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Safety and Tolerability of Lamotrigine for Bipolar Disorder

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Abstract

Tolerability and safety are important considerations in optimising pharmacotherapy for bipolar disorder. This paper reviews the tolerability and safety of lamotrigine, an anticonvulsant recommended in the 2002 American Psychiatric Association guidelines as a first-line treatment for acute depression in bipolar disorder and one of several options for maintenance therapy.

This paper reviews the tolerability and safety of lamotrigine using data available from a large programme of eight placebo-controlled clinical trials of lamotrigine enrolling a total of nearly 1800 patients with bipolar disorder. This review is the first to collate all the safety information from these clinical trials, including data from four unpublished studies.

The results these trials in which 827 patients with bipolar disorder were given lamotrigine as monotherapy or adjunctive therapy for up to 18 months for a total of 280 patient-years of exposure demonstrated that lamotrigine is well-tolerated with an adverse-event profile generally comparable with that of placebo. The most

common adverse event with lamotrigine was headache. Lamotrigine did not appear to destabilise mood and was not associated with sexual adverse effects, weight gain, or withdrawal symptoms.

Few patients experienced serious adverse events with lamotrigine, and the incidence of withdrawals because of adverse events was low. Serious rash occurred rarely (0.1% incidence) in the clinical development programme including both controlled and uncontrolled clinical trials. These findings – considered in the context of data showing lamotrigine to be effective for bipolar depression – establish lamotrigine as a well-tolerated addition to the psychotropic armamentarium.

Lamotrigine, an anticonvulsant marketed since 1990 for epilepsy, has also demonstrated efficacy in bipolar disorder.[1-12] Lamotrigine can treat and prevent depressive episodes without destabilising mood, in contrast to other treatments employed for depression in bipolar disorder.[13-17] In controlled clinical trials, lamotrigine was effective versus placebo for the acute treatment of depressive episodes of bipolar I disorder, as maintenance treatment for rapid-cycling bipolar II disorder, and as maintenance treatment for patients with bipolar I disorder who were recently manic or depressed.[1,5,11,12] Based on these and other data, the 2002 American Psychiatric Association guidelines recommend lamotrigine as a first-line treatment for acute depression in bipolar disorder and as one of several options for maintenance therapy.[18]

In addition to efficacy, tolerability and safety are important considerations in optimising pharmacotherapy for bipolar disorder, a condition that often requires the use of medication on a long-term basis. Furthermore, because adverse effects are a leading cause of noncompliance with treatment,[19,20] well tolerated regimens are an essential component of bipolar disorder management.

This paper reviews the tolerability and safety of lamotrigine using data available from a large programme of eight placebo-controlled clinical trials of lamotrigine enrolling a total of nearly 1800 patients with bipolar disorder. This review is the first to collate all the safety information from these clinical trials, including data from four unpublished studies.

1. Lamotrigine in Epilepsy

Lamotrigine was first introduced into clinical practice as an antiepileptic drug in Europe in 1990, and its safety and tolerability profiles in epilepsy are well characterised based on its clinical use and extensive study in clinical trials. Information on the tolerability of lamotrigine in epilepsy is germane to understanding the drug's profile in bipolar disorder – particularly in light of the fact that the dosage for bipolar disorder is comparable with that for epilepsy. Compared with the older antiepileptic drugs carbamazepine and phenytoin, lamotrigine monotherapy is associated with a lower incidence of neurological adverse events such as asthenia, dizziness, and somnolence. Lamotrigine moderately enhances cognitive function.[21-24] Unlike the antiepileptic valproate, lamotrigine does not cause weight gain,[25] and close monitoring of blood levels is not required.

The most common adverse event leading to discontinuation is rash.[23] Although generally manageable, it may in rare cases lead to serious consequences (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis). In early epilepsy clinical trials, rash leading to hospitalisation and discontinuation of treatment or rash reported to be Stevens-Johnson syndrome was reported among 0.3% of adult patients.[26] Subsequent study has suggested that the risk of rash with lamotrigine can be minimised through appropriate precautions – specifically, by adhering to current dosage recommendations that specify a gradual dose-titration schedule and recommend adjustment of the lamotrigine dose when the drug is given with certain concomitant medications. Considered in aggregate, the data from epilepsy clinical trials and from >12 years of experience in clinical practice show that lamotrigine is generally well tolerated.[21-27]

Table I. Summary of large, placebo-controlled clinical trials with lamotrigine[1,5,11,12,28-31]

