Research Review

Lamotrigine [Lamictal®] review

Bipolar I disorder
At least one episode of mania (current or past). Usually (but not necessarily) episodes of depression.

Bipolar II disorder
Episodes of hypomania and depression. No manic episodes.

Mania
Pathologically elevated or euphoric mood (often also irritable) lasting at least one week. There is evidence of marked impairment of functioning. Delusions or hallucinations may occur and hospitalisation may be required.

Hypomania
Pathologically elevated (or irritable) mood lasting at least 2–4 days. While mood and behaviour are distinctly different from normal, functioning is not severely impaired. Psychotic features do not occur and hospitalisation is unnecessary.

About the reviewer -
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Charles Hornabrook was born in Wellington, New Zealand and trained in Victoria University, Wellington (intermediate) and Otago University, Dunedin (medicine). He completed his postgraduate psychiatry training in Wellington, during which time he held a lecturer position (Department of Psychological Medicine, Otago University) and undertook research on interview skills training. He undertook a consultant position in neuropsychiatry in Newcastle, NSW and then became clinical director of the Hunter Valley Community Mental Health Service over a period of 3 years. After this he returned to Wellington in 2001 to take up his present positions as consultant psychiatrist in Consultation – Liaison Psychiatry and Director of Training for the RANZCP training programme in the greater Wellington region. His main interests are in outcome measures, clinical education, consultation-liaison psychiatry (Palliative care, treatment resistant asthma, neurological conditions and chronic illnesses) and Old Age Psychiatry.

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This and other Research Review publications are intended for New Zealand medical professionals.

Bipolar Disorder
Bipolar disorders (see opposite) are among the most prevalent and potentially severe psychiatric disorders. Characterised by significant mood swings (manic or major depressive episodes) and a tendency to remission and recurrence, these chronic conditions imply a high degree of morbidity and incapacity, frequently disrupting work, school, family, and social life[1-3] and without effective treatment, the illness is associated with an increased risk of suicide.[2,4] Bipolar disorders (BD) are one of the leading causes of worldwide disability, especially in the 15–44 years age group; they are deemed responsible for 2.5% of total global years of life with disability (YLD).[5]

The lifetime prevalence rate of bipolar spectrum disorder worldwide is traditionally estimated to be about 1% of the population;[5,6] new evidence suggests that the rate is as much as 5% and in the US, BD is associated with 96.2 million lost workdays and USD$14.1 billion in salary-equivalent lost productivity per year.[7]

Current Treatment Approaches
The aims of intervention are to alleviate mania and bipolar depressive symptoms; to prevent relapse and suicide; to optimise social and occupational functioning; and to improve quality of life, with minimal adverse effects of treatment.[8]

Recent evidence supports extended-release carbamazepine, or a combination of lithium or valproate semisodium plus an atypical antipsychotic as the most effective approach for acute mania;[9-11] lithium, lamotrigine, olanzapine, and aripiprazole are options for maintenance therapy.[9,11-13] Several evidence-based guidelines recommend lamotrigine for the prophylaxis of mild to moderate bipolar depression;[3,11,14-18] there is consensus that in bipolar depression, antidepressants should be used only in combination with antimanic agents in order to avoid switching of phases.[19-21] New data support quetiapine monotherapy as a first-line option in the management of bipolar depression.[11] Lithium and lamotrigine monotherapy, olanzapine plus selective serotonin reuptake inhibitors (SSRI), and lithium or valproate plus SSRI/bupropion are the other first-line options.[11-13]

During the maintenance phase commonly used agents such as lithium, valproate semisodium or olanzapine appear to be most effective in preventing manic relapses; lamotrigine is more effective in preventing depressive relapses.[11,12] Lithium plus valproate may be more effective than lithium alone in preventing affective relapses.[12] There is recent evidence to support the combination of olanzapine and fluoxetine as a second-line maintenance therapy for bipolar depression.[11] Similarly, the combination of lithium or valproate plus olanzapine seems to be more effective than monotherapy with a mood stabiliser in preventing manic episodes.[12] New data also support quetiapine monotherapy as a second-line option for the management of acute bipolar II depression.[11]

