

The role of lamotrigine in the management of bipolar disorder

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Abstract: Lamotrigine has emerged with a distinct place in the pharmacological treatment of bipolar disorder, with the potential to treat and prevent bipolar depression, which is the dominant and arguably most disabling and under-treated phase of the illness. This review examines the published clinical trials of lamotrigine in bipolar treatment. While the data supports its tolerability and safety, the strongest evidence for its efficacy lies in the prevention of bipolar depression, with weaker evidence for the treatment of acute bipolar depression, refractory unipolar and bipolar depression, and rapid cycling bipolar disorder. The total number of published well designed trials is small, even the maintenance evidence is derived from two studies. However, this relative inadequacy compares favorably with the alternative treatment options for bipolar depression, which are marked by poor efficacy or risk of polarity switch. The designation of lamotrigine as first-line treatment for bipolar depression prophylaxis should be done in cognizance of this context, and it would seem prudent to await greater evidence of efficacy before designating lamotrigine as first-line treatment for other bipolar indications. Further randomized controlled trials are required to consolidate the available findings and to explore the boundaries of lamotrigine's efficacy, which may encompass the soft spectral disorders.

Keywords: Lamotrigine, bipolar disorder, bipolar depression, clinical trials, efficacy

Introduction

Bipolar disorder has been estimated to have a population lifetime prevalence of between 0.3%–1.5% (Weissman et al 1996), but this figure based on DSM-III criteria may belie the extent of the full spectrum. The highly recurrent course of bipolar disorder (Angst and Sellaro 2000), its poor functional outcomes (Mitchell et al 2004) and over-representation in the completed suicide population (Rihmer and Kiss 2002) have been well-documented in the literature. In particular, more recent understanding of the natural course of bipolar disorder has highlighted its disease burden and challenged its historical conceptualization as an episodic illness with full inter-episode recovery (Kraepelin 2002). Judd and colleagues (Judd et al 2002) have demonstrated that over the course of 12.8 years, their cohort of 146 patients with bipolar I disorder were symptomatic 47.3% of the time. Significantly, depressive symptoms (present over 31.9% of the total follow-up period) predominated over symptoms of any other phases. Frequent changes in symptom levels and polarity, and the predominance of subsyndromal and minor symptoms were also demonstrated. Paykel et al (2006) reported comparable trends in 204 patients with bipolar I disorder, studied over 18 months. In bipolar II disorder, symptomatic illness has been estimated to be present over 53.9% of the 13.4-year follow-up, with depression evident for 50.3% of total follow-up time, during which subsyndromal and minor symptoms dominated over major depression (Judd et al 2003). These findings indicate a need for treatments directed towards the alleviation and prevention of depression, and milder albeit still disabling subthreshold depressive symptoms in bipolar disorder.

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The pharmacological management of bipolar disorder is rising in complexity, with the continual refining of the illness spectrum and an expanding pharmacopeia of medication options that, in monotherapy or in combination, may provide more sophisticated means of targeting phasic symptoms, polarity changes, and subclinical or minor symptoms. Lithium undoubtedly retains the broadest evidence base, with substantiated efficacy in treating manic and depressive phases, prophylaxis (Tondo et al 1998; Maj 2003) and the reduction of suicide risk (Baldessarini et al 2003). However, its side effect profile and lesser efficacy in certain subgroups (Calabrese and Woyshville 1995) have led to investigations of second generation anticonvulsants and atypical antipsychotics as alternative treatments. Valproate and carbamazepine are options in the treatment of mania, mixed states and those with rapid cycling illness and comorbid substance abuse (Greil 1998; Bowden and Singh 2005), but lack full support in prophylaxis and the treatment of bipolar depression. Atypical antipsychotics, such as risperidone, olanzapine, quetiapine and aripiprazole, all have some evidence of efficacy in the treatment of mania (Segal et al 1998; Berk et al 1999; Keck et al 2003; Ketter 2004), but they may find a further strength in the growing body of evidence for their use in bipolar depression (Tohen et al 2003; Calabrese et al 2005). Newer anticonvulsants, including gabapentin, topiramate and levetiracetam, have had limited investigation that have not yielded promising findings in relation to bipolar disorder management (Bowden and Karren 2006).