Study no./ manufacturer's protocol no.	No. of patients randomised/no. of patients in the safety population	Study design	Patient population	Treatments	Duration of double-blind treatment (weeks)
Study 1: SCAB2003 (105-605)[12]	463/460	Randomised, double-blind, parallel-group, placebo-controlled	Maintenance treatment of currently or recently depressed patients with bipolar I disorder	Lamotrigine monotherapy 50, 200 or 400mg daily; lithium 0.8–1.1 mEq/L; placebo	76
Study 2: SCAB2006 (105-606)[11]	175/173	Randomised, double-blind, parallel-group, placebo-controlled	Maintenance treatment of currently or recently manic or hypomanic patients with bipolar I disorder	Lamotrigine monotherapy 100–400mg daily; lithium 0.8–1.1 mEq/L; placebo	76
Study 3: SCAA2012 (105-614)[5]	182/180	Randomised, double-blind, parallel-group, placebo-controlled	Maintenance treatment of patients with rapid-cycling bipolar I or II disorder	Lamotrigine monotherapy 100–500mg daily; placebo	26
Study 4: SCAB2005 (105-611)[28]	137/137	Randomised, double-blind, parallel-group, placebo-controlled	Maintenance treatment of patients with rapid-cycling bipolar I or II disorder	Lamotrigine adjunctive therapy 50–400mg daily; placebo	32
Study 5: SCAB2001 (105-602)[1]	195/194	Randomised, double-blind, parallel-group, placebo-controlled	Acute treatment of depression in patients with bipolar I disorder	Lamotrigine monotherapy 50mg or 200mg daily; placebo	7
Study 6: SCAA2010 (105-603)[29]	206/204	Randomised, double-blind, parallel-group, placebo-controlled	Acute treatment of depression in patients with bipolar I or II disorder	Lamotrigine monotherapy 100–400mg daily; placebo	10
Study 7: SCAA2008 (105-609)[30]	216/215	Randomised, double-blind, parallel-group, placebo-controlled	Acute treatment of manic or mixed episode in patients with bipolar I or II disorder	Lamotrigine monotherapy 50mg daily; lithium 0.8–1.3 mEq/L; placebo	3
Study 8: SCAB2009 (105-610)[31]	229/229	Randomised, double-blind, parallel-group, placebo-controlled	Acute treatment of manic episode in patients with bipolar I or II disorder	Lamotrigine adjunctive therapy 200mg daily; lithium 0.8–1.3 mEq/L; placebo	6

2. Safety and Tolerability of Lamotrigine in Bipolar Disorder Clinical Trials

Data from controlled clinical trials of patients with bipolar disorder constitute a key source of safety information about lamotrigine because they are derived from large samples of patients with the target illness, provide comparisons with placebo or other comparators, and are consistently obtained and categorised across studies. The safety and tolerability of lamotrigine were assessed in eight placebo-controlled clinical trials enrolling patients with bipolar disorder (table I).[1,5,11,12,28-31] Four of the studies evaluated lamotrigine as maintenance therapy,[5,11,12,28] and four evaluated lamotrigine as acute therapy for mood episodes.[1,29-31] All studies enrolled outpatients aged ≥18 years with a diagnosis of bipolar disorder as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.[32] All studies were of parallel-group design with double-blind treatment periods ranging from 3–76 weeks, during which lamotrigine was administered as monotherapy[1,5,11,12,29,30] or adjunctive therapy[28,31] at daily doses ranging from 50–500mg (table I). Some studies employed a flexible-dose regimen in which the dose was adjusted (to a maximum of 500mg) to optimise efficacy and/or tolerability. In all of the long-term monotherapy studies (studies 1–3),[5,11,12] the double-blind treatment period was preceded by an open-label, dose-titration phase during which the lamotrigine dose was escalated to a predefined target level and other psychotropic medications were gradually discontinued.