Various forms of psychosocial interventions (cognitive-behavioural therapy, psychoeducation or family-focused therapy) have proven efficacious as adjunctive treatments in the prevention of all relapses of bipolar disorders, regardless if manic or depressive relapses.[22-24] When used in conjunction with pharmacotherapy, these interventions may prolong time to relapse, reduce symptom severity, and increase medication adherence. Inadequately treated cases are associated with increased costs of care, as well as a higher burden of illness for the individual, families, and caregivers.[25]

About lamotrigine
Lamotrigine is a phenyltriazine derivative and a well established anticonvulsant agent recommended in the 2002 American Psychiatric Association guidelines as a first-line treatment for acute depression in bipolar disorders and as one of several options for maintenance therapy.[14] The mechanism by which lamotrigine alleviates bipolar disorders is not known; its primary mode of action involves inhibition of voltage-dependent sodium channels, thereby modulating presynaptic transmitter release of glutamate.[26] It is thought that the beneficial effects may be as a result of secondary or tertiary drug actions on intracellular mechanisms, or signalling pathways in bipolar disorders.[26]

Lamotrigine has proven effective as maintenance therapy for patients with bipolar I disorder: significantly delaying time to intervention with additional pharmacotherapy or ECT for any mood episode (mania, hypomania, depression and mixed episodes); prophylaxis of bipolar depressive episodes; prolonging time to intervention for a new depressive episode; and delaying time to intervention for mania.[27,28] In a recent open-label medication augmentation trial for treatment-resistant bipolar depression, lamotrigine appeared to be superior to inositol and risperidone.[29]

Data reviewed from 827 patients with bipolar disorders who received lamotrigine as monotherapy or adjunctive therapy for periods of between <1 week to 100 weeks for a total of 280 patient-years of exposure demonstrated good tolerability of lamotrigine, with an adverse-event profile generally comparable with that of placebo.[30] Similarly, in a large heterogeneous sample of patients taking an average of 2.4 concomitant prescription psychiatric medications in a real-world setting, lamotrigine proved to be well tolerated.[31] Serious rash is the main safety concern with lamotrigine. Major risk factors for serious rash are high initial doses of lamotrigine, rapid dose escalation, and concomitant valproate use.[31]

In New Zealand, lamotrigine is approved for the prophylaxis of bipolar depressive episodes; for funding criteria see www.pharmac.govt.nz.

Major studies on safety and efficacy of lamotrigine

A placebo–controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder[27]

Authors: Bowden CL et al

Summary: Both lamotrigine and lithium were superior to placebo for the prevention of relapse or recurrence of mood episodes in patients with bipolar I disorder who had recently experienced a manic or hypomanic episode.

Method: 349 patients met screening criteria and entered an 8- to 16-week open-label phase during which treatment with lamotrigine was initiated as adjunctive therapy or monotherapy and other psychotropic drugs were discontinued. The 175 patients who responded to lamotrigine were randomised to double-blind maintenance treatment with lamotrigine (100–400 mg/day; n=59), lithium (titrated to serum levels of 0.8–1.1 mEq/L; n=46), or placebo (n=70), for up to 76 weeks. The primary efficacy endpoint was the time to intervention (addition of pharmacotherapy or ECT) for any mood episode.

Results: Both lamotrigine and lithium were significantly superior to placebo on time to intervention for any mood episode; lamotrigine and lithium did not differ from each other on this parameter (p=0.46). Median survival data are shown in table opposite. Lamotrigine, but not lithium, was superior to placebo at prolonging the time to a depressive episode; lamotrigine and lithium did not differ from each other on this parameter (p=0.36). Lithium, but not lamotrigine, was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode; a trend favoured lithium over lamotrigine on this parameter (p=0.09). The most common treatment-emergent adverse event reported for lamotrigine was headache. The majority of adverse events were mild to moderate in intensity and resolved without sequelae.

Comment: This study confirmed the efficacy and tolerability of lamotrigine and lithium in preventing relapse or recurrence of mood disorders in patients who had recently experienced a manic or hypomanic episode. It would suggest that lamotrigine be considered as an additional mood stabiliser particularly for the bipolar patient with a recent depressive episode and is probably easier to monitor than lithium (the gold standard maintenance treatment). The main adverse effects with lamotrigine were headache and rash.

Median survival data

	Lamotrigine (n = 58)	*P* value vs Placebo	Lithium (n = 44)	*P* Value vs Placebo	Placebo (n = 69)
Survival in study					
Survival, median (95% CL)	85 (44, 142)	.03	101 (59, 202)	.07	58 (34, 108)
No. of events	40		34		58
Time to intervention					
Mood episode					
Survival, median (95% CL)	141 (71, >547)	.02	292 (123, >547)	.003	85 (37, 121)
No. of events	28		18		49
Mania					
Survival, median (95% CL)	NE	.28	NE	.006	203 (108, >547)
No. of events	20		8		28
Depression					
Survival, median (95% CL)	NE	.02	NE	.17	269 (183, >547)
No. of events	8		10		21

Abbreviations: CL, confidence limits; NE, not evaluable when probability of survival fails to reach 50%

A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder[28]

Authors: Calabrese JR et al

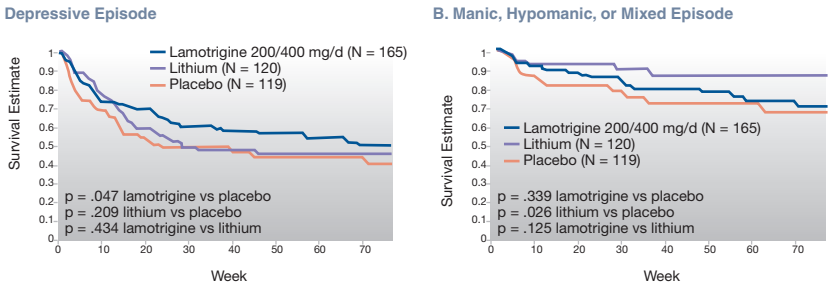
Summary: Lamotrigine and lithium were both superior to placebo for the prevention of mood disorders in patients with bipolar I disorder who had recently experienced a depressive episode. Lamotrigine was primarily effective in preventing depressive episodes and lithium primarily effective in preventing manic episodes.

Method: 966 patients who met screening criteria entered an 8- to 16-week open-label phase, during which lamotrigine (titrated to 200 mg/day) was added to current therapy and concomitant drugs were gradually withdrawn. 463 patients stabilised on lamotrigine were then randomised to double-blind maintenance treatment with lamotrigine (50, 200, or 400 mg/day; n=221), lithium (titrated to serum levels of 0.8–1.1 mEq/L; n=121), or placebo (n=121), for up to 18 months. The primary outcome was time from randomisation to intervention (addition of pharmacotherapy) for any mood episode (depressive, manic, hypomanic, or mixed).

Results: Both lamotrigine and lithium were significantly superior to placebo at delaying time to intervention for any mood episode; lamotrigine and lithium did not differ from each other on this measure (p=0.915). Median survival times for lamotrigine, lithium, and placebo were 200, 170, and 93 days, respectively. Interventions for emerging symptoms of depression out numbered interventions for manic symptoms by nearly 3:1. Lamotrigine, but not lithium, was statistically superior to placebo at delaying intervention for depressive symptoms; lamotrigine and lithium did not differ from each other on this measure (p=0.434). The estimated proportions of patients who were intervention-free for depression at 1 year were 57%, 46%, and 45% for lamotrigine, lithium, and placebo, respectively (full survival data are shown in Figure 1). Lithium, but not lamotrigine, was statistically superior to placebo at prolonging the time to intervention for a manic or hypomanic episode; lamotrigine and lithium did not differ from each other on this measure (p=0.125). The estimated proportions of patients without intervention for mania at 1 year were 77%, 86%, and 72% for lamotrigine, lithium, and placebo, respectively. Across all treatment groups, the most frequent adverse event was headache. Neither drug was associated with worsening symptoms of any phase of the illness.

Comment: This study solidified the findings that lamotrigine could be efficacious when titrated slowly to usually 200 mg/day and was possibly more effective than lithium in treating depressive symptoms in addition to delaying time to relapse to episodes of depression. Once again the most troublesome side effect for lamotrigine was rash (one patient experienced a mild Stevens Johnson syndrome in the open-label part of the study), which would necessitate cessation of lamotrigine as the most likely culprit. Lithium was equally effective as lamotrigine in prevention of mood episodes, but more effective against mania rather than depression.

Time to Intervention for (A) Depressive Episode and (B) Manic, Hypomanic, or Mixed Episode: Kaplan-Meier Survival Curves



A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder[33]

Authors: Goodwin GM et al

Summary: In this pooled analysis of data from the two above-mentioned clinical trials, lamotrigine and lithium each stabilised mood by delaying the time to treatment for a mood episode, in differing and potentially complementary ways; lamotrigine was more effective than placebo for preventing depression, and lithium was more effective for mania.

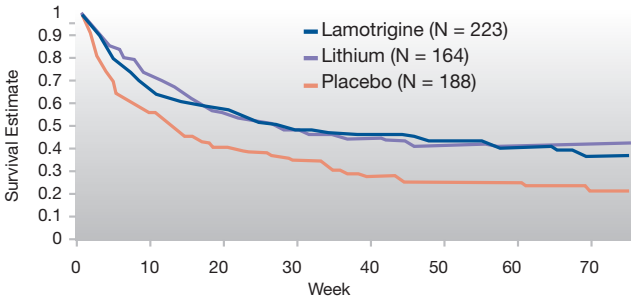
Method: The two 18-month double-blind trials were prospectively designed for combined analysis of lamotrigine and lithium versus placebo as maintenance treatment for bipolar I disorder in recently depressed or manic patients. A total of 1315 patients with bipolar I disorder entered the initial open-label phase, and 638 were stabilised and randomised to receive double-blind lamotrigine (n=280), lithium (n=167), or placebo (n=191). The primary outcome was the time to intervention for any mood episode.

Results: Both lamotrigine and lithium were superior to placebo for time to intervention for any mood episode (see Figure opposite). Median times to intervention were 86, 184, and 197 days for the placebo, lithium, and lamotrigine groups respectively, lamotrigine and lithium were not statistically different. Lamotrigine was superior to placebo for time to intervention for depression (median survival: placebo, 270 days; these values were not calculable for the lithium or lamotrigine group); again, lamotrigine and lithium were not statistically different. Lithium and lamotrigine were statistically superior to placebo for time to intervention for mania (median survival not calculable for any group). Results of additional analyses adjusting for index mood were similar; however, only lithium remained superior to placebo for time to intervention for mania. There was no evidence that either lithium or lamotrigine caused affective switch. Overall, the incidence of adverse events associated with lamotrigine was similar to that seen with placebo. However, more diarrhoea and tremor were reported by patients treated with lithium than those treated with lamotrigine ($p<0.05$).

Comment: The international expert in Guy Goodwin has combined with the lead authors and experts to combine the data of the two previous studies and confirm the relative efficacy for lamotrigine in delaying onset to further depressive episode and lithium delaying relapse to further manic episode. Interestingly the index episode was largely predictive of the same polarity of symptoms on relapse and would be useful for doctors and patients being vigilant for early symptoms and selection of long-term drug treatments. Lithium and lamotrigine have a place in stabilising mood, in different and possibly complimentary ways and should be considered in the management of this serious and recurrent psychiatric condition.

Time to Intervention for a Mood Episode

Any Mood Episode



Lamotrigine vs. placebo, p < .001; lithium vs. placebo, p < .001; lamotrigine vs. lithium, p=. 629

Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone[29]

Authors: Nierenberg AA et al

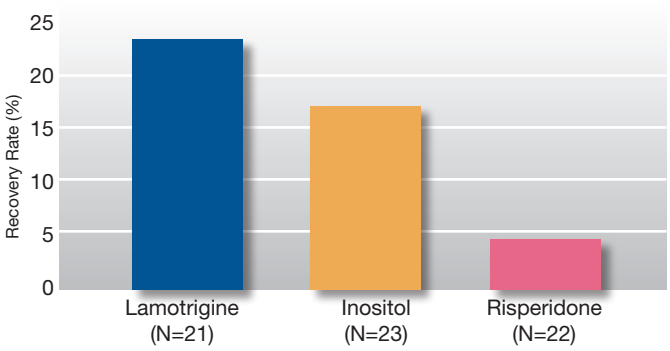
Summary: In this comparison of three possible supplementary treatments for patients with treatment-resistant bipolar depression, lamotrigine appeared advantageous over inositol and risperidone.

Method: The NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) enrolled 66 patients with bipolar I or bipolar II disorder, all of whom were in a current major depressive episode that was nonresponsive to a combination of adequate doses of established mood stabilisers plus at least one antidepressant. Patients were randomised to receive open-label adjunctive treatment with lamotrigine, inositol, or risperidone for up to 16 weeks. The primary outcome was the rate of recovery within equipoise randomisation strata. Recovery was defined as no more than two symptoms meeting DSM-IV threshold criteria for a mood episode and no significant symptoms present for 8 weeks.

Results: For the primary outcome measure (protocol-defined recovery within equipoise randomisation strata), no significant between-group differences were observed for lamotrigine, inositol, and risperidone. However, overall recovery rates were 23.8% for lamotrigine, 17.4% for inositol, and 4.6% for risperidone (see Figure opposite). Lamotrigine was associated with lower depression ratings and Clinical Global Assessment of Functioning scores, compared with inositol and risperidone. In addition, compared with patients randomised to inositol or risperidone, patients randomly assigned to lamotrigine remained in the randomised phase of treatment for a significantly longer time.

Comment: This study reminds one of the difficulties of treating this treatment-resistant bipolar depression effectively with currently available medications. In addition, no patients accepted ECT rather than the medication trial, possibly as part of the entry criteria into the study and perhaps the relative stigma and fear of ECT as treatment. Of the three agents compared none of the medications was significantly more effective than the other in promoting recovery, indicating that treatment-resistant bipolar depression is a serious clinical problem with inadequate medical choices for the patient and clinician. Lamotrigine was superior to the other two agents in antidepressant effect but not strikingly so in terms of what matters to the patient, namely, recovery.

Recovery Rates of Patients With Treatment-Resistant Bipolar Depression Randomly Assigned to Open-Label Antidepressant Augmentation With Lamotrigine, Inositol, or Risperidone.



Recovery was defined as no more than two symptoms meeting DSM-IV threshold criteria for a mood episode and no significant symptoms present for 8 weeks.

Rash in multicentre trials of lamotrigine in mood disorders: clinical relevance and management[34]

Authors: Calabrese JR et al

Summary: Rates of serious rash associated with lamotrigine were rare, in this analysis of rash rates in clinical trials of lamotrigine in DSM-IV unipolar depression or bipolar disorder.

Method: Rates of lamotrigine-related rash were retrospectively analysed from 12 multicentre studies, including 1 open-label study, 7 randomised controlled acute trials, and 4 randomised controlled maintenance trials from 1996 to 2001.

Results: In controlled settings, 1198 patients received lamotrigine and 1056 patients received placebo; rates of benign rash (e.g. isolated, self-limited eruptions without internal organ involvement) occurred in 8.3% and 6.4% of lamotrigine and placebo-treated patients, respectively (see table opposite). Whereas no cases of serious rash occurred with lamotrigine or with comparators, one case (i.e. requiring discontinuation of medication and hospitalisation) occurred in placebo-treated patients. In the open-label setting, 1955 patients received lamotrigine. Overall, the lamotrigine-related rash rate was 13.1%. Two cases of serious lamotrigine-related serious rash (0.1%) occurred and one lamotrigine recipient developed nonserious Stevens-Johnson syndrome, which did not require hospitalisation. There were no reports of toxic epidermal necrolysis related to lamotrigine in any setting.

Comment: Rates of rash were between 8.3% and 13.1% in controlled trial and open-label settings, respectively. Serious rash was rare in the period described; only two cases (out of approximately 3000 patients) were seen and none was life threatening. Recommendations to start low and go slow in commencing lamotrigine would appear to reduce the risk of serious rash significantly. One should warn the patient and maintain clinical vigilance for rashes that might require cessation of lamotrigine. In terms of adverse event and general side effects, lamotrigine would still be seen as competitive with the other mood stabilisers, lithium, valproate and carbamazepine as choice in management of this serious and often refractory bipolar disorder.

Summary of Rash data in Controlled and Open-Label Trials of Lamotrigine in Mood Disorders

Studies/Phases	Treatment	N	Rash		
			No. of Cases	%	No. of Cases of Serious Rash
All controlled studies	LTG	1198	100	8.3	0
	PBO	1056	68	6.4	1
	Comparators	427	26	6.1	0
Monotherapy studies	LTG	686	66	9.6	0
	PBO	631	45	7.1	0
	Comparators	183	17	9.3	0
Add-on studies	LTG	142	11	7.7	0
	PBO	146	11	7.5	1
	Li	78	0	0	0
Monotherapy continuation phases	LTG	370	23	6.2	0
	PBO	279	12	4.3	0
	Li	166	9	5.4	0
All open-label phases	LTG	1955	257	13.1	2

Abbreviations: Li = lithium, LTG = lamotrigine, PBO = placebo.

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