after discontinuation of lamotrigine.[23]

READMINISTRATION OF LAMOTRIGINE AFTER OCCURRENCE OF RASH

Because lamotrigine has a unique role in bipolar disorder, especially in the long-term prophylaxis of depressive episodes, clinicians may wish to carefully reflect on the value of retrying lamotrigine after the emergence of rash in lamotrigine-treated patients. Until now, no reliable data from controlled trials have been available to resolve concerns over this issue. However, case reports on bipolar disorder and epilepsy suggest the possibility of successfully reintroducing lamotrigine in patients who have previously experienced rash during lamotrigine treatment, although these reports require careful interpretation because of the small number of cases and publication bias.

In 1 case report on bipolar disorder, lamotrigine was reintroduced to a patient in whom a rash had developed at 2 weeks after initiation of lamotrigine with 25 mg/d as a starting dose.[27] Reintroduction of lamotrigine was started with an initial dose of 12.5 mg/d for 2 weeks and then increased to 25 mg/d for 2 weeks, 50 mg/d for 2 weeks, 75 mg/d for 2 weeks, and finally 100 mg/d, and the rash did not reappear. In another case report of bipolar disorder in a patient who had developed rashes after achieving a dosage of 300 mg/d, lamotrigine was restarted with a dose of 5 mg/d for 3 days, then with the dose increasing by 5 to 10 mg/d every 3 days for 3 weeks, followed by 25-mg/d increments up to 300 mg/d.[28] The rash reappeared when the dose increased from 275 to 300 mg/d and persisted for 2 weeks after the lamotrigine dose was decreased to 150 mg/d and prednisone was applied. Recently, a prospective, open-label case series to investigate the safety of rechallenge with lamotrigine after an initial rash in patients with refractory bipolar depression was conducted in a private practice setting.[29] Patients who developed an initial rash while on lamotrigine and who were refractory to other treatments were offered rechallenge with the medication using very-low-dose titration based on the manufacturer's prescribing information. Of 27 patients rechallenged with lamotrigine, 5 patients required discontinuation because of rash or inflammation. Two of these cases were potentially serious, and all resolved with discontinuation of lamotrigine. No patients developed Stevens-Johnson syndrome or toxic epidermal necrolysis after rechallenge. This study also conducted a meta-analysis of the literature and identified 48 cases of lamotrigine rechallenge, with an overall success rate of 87%. When combining the studies, a pooled analysis showed a success rate of 85%. According to that study, the rate of recurrent rash was elevated when rechallenge began within 4 weeks of the initial rash (36% vs 7%, $P = 0.002$) and was reduced when the initial rash had no signs of potential seriousness (0% vs 23%, $P = 0.01$).

One case report of epilepsy found that 16 of 19 patients were successfully rechallenged with a slow titration schedule, and another study reported that 6 of 8 patients had no recurrence of rash.[30,31] In another case report, 3 patients with allergic skin responses to lamotrigine continued lamotrigine with concomitant use of antiallergic medications, and the rash gradually disappeared in these patients.[32] In a case series of pediatric and adolescent epileptic patients, lamotrigine was reintroduced after at least 6 weeks of discontinuation and using a very slow titration schedule. The rash did not reappear in any of the participants (n = 7).[33] These case reports of rechallenge with lamotrigine suggest that a high target dose, fast dose increase increments, and concomitant administration of anticonvulsants played a major role in rash recurrence. A more conservative dose and slower up-titration of lamotrigine might be needed for patients for whom it has been decided to reintroduce the drug. We believe that lamotrigine rechallenge in bipolar depression is an underused option in our clinical armamentarium, and further studies are needed to guide us in this area.

MANIA

In the 12 placebo-controlled trials for bipolar disorder, serious AEs of mania, hypomania, and mixed mania occurred in 2.5% of 1256 patients with lamotrigine treatment (Table 6). This was comparable to the level found in patients treated with a placebo (2.2% of 1094 patients) and lithium (2.5% of 280 patients). Among them, the incidence considered to be related to the treatment drug was 0.5%, 0.3%, and 1.1% for lamotrigine, placebo, and lithium patients, respectively. Long-term use of lamotrigine does not seem to be associated with mood episode switches. In the maintenance-treatment trials, the incidence of serious AEs of mania, hypomania, and mixed mania were 4.5%

TABLE 6. No. of Patients (%) With Serious AEs Across 12 Controlled Clinical Trials

Serious AE	Placebo (n = 1094)	Lamotrigine (n = 1256)	Lithium (n = 280)
Any nonfatal SAEs			
Total	79 (7.2)	83 (6.6)	23 (8.2)
All mania	24 (2.2)	31 (2.5)	7 (2.5)
Depression	13 (1.2)	14 (1.1)	5 (1.8)
Psychosis	1 (<1)	6 (<1)	4 (1.4)
Suicide ideation	7 (<1)	7 (<1)	—
Attempted suicide	6 (<1)	5 (<1)	—
Drug-related SAEs			
Total	14 (1.3)	19 (1.5)	7 (2.5)
All mania	4 (<1)	7 (<1)	3 (1.1)
Depression	4 (<1)	5 (<1)	—
Psychosis	—	3 (<1)	—
Suicide ideation	1 (<1)	1 (<1)	
Attempted suicide	—	—	—
Syncope	1 (<1)	1 (<1)	—
Nausea	1 (<1)	—	2 (<1)
Diarrhea	1 (<1)	—	2 (<1)
Motor dysfunction	2 (<1)	—	—
Agitation	1 (<1)	—	—
Abortion	1 (<1)	—	—
Lithium toxicity	—	1 (<1)	—
Accidental injury	—	1 (<1)	—
Fatal SAEs	1*	1*	—

*Suicide.

of 437 patients with lamotrigine and 4.0% of 347 patients with placebo (studies 7 and 9–11). As for associations with lamotrigine dose, in the fixed-dose trial of the 7-week acute treatment period with variable lamotrigine dose, serious AEs of mania, hypomania, and mixed mania occurred in 4.6% of patients treated with placebo (3 of 65 patients), 3.0% of patients treated with lamotrigine 50 mg/d (2 of 66 patients), and 7.9% of those treated with lamotrigine 200 mg/d (5 of 63 patients) (study 8). However, of the 7 patients with manic relapses in both lamotrigine treatment groups, 6 patients experienced these episodes during the first 3 weeks of treatment with lamotrigine at a dose of 50 mg/d or less. In the one other patient, a manic episode occurred at 3 days after dose increment to 100 mg/d. In the fixed-dose trial for 76 weeks of maintenance treatment, survival data for lamotrigine 50, 200, and 400 mg/d monotherapy were not significantly different from placebo for time to intervention for an emerging manic or hypomanic episode (study 9). Moreover, the incidence of mania, hypomania, and mixed mania during the study periods were higher with lamotrigine 50 mg/d (12% of 50 patients) than with lamotrigine 200 and 400 mg/d (3.5% of 169 patients).

These data from clinical trials suggest that unlike antidepressants, lamotrigine does not precipitate manic symptoms.

SUICIDE

Although the package insert for lamotrigine (revised at April, 2010)[26] contains a warning about worsening of suicide risk associated with bipolar disorder, there is no evidence of an association between lamotrigine and increased suicidality in the data of clinical trials.

Across the 12 controlled clinical trials of lamotrigine in bipolar disorder, suicide events occurred in 0.5% of 1094 patients treated with placebo and 0.3% of 1256 patients treated with lamotrigine (Table 6). Development of suicide ideation as a serious AE in these trials did not seem to differ between the 2 groups (0.6% for the placebo group and 0.5% for the lamotrigine group). In the maintenance-treatment trials (studies 7 and 9–11), suicide events occurred in only 0.3% of 347 patients (n = 1) treated with placebo and in 0.5% of 437 patients (n = 2) treated with lamotrigine, and suicidal ideation as a serious AE was observed in 0.3% (n = 1) and 0.2% (n = 1) of patients, respectively.

However, pooled analysis of 199 clinical trials of antiepileptic drugs including lamotrigine in epilepsy showed twice the risk of suicidal thoughts or behavior in patients treated with antiepileptic drugs compared with those receiving placebo, and recently, this warning was added to the package insert for lamotrigine.[26]

WEIGHT GAIN

In the controlled clinical trials, reports of significant weight gain as an AE in lamotrigine treatment groups were very rare, and the currently available data offer no evidence of an association between lamotrigine treatment and weight gain. In the 26-week comparison of lamotrigine monotherapy and placebo, the mean weight change of completers was −0.3 kg for placebo (n = 35) and 1.1 kg for lamotrigine (n = 35) (study 7). When placebo, lamotrigine 50 mg/d, and lamotrigine 200 mg/d were compared for 7 weeks of acute treatment as monotherapy, mean weight change was 0.2, −0.4, and 0.0 kg, respectively (study 8). In the clinical trial for maintenance treatment with lamotrigine in bipolar disorder over 76 weeks, observed mean weight change was 1.2 kg for placebo, 4.2 kg for lithium, and −2.2 kg for lamotrigine (study 10). Mean weight change was significantly lower in the lamotrigine treatment group compared with the lithium treatment group, but the change was not significant when compared with the placebo group. The incidence of patients with a 7% or greater increase in body weight from baseline was 6% for the placebo group, 10% for the lithium treatment group, and 7% for the lamotrigine treatment group. However, in another 76-week maintenance study with flexible doses of lamotrigine, the incidence rate of patients with 7% or greater increase was 11%, 10%, and 2% for the lamotrigine, lithium, and placebo groups, respectively. In epilepsy research, a retrospective review of 32 trials, including 463 epileptic patients receiving lamotrigine treatment for at least 6 months, reported a mean weight increase of 0.5 kg.[34]

SEDATION

The incidence rate of sedation as an AE was consistently found to be slightly higher in lamotrigine compared with placebo. Across the 12 controlled trials of lamotrigine in bipolar disorder, sedation occurred in 4.8% of 1094 patients treated with placebo, 7.0% of 1256 patients treated with lamotrigine, and 9.6% of 280 patients treated with lithium (Table 2). This trend also was observed when long-term trials were examined separately (6.9% vs 9.4% in placebo and lamotrigine groups, respectively) (studies 7 and 9–11). Results of multiple fixed-dose studies with lamotrigine showed no evidence of any association between lamotrigine dose and sedation. The incidence of sedation was 7.0% of 200 patients treated with lamotrigine 50 mg/d and 5.1% of 503 patients treated with lamotrigine 200 mg/d (partially including patients treated with lamotrigine 400 mg/d) (Table 5).

PREGNANCY-RELATED SAFETY

Until now, no evidence of AEs associated with pregnancy has been found with lamotrigine, and lamotrigine is classified as a pregnancy category C medication. Currently, several pregnancy registries are gathering data on the effects of lamotrigine exposure during pregnancy. The data from the registries show that major birth defects after exposure to lamotrigine during the first trimester occurred in approximately 1% to 5.6% of those treated (vs 2%–3% in the general population).[35] Most of the reported data showed that rates of major malformation were within the expected baseline rates, although the sample size was too small to allow for generalizations about characteristic abnormalities. However, observed data from these registries partly suggest a teratogenic risk of lamotrigine exposure. The North American Antiepileptic Drug Pregnancy Registry showed that among 564 infants with exposure to lamotrigine in the first 5 days after birth, 5 infants (0.89%) had an oral cleft.[36] This is a significantly higher prevalence compared with that in the general population (0.037%). In this registry, the relative risk of isolated cleft palate attributed to lamotrigine was 32.8 (95% confidence interval, 10.6–101.3), and that of isolated cleft lip was 17.1 (95% confidence interval, 4.3–68.2).[36] The UK Epilepsy and Pregnancy Register reported that hypospadias and gastrointestinal defects seemed to be overrepresented in the population with lamotrigine exposure.[37] Across the controlled trials with lamotrigine in bipolar disorder, a total of 7 patients became pregnant after enrollment in the studies, and 2 of them received lamotrigine. Of these 2 pregnancies, one resulted in a normal birth and the other was electively terminated.[23]

PEDIATRIC AND ELDERLY POPULATIONS

In bipolar disorder, the effectiveness and safety of lamotrigine in patients younger than 18 years have not yet been established. In epilepsy, as previously mentioned, the data have shown that the incidence of serious rashes seemed to be

approximately 3 times more frequent in the pediatric population (1%) than in the adult population (0.3%)[20] As to milder forms of rashes, pediatric patients also had a slightly higher incidence of any rash (12.6% vs 10.7%) and of rashes leading to discontinuation of therapy (4.7% vs 3.5%) compared with adult patients.[38] The analysis of the higher risk of rash in pediatric patients suggests that the concomitant use of valproic acid and doses exceeding current recommendations for starting doses or recommended rates of dose escalation are strong factors for increasing the risk of lamotrigine-related serious rashes.[14] Data from 2 pediatric clinical trials (168 patients in the lamotrigine group and 171 patients in the placebo group) showed that dizziness, ataxia, nausea, and tremor occurred in at least 10% of patients with lamotrigine and were significantly more common with lamotrigine than with placebo.[39,40] A prospective study evaluated the effect of lamotrigine on body growth in children and adolescents with a total of 103 epileptic patients treated with lamotrigine monotherapy for approximately 19 months.[41] In this study, patients exhibited normal growth as measured by changes from pretreatment standard deviation scores for height, weight, and body mass index.

Recently, 2 open-label trials of lamotrigine in pediatric bipolar disorder were published. A 14-week open trial (n = 46) showed AEs in more than 10% of patients, including sedation, stomachache, increased urination, and increased appetite.[42] Benign rash occurred in 6.4% of patients (n = 3), and no serious rash, significant weight gain, or other abnormalities were observed in laboratory testing. In another 12-week open trial (n = 39), the AEs reported in more than 10% of patients were gastrointestinal complaints, headache, cold symptoms, and dermatological effects.[43] Thirteen (33.3%) of the 39 patients developed skin rashes, and among them, benign rash of unknown etiology was reported in 7 cases (17.9%). None of them developed a serious rash. There were no significant increases in weight from baseline to end point, and no other abnormalities were found in laboratory testing.

Lamotrigine therapy in elderly patients seems to be favorable considering its AE profile and neutral effect on cognitive function.[44] Although based on studies with small sample sizes in epilepsy, lamotrigine seems to be generally well tolerated in elderly patients, and rates of AE events are thought to be similar to those reported for younger patients.[45–47] The most common side effects reported with lamotrigine therapy in elderly people were headache, nausea, diarrhea, somnolence, dizziness, and rash; patients were less likely to discontinue prematurely compared with other antiepileptic drugs.[45–47]

DRUG INTERACTIONS

Lamotrigine is metabolized exclusively by glucuronidation, which also is a primary pathway for elimination of valproate.[48] Valproate reduces lamotrigine clearance, resulting in a marked prolongation of elimination half-life and a doubling of lamotrigine plasma levels.[24,49] Concomitant use of valproate is associated with an increased risk of serious rash.

Lamotrigine is eliminated more rapidly by enzyme-inducing drugs, including carbamazepine, phenytoin, phenobarbital, primidone, methsuximide, rifampicin, and, to a lesser extent, oxcarbazapine.[50–52] However, plasma levels of these drugs are not affected by lamotrigine, and lamotrigine is unlikely to induce mixed-function oxygenase enzymes.[53] The presence of oral contraceptives decreased lamotrigine plasma concentration by more than 50%.[54]

In vitro metabolism of lamotrigine was not significantly affected by clozapine, fluoxetine, phenelzine, risperidone, or trazodone and was minimally affected by amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam.[55]

However, the negative results of pharmacokinetic interactions in vitro do not seem to guarantee the safety of concomitant administration. Although sertraline had no effect on lamotrigine metabolization in vitro, a case report showed a doubling of lamotrigine blood level in 2 patients using lamotrigine after concomitant administration of sertraline.[56] Another case report showed tripling of plasma levels of clozapine with concomitant use of lamotrigine.[57] Concomitant administration of lamotrigine was associated with increased signs of carbamazepine toxicity without effecting carbamazepine pharmacokinetics.[58]

CONCLUSIONS

This paper reviewed the tolerability and safety of lamotrigine using data available from 12 placebo-controlled clinical trials of lamotrigine, enrolling a total of approximately 2700 patients with bipolar disorders. This review is the most extensive one to date collating all safety and tolerability information from these clinical trials, including data from 7 unpublished studies.

The most common AE in the 12 placebo-controlled clinical trials with lamotrigine was headache, followed by nausea. Other common AEs included insomnia, somnolence, back pain, fatigue, rash, rhinitis, and abdominal pain. Lamotrigine was found to be minimally associated with switching or destabilized mood and showed little involvement with sexual adverse effects, sedation, weight gain, or withdrawal symptoms. Serious rash was found not to be related to the use of lamotrigine, although it has been estimated at 0.8% in epilepsy clinical trials. Rechallenge may be a viable option, but one whose risks warrant more careful consideration. In addition, rechallenge should be avoided in early phases of the initial rash, particularly within the first month. Lamotrigine rechallenge in bipolar disorder may be an underused option, but further studies are clearly needed to guide us in this area.

Our review has several limitations. A weakness of the pooled data is that sources of bias are not controlled for by the present authors' own method. Pooled data do not allow for screening of inadequately designed studies, resulting in limitations on the generalizability of the results. Hence, only methodologically sound studies should be included in pooled studies. Best-evidence meta-analysis would be the optimal study method to overcome this issue. In addition, adding a study-level predictor variable that reflects the methodological quality of the studies to examine the effect of study quality on effect size also would improve the meta-analytic approach.

In conclusion, lamotrigine may be safe and tolerable in patients with bipolar disorder and effective in long-term regulation of mood symptoms. However, more data are needed to support the use of lamotrigine, especially to determine whether it would sufficiently and adequately replace the older mood stabilizers because the impact of AEs of medication on physicians' treatment decisions and patients' acceptance of mood stabilizers is evident.

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