2.1 Demographics and Baseline Clinical Characteristics

The demographics and baseline clinical characteristics of patients in the eight placebo-controlled

Table II. Demographics, medication exposure and clinical characteristics of patients in eight placebo-controlled clinical studies in patients with bipolar disorder[1,5,11,12,28-31]

	Placebo	Lithium	Lamotrigine
No. of patients	685	280	827
No. of females (%)	363 (53)	152 (54)	468 (57)
No. of males (%)	322 (47)	128 (46)	359 (43)
Race (number of patients [%])			
White	577 (84)	226 (81)	690 (83)
Black	38 (6)	20 (7)	56 (7)
Asian	46 (7)	25 (9)	43 (5)
Hispanic	6 (<1)	3 (1)	11 (1)
Oriental	1 (<1)	0 (0)	2 (<1)
Other	17 (2)	6 (2)	25 (3)
Mean age (years)	40	41	41
Mean duration of treatment (days)	97	130	124
Minimum duration of exposure (no. of patients)			
<1 week	NA	280	827
4 weeks	NA	198	591
8 weeks	NA	115	396
16 weeks	NA	85	268
24 weeks	NA	77	240
36 weeks	NA	60	125
48 weeks	NA	52	106
52 weeks	NA	44	93
60 weeks	NA	18	50
76 weeks	NA	12	33
92 weeks	NA	1	1
100 weeks	NA	0	1
Average total daily dose in mg (SD)	NA	881 (242)	146 (114)
Total patient-years of exposure	181	100	280
Prestudy history of attempted suicide (%)			
Studies 1 and 2[11,12]	29	37	33
Study 3[5]	39	NA	27
Study 4[28]	41	NA	38
Study 5[1]	36	NA	32
Study 6[29]	37	NA	32
Study 7[30]	46	50	32
Study 8[31]	18	21	16
Pre-study history of hospitalisation for mood episode (%)			
Studies 1 and 2[11,12]	63	64	58
Study 3[5]	NR	NR	NR
Study 4[28]	72	NA	69
Study 5[1]	62	NA	44–51
Study 6[29]	47	NA	52
Study 7[30]	74	75	76
Study 8[31]	66	74	74

NA = not applicable; **NR** = not recorded; **SD** = standard deviation.

clinical trials did not differ among treatment groups and were comparable with those of the general population of patients with bipolar disorder.[33] Overall, slightly more than half of patients in each medication group were female, and approximately four out of five patients were White (table II). In nearly all studies, the majority of patients had a history of hospitalisation for a mood episode, and many patients (16–50%) had a history of one or more suicide attempts (table II).

2.2 Extent of Exposure

In the controlled clinical trials, lamotrigine was administered to 827 patients as monotherapy (six studies) or adjunctive therapy (two studies) at a mean dose of 146 mg/day (standard deviation [SD] = 114 mg/day) for periods ranging from <1 week to 100 weeks (mean 124 days [17.7 weeks]) for a total of 280 patient-years of exposure (table II).[1,5,11,12,28-31] Of the 190 patients receiving lamotrigine (in a blinded design) for at least 6 months (i.e. 27–30 weeks) and the 105 patients receiving lamotrigine (in a blinded design) for at least 1 year (i.e. 51–54 weeks), approximately half (n = 96 and n = 52, respectively) received a cumulative average total daily dose in the range of 200–400mg.

Lithium, given as a control treatment to 280 patients in four studies (studies 1, 2, 7 and 8), was administered at doses necessary to maintain plasma levels between 0.8–1.3 mEq/L.[11,12,30,31] The mean daily dose and duration of lithium treatment were 881mg (SD = 242mg) and 130 days, respectively, with a total of 100 patient-years of exposure. The number of patients receiving placebo (included as a control in all eight studies) was 685.

2.3 Laboratory Evaluations, Physical Examination and Vital Signs

Across the eight placebo-controlled trials there was no evidence of changes in mean laboratory parameters in patients receiving lamotrigine.[1,5,11,12,28-31] Across all treatment groups, few

Table III. Number of patients with adverse events[a] according to their treatment group across eight controlled clinical trials[1,5,11,12,28-31]

Adverse event	Number of patients (%)		
	placebo (n = 685)	lithium (n = 280)	lamotrigine (n = 827)
Headache	147 (21)	38 (14)	204 (25)
Nausea	102 (15)	45 (16)	118 (14)
Infection	73 (11)	22 (8)	87 (11)
Dizziness	52 (8)	20 (7)	77 (9)
Any rash	53 (8)	12 (4)	73 (9)
Somnolence	43 (6)	27 (10)	72 (9)
Pain	51 (7)	11 (4)	71 (9)
Back pain	30 (4)	7 (3)	56 (7)
Insomnia	47 (7)	20 (7)	61 (7)
Accidental injury	42 (6)	16 (6)	55 (7)
Influenza	52 (8)	16 (6)	49 (6)
Diarrhoea	63 (9)	39 (14)[b]	47 (6)
Dyspepsia	31 (5)	12 (4)	46 (6)
Mania (mania, hypomania, or mixed episodes)	27 (4)	9 (3)	45 (5)
Dry mouth	27 (4)	7 (3)	44 (5)
Fatigue	29 (4)	13 (5)	42 (5)
Vomiting	25 (4)	24 (9)[b]	40 (5)
Tremor	36 (5)	32 (11)[b]	41 (5)
Rhinitis	31 (5)	12 (4)	36 (4)
Abnormal thoughts	11 (2)	13 (5)[b]	11 (1)

a Adverse events reported in at least 5% of patients in any treatment group are listed regardless of their suspected cause.

b Statistically significantly higher versus placebo; differences were considered significant when $p < 0.05$ using the two-sided Fisher's exact test.

patients had significant changes in laboratory parameters or had laboratory abnormalities that were recorded as adverse events. In the controlled studies, there was no evidence that lamotrigine had any effect on physical examination results or vital signs (systolic and diastolic blood pressure and heart rate).

2.4 Adverse Events

Reports of adverse events comprised the primary source of information about tolerability of lamotrigine in controlled clinical trials. An adverse event was defined as any untoward medical occurrence reported by a patient or a physician-investigator during a clinical trial regardless of whether the patient or physician considered the event to be caused by the study medication. Adverse events occur and are reported at a background frequency whether or not active study medication is administered. In randomised, placebo-controlled studies, the incidence of adverse events in the placebo group provides an index of the background frequency of adverse events unrelated to medication.

The adverse-event profile of lamotrigine in the controlled clinical trials was generally comparable with that of placebo and did not differ between the short-term and the long-term clinical trials.[1,5,11,12,28-31] The most common adverse events with lamotrigine were headache, nausea and infection, which were reported with similar frequency between lamotrigine-treated patients and placebo-treated patients (table III). With the exception of diarrhoea, which was reported at a significantly ($p = 0.01$) higher incidence with placebo (9%) than with lamotrigine (6%), the incidences of individual adverse events did not significantly differ between lamotrigine and placebo. There was no evidence of an association between lamotrigine dose and adverse events; using the two-sided Cochran-Armitage trend test, there was no statistically significant trend in the incidence of individual adverse events with dose (placebo and lamotrigine 50mg, 200mg and 400mg; [table IV]).[34] Moreover, the incidence of individual adverse events generally did not differ between the lamotrigine group and the lithium group with the following exceptions. Compared with lithium, lamotrigine was associated with a higher incidence of headache (25% vs 14%) and rash (9% vs 4%).[34] Compared with lamotrigine, lithium was associated with a higher incidence of diarrhoea (14% vs 6%) and tremor (11% vs 5%).[34]

The percentage of patients in the eight controlled bipolar disorder studies with post-treatment adverse events was comparable between the placebo (13%), lithium (10%) and lamotrigine (11%) treatment groups.[34] With the exception of headache and nausea, post-treatment adverse events were reported in ≤1% of patients in any treatment group. Headache was reported in 1% of patients in the placebo and lamotrigine groups and 2% of patients in the lithium group.[34] The incidence of nausea was higher in the placebo group (2%) than in the lithium (<1%) and lamotrigine (<1%) groups.[34] No patient reported 'drug withdrawal effects' as a post-treatment adverse event.

Lamotrigine was well tolerated as adjunctive therapy during the open-label, dose-titration phase of the long-term monotherapy clinical trials (studies 1, 2 and 3)[5,11,12] when administered in combination

Table IV. Number of patients with adverse events[a] as a function of lamotrigine dose across eight controlled clinical trials[1,5,11,12,28-31]

Adverse event	Number of patients (%)				
	placebo (n = 685)	lamotrigine 50mg (n = 200)	lamotrigine 200mg (n = 259)	lamotrigine 400mg (n = 47)	lamotrigine flexible dosage (n = 321)
Headache	147 (21)	55 (28)	46 (18)	10 (21)	93 (29)
Nausea	102 (15)	28 (14)	31 (12)	8 (17)	51 (16)
Infection	73 (11)	14 (7)	24 (9)	5 (11)	44 (14)
Dizziness	52 (8)	15 (8)	14 (5)	7 (15)	41 (13)
Somnolence	43 (6)	14 (7)	16 (6)	5 (11)	37 (12)
Pain	51 (7)	15 (8)	18 (7)	2 (4)	36 (11)
Any rash	53 (8)	20 (10)	20 (8)	1 (2)	32 (10)
Insomnia	47 (7)	10 (5)	22 (8)	5 (11)	24 (7)

a Adverse events reported in at least 10% of patients in any dosage group are listed regardless of their suspected cause.

Table V. Number of patients (%) with a manic, hypomanic, or mixed episode reported as a serious adverse event[a] across eight controlled clinical trials[1,5,11,12,28-31,34]

	Lamotrigine (n = 827)	Placebo (n = 685)	Lithium (n = 280)
All mania[a]	27 (3)	18 (3)	7 (3)
Mania	21 (3)	15 (2)	7 (3)
Hypomania	2 (<1)	1 (<1)	0 (0)
Mixed	4 (<1)	3 (<1)	0 (0)

a A serious adverse event was defined as any untoward experience, regardless of its suspected cause, that was fatal, life-threatening or permanently disabling; was a congenital anomaly or cancer; or that required inpatient hospitalisation.

with other psychoactive medications during controlled studies of adjunctive therapy (studies 4 and 8).[28,31] At study entry, the majority of patients in all five studies were using concomitant psychoactive medications including lithium, valproate, carbamazepine, antidepressants, antipsychotics and benzodiazepines. The addition of lamotrigine to these regimens did not result in any new or unexpected adverse events or events suggestive of drug interactions. Overall, the incidence of adverse events with lamotrigine during the open-label dose-titration phases of these studies was similar to that observed in the later double-blind phases. In studies 1 and 2,[11,12] adverse events that occurred in at least 5% of patients and were numerically more common during the open-label titration phases compared with the double-blind monotherapy phases were: headache (25%), rash (11%), dizziness (10%), diarrhoea (8%), dream abnormality (6%) and pruritus (6%). These findings suggest that lamotrigine can be safely used in combination-therapy regimens.

2.5 Serious Adverse Events

A serious adverse event was defined as any untoward experience, regardless of its suspected cause, that was fatal, life-threatening or permanently disabling; was a congenital anomaly or cancer; or that required inpatient hospitalisation. Serious adverse events occurred infrequently in the placebo-controlled bipolar disorder studies.[34] The overall incidence of serious adverse events was comparable among patients receiving lamotrigine (8%), lithium (8%) or placebo (7%). The most common serious adverse event was mania (i.e. manic, mixed or hypomanic episode), reported by 3% of patients in each of the placebo, lamotrigine and lithium groups (table V). No other serious adverse event was reported by more than 2% of patients in a treatment group.

A total of four patients died while taking randomised treatment (three lamotrigine, one placebo)[34] in the eight controlled clinical trials. None of the deaths were considered to be related to study drug. Three of the deaths (two lamotrigine, one placebo) were suicide, which is consistent with the type of mortality often seen with bipolar disorder.

2.6 Pregnancies

A total of seven patients became pregnant while participating in the eight placebo-controlled clinical trials. Two of these patients were taking open-label lamotrigine, while five patients had been assigned to placebo.[34] Of the two pregnancies in the lamotrigine group, one resulted in the birth of a normal, healthy infant and one was electively terminated.[34] Of the pregnancies that occurred in the placebo group, four resulted in spontaneous abortions, and one was electively terminated.[34] There was no evidence of any adverse events associated with pregnancy in patients in the lamotrigine group. Lamotrigine is a pregnancy category C medication.

2.7 Discontinuations Because of Adverse Events

Across the eight controlled clinical trials, the percentage of patients withdrawn from the study because of an adverse event was comparable between the lamotrigine group (12%) and the placebo group (10%) and was higher in the lithium group (18%).[1,5,11,12,28-31,34] Among lamotrigine-treated patients, the most common adverse events leading to withdrawal from the study and the only ones leading to withdrawal of >1% of patients were rash (3%) and mania (2%). The finding that rash was the most common adverse event leading to withdrawal is not surprising given that the study protocol specified that patients with a rash were to be discontinued

unless the rash was clearly unrelated to study medication. Among lithium-treated patients, the most common adverse events leading to withdrawal from the study and the only ones leading to withdrawal of >1% of patients were nausea (4%), tremor (3%), somnolence (2%), dizziness (2%) and mania (2%). No individual adverse event led to the withdrawal of >1% of patients in the placebo group.

2.8 Adverse Events of Special Interest in Bipolar Disorder

Several specific adverse events are of interest in evaluating lamotrigine safety because the events have been previously reported in association with bipolar disorder, with lamotrigine given for epilepsy, or with other medications used to treat bipolar disorder. In the placebo-controlled clinical trials,[1,5,11,12,28-31,34] the incidence of such adverse events – which included suicide, mania, rash, sexual adverse effects and fluctuations in bodyweight – was low in the lamotrigine group and was generally comparable between lamotrigine and placebo.

2.8.1 Suicide

Suicide and suicide attempts are common among patients with bipolar disorder: 20–50% of patients attempt suicide at least once, and 15% commit suicide during their lifetimes.[35] It is crucial that a drug prescribed for bipolar disorder does not increase the risk of suicide or the incidence of suicide attempts. Across the controlled studies of lamotrigine in bipolar disorder,[1,5,11,12,28-31,34] there were no suicide events among lithium-treated patients, two suicide events among lamotrigine-treated patients (two suicides per 280 patient-exposure years, or 0.7% per year), and one suicide event among placebo-treated patients (one suicide per 181 patient-exposure years, or 0.6% per year). The rate of suicide attempts was 1.8% per year with lamotrigine and 1.1% per year with placebo. The rates of suicide and suicide attempts with lamotrigine were not statistically significantly different (1-sided p-value) compared with placebo. These rates were somewhat lower than rates observed in a recent review of placebo-controlled clinical trials in depressed patients.[36] Although the low number of suicide events renders comparisons difficult, these data suggest that lamotrigine does not increase the risk of suicide or suicide attempts in patients with bipolar disorder.

2.8.2 Mania

Antidepressants, which are often used to manage acute depressive symptoms in bipolar disorder, can destabilise mood by inducing mania (i.e. by causing manic or affective 'switches') or cycle acceleration (i.e. rapidly alternating manic and depressive episodes).[13,37-39] Unlike antidepressants, lamotrigine does not appear to be associated with destabilisation of mood. Across all controlled studies, the incidences of adverse events of mania, hypomania, or mixed episodes were low; were comparable among the lamotrigine and placebo groups; and did not vary with dose of lamotrigine (table VI). The incidences of serious adverse events of mania, hypomania or mixed episodes were also low (table V). Pooled results of the two 18-month monotherapy studies[11,12] considered separately mirror those from the pooled database of all placebo-controlled studies (table VII) [these two studies were designed to be combined for analysis]. Furthermore, in the 18-month monotherapy studies, lamotrigine did not precipitate or worsen manic symptoms as measured by the Mania Rating Scale; and the time to intervention for mania or to an adverse event of mania did

Table VI. Number of patients (%) with a manic, hypomanic or mixed episode reported as an adverse event[a] across eight controlled clinical trials[1,5,11,12,28-31,34]

	Lamotrigine (all doses) [n = 827]	Lamotrigine 50mg (n = 200)	Lamotrigine 200mg (n = 259)	Lamotrigine 400mg (n = 47)	Lamotrigine flexible dose (n = 321)	Placebo (n = 685)	Lithium (n = 280)
All mania[b]	45 (5)	12 (6)	13 (5)	2 (4)	18 (6)	27 (4)	9 (3)
Mania	28 (3)	8 (4)	11 (4)	1 (2)	8 (2)	18 (3)	8 (3)
Hypomania	11 (1)	1 (<1)	1 (<1)	0 (0)	9 (3)	7 (1)	2 (<1)
Mixed	6 (<1)	3 (2)	1 (<1)	1 (2)	1 (<1)	4 (<1)	0 (0)

a Serious adverse events were also included in the frequency counts of adverse events.

b All mania is incidence of manic plus hypomanic plus mixed episodes.

Table VII. Number of patients (%) with a manic, hypomanic or mixed episode reported as an adverse event[a] for studies 1 and 2[11,12][b]

	Lamotrigine (n = 227)	Placebo (n = 190)	Lithium (n = 166)
All mania[c]	11 (5)	13 (7)	6 (4)
Mania	9 (4)	11 (6)	6 (4)
Hypomania	0 (0)	0 (0)	1 (<1)
Mixed	2 (<1)	3 (2)	0 (0)

a Serious adverse events were also included in the frequency counts of adverse events.

b Study 1 was an 18-month monotherapy trial conducted in depressed or recently depressed patients with bipolar I disorder. Study 2 was an 18-month monotherapy trial conducted in manic or recently manic patients with bipolar I disorder.

c All mania is incidence of manic plus hypomanic plus mixed episodes.

not differ between lamotrigine and placebo. These data are consistent with a lack of mood destabilisation with lamotrigine treatment.

2.8.3 Rash

In early epilepsy clinical trials, lamotrigine was associated with rare occurrences of rash leading to hospitalisation and discontinuation or rash reported to be Stevens-Johnson syndrome.[23,26] These cases, occurring in 0.3% of adults in epilepsy clinical trials, were almost always observed within the first few weeks of initiation of lamotrigine.[23,26] In post-marketing experience, rare cases of toxic epidermal necrolysis and/or rash-related deaths have been reported in association with lamotrigine therapy; however, their numbers are too few to permit a precise estimate of the rate.[26] In response to assessments suggesting that the risk of rash associated with lamotrigine may be increased with the use of high initial doses, rapid dose-escalation, and concomitant administration of valproate,[26,40] dosage recommendations intended to minimise the risk of serious rash were employed in controlled clinical trials of lamotrigine in bipolar disorder. Lamotrigine, like all anticonvulsants, should be initiated at a low dose and increased slowly to an effective maintenance dose; and lamotrigine dose should be adjusted depending on whether concomitant valproate is administered (table VIII). Adherence to the recommended dosage schedules is considered important in minimising the incidence of rash.[23] The immune system tolerance to lamotrigine is lost following interruption in dosage of ≥1 week. Therefore, patients should be advised to re-titrate lamotrigine following any interruption in therapy of more than a few days.

In controlled bipolar disorder clinical trials, the incidence of any rash with lamotrigine (9% of 827 patients) did not differ significantly from that with placebo (8% of 685 patients).[1,5,11,12,28-31,34] These adverse events categorised as rash encompassed both serious and non-serious cases and included those reported as rash, urticaria, erythema multiforme, maculopapular rash, bullous eruption, pustular rash or Stevens-Johnson syndrome.

Serious rash, which was defined as any rash associated with hospitalisation and discontinuation of lamotrigine or rash reported as Stevens-Johnson syndrome or toxic epidermal necrolysis, was not observed in patients randomised to lamotrigine (0% of patients) but occurred in one patient receiving placebo (0.06% of patients) in the placebo-controlled clinical trials. Across all controlled and uncontrolled bipolar disorder studies in the lamotrigine development programme, serious rash was reported among three of 2272 (0.1%) patients.[34] All three patients were receiving open-label lamotrigine. Two of these patients had a rash associated with hospitalisation and discontinuation of lamotrigine, and the third patient had a rash that was reported as mild Stevens-Johnson syndrome and that did not lead to hospitalisation. All three rashes resolved after the discontinuation of lamotrigine. A review by independent dermatological experts determined that none of the three cases were Stevens-Johnson syndrome.[34] Thus, while serious rash did occur during the bipolar disorder clinical trials, its incidence was very low. In all cases, resolution was uneventful. This finding supports the appropriateness of the dose-escalation protocol used in bipolar disorder clinical trials. No new risk factors for lamotrigine-associated serious rash were identified during the bipolar disorder clinical trials programme.

2.8.4 Sexual Adverse Effects

Sexual adverse effects are common with many bipolar disorder treatments, particularly the selec-

Table VIII. Recommended dose-escalation schedule for adults treated for bipolar disorder[a]

Treatment regimen	Weeks 1–2	Weeks 3–4	Week 5	Target stabilisation dose (week 6)[b]
Lamotrigine given as monotherapy or adjunctive therapy with drugs not known to interact with lamotrigine (e.g. lithium)	25mg (once a day)	50mg (once a day or two divided doses)	100mg (once a day or two divided doses)	200mg range 100–400mg (once a day or two divided doses)
Lamotrigine given as adjunctive therapy with enzyme inhibitors (e.g. valproate)	12.5mg (25mg given on alternate days)	25mg (once a day)	50mg (once a day or two divided doses)	100mg maximum daily dose of 200mg (once a day or two divided doses)
Lamotrigine given as adjunctive therapy with enzyme inducers (e.g. carbamazepine, phenobarbital) in patients not taking valproate	50mg (once a day or two divided doses)	100mg (two divided doses)	200mg (two divided doses)	300mg in week 6 increasing to 400mg if necessary in week 7 (two divided doses)

a In patients taking psychotropic medicines where the pharmacokinetic interaction with lamotrigine is currently not known, the dose escalation protocol recommended for lamotrigine with concurrent valproate should be used.

b The target stabilisation dose varies depending on clinical response.

tive serotonin reuptake inhibitors and other medications affecting serotonergic function.[41,42] Lamotrigine was not associated with sexual adverse effects in the placebo-controlled clinical trials. Sexual adverse events of anorgasmia, impotence, and ejaculation disorder were reported by <1% of patients treated with lamotrigine and occurred at an incidence comparable to that with placebo (<1%).

2.8.5 Fluctuations in Bodyweight

Many pharmacotherapies for bipolar disorder, including lithium, valproate and the atypical antipsychotics, frequently cause clinically significant fluctuations in bodyweight.[43-48] The adverse event data from the controlled trials of lamotrigine suggest that it is not associated with fluctuations in bodyweight.[1,5,11,12,28-31] Weight gain was reported as an adverse event by 2% of lamotrigine-treated patients, 1% of lithium-treated patients and 2% of placebo-treated patients. Weight loss was reported as an adverse event by <1% of lamotrigine-treated patients and <1% of placebo-treated patients.

These adverse event data are complemented by data from the two 18-month controlled clinical trials (studies 1[12] and 2[11]), in which lamotrigine monotherapy was not associated with clinically significant changes from baseline weight. After 18 months of randomised treatment, lamotrigine-treated patients had a mean weight decrease of 2.2kg while placebo-treated patients had a mean weight increase of 1.2kg.

2.9 Drug Interactions

Several additional studies have been conducted to assess potential drug interactions between lamotrigine and other medications commonly used in the management of bipolar disorder. The risk of drug interactions between lamotrigine and bupropion or lithium appears to be negligible. In a study conducted in healthy volunteers, steady-state bupropion sustained-release (SR) [150mg twice daily] did not significantly affect the single-dose pharmacokinetics of lamotrigine 100mg.[49] Likewise, the pharmacokinetics of lithium (administered as anhydrous lithium gluconate 2g twice daily for 6 days) were not affected by the concomitant administration of lamotrigine 100mg daily, and both medications were well-tolerated in combination.[50] Furthermore, in preclinical studies, lamotrigine did not inhibit the activity of cytochrome P450 (CYP) 2D6; and metabolism of the drug was not affected by clinically relevant concentrations of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine, risperidone, sertraline or trazodone.[34]

Previous studies in patients with epilepsy establish that lamotrigine interacts with enzyme-inducing anticonvulsants as well as the enzyme-inhibiting

anticonvulsant valproate.[51,52] Lamotrigine is eliminated more rapidly in patients taking enzyme-inducing anticonvulsants – including carbamazepine, phenytoin, phenobarbital, and primidone – than in patients who are not.[26] Moreover, valproate given with or without enzyme-inducing antiepileptic drugs reduces the clearance and approximately doubles the elimination half-life of lamotrigine.[26] Lamotrigine is metabolised almost exclusively by glucuronidation, which is also the primary pathway for elimination of valproate. To minimise the potential for clinically significant interactions involving lamotrigine and these drugs, the recommended starting and maintenance doses of lamotrigine are adjusted based on whether or not concomitant anticonvulsants are administered (table VIII). The lamotrigine prescribing information specifies that the lamotrigine dose should be reduced when administered with anticonvulsants with enzyme-inhibiting activity (e.g. valproate) and increased when administered with anticonvulsants with enzyme-inducing activity (e.g. carbamazepine).[26]

3. Conclusions

The results of controlled clinical trials in which 827 patients with bipolar disorder were given lamotrigine as monotherapy or adjunctive therapy for up to 18 months demonstrated that lamotrigine is well tolerated with an adverse-event profile generally comparable to that of placebo. The most common adverse event with lamotrigine was headache, which was reported with comparable frequency in the placebo group. Unlike some other pharmacotherapies for bipolar disorder, lamotrigine did not appear to destabilise mood; and it was not associated with sexual adverse effects, weight gain or withdrawal symptoms even after long-term treatment. Few patients experienced serious adverse events with lamotrigine, and the incidence of therapy withdrawals because of adverse events was low. Serious rash was reported very rarely (0.1% incidence) in the clinical development programme including both controlled and uncontrolled clinical trials. When rash did occur, it resolved uneventfully upon discontinuation of study medication. These findings – considered in the context of efficacy data showing lamotrigine to be particularly effective for bipolar depressive episodes, as maintenance therapy for patients with bipolar I disorder and as maintenance therapy for patients with rapid-cycling bipolar II disorder – establish lamotrigine as an important and well tolerated addition to the psychotropic armamentarium.

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