It remains that few medications have an adequate evidence base for the treatment and prevention of bipolar depression, despite its phenotypic dominance in bipolar disorder. The use of antidepressants remains controversial, in view of concerns for the risk of antidepressant-induced mania and cycle acceleration (Goldberg and Truman 2003). In this regard, lamotrigine, with its apparent efficacy in the treatment and prevention of bipolar depression, may have a unique place in the bipolar pharmacological armamentarium. Ketter (Ketter and Calabrese 2002) has classified maintenance therapies into those that stabilize mood from above (mania or hypomania) and those that do so from below (depression), with lamotrigine the sole member of the latter category. This paper aims to review the evidence for the efficacy of lamotrigine in bipolar disorder, and to provide some practical recommendations in the clinical setting.

Methods

A literature search for publications up until August 2006 was performed, based on the MEDLINE database and

supplemented by identifying relevant references from individual articles. Key search terms used included lamotrigine, bipolar disorder, bipolar depression, mania, mixed state, major depression, maintenance, pharmacology, pharmacokinetics, pharmacodynamics, and clinical trial. Original research and review articles were studied.

The pharmacology of lamotrigine

Anticonvulsants are not equivalent to mood stabilizers, although several drugs straddle both categories, a fact that may have generated often-unfulfilled expectations of effectiveness of anticonvulsants when applied to bipolar disorder. The established cross-efficacy of agents such as valproate, carbamazepine and lamotrigine has nevertheless contributed to the still imprecise understanding of the pathophysiology of bipolar disorder and the development of its treatments, although the lack of class effects within the anticonvulsants is noteworthy, and complicates extrapolation of mechanism of action to pathophysiology. Some agents, such as topiramate, do not show efficacy in the disorder, while others, such as valproate, show preferential efficacy in the manic phase.

Lamotrigine, a phenyltriazine derivative, has been demonstrated to possess multiple mechanisms of action, a summary of which has been detailed elsewhere (Ketter et al 2003; Hahn et al 2004). Briefly, these include the selective blockade of the N- and P-type calcium channels in focal brain regions, and the voltage-dependent blockade of sodium channels via its action on the slow inactivation state that occurs when sodium channels are over-activated. Lamotrigine has also been shown to inhibit the release of excitatory amino acids such as glutamate and aspartate, and may have some agonistic effects on γ -aminobutyric acid (GABA) (Ketter et al 2003; Hahn et al 2004). It selectively suppresses supranormal neuronal activities without affecting the basal neurophysiological state, which has clear implications in neuronal stabilization in seizure disorders, but may also be a plausible explanation of its action in bipolar disorder, even though the pathophysiology of this condition is less clear (Hahn et al 2004). Lamotrigine is also believed to act on serotonin reuptake, which may contribute to its antidepressant effects (Hahn et al 2004; Bourin et al 2005). There is evidence of peripherical glutamate dysregulation in bipolar disorder (Berk et al 2000), and the glutamatergic activity of lamotrigine may also be implicated in its therapeutic and neuroprotective effects.

The absorption of lamotrigine after oral administration is rapid, complete and unaffected by food ingestion. It undergoes minimal first-pass metabolism, and has a bioavailability

of 98% (Peck 1991; Keck and McElroy 2002; Hahn et al 2004). Peak plasma concentrations are reached in 1.4 to 4.8 hours, and plasma protein binding is approximately 55%, which makes interaction with high plasma protein-binding drugs unlikely (Keck and McElroy 2002; Hahn et al 2004). Lamotrigine primarily undergoes hepatic metabolism through glucuronidation, producing inactive metabolites that mainly consist of lamotrigine 2N-glucuronide, and to a lesser extent the 5N-glucuronide, N-oxide and N-methyl metabolites, all of which are renally excreted (Sinz and Rimmel 1991; Hachad et al 2002). The kinetics of lamotrigine is linear within the daily dose range of 100 to 700 mg. Its mean elimination half-life is approximately one day in healthy volunteers (Peck 1991). Clearance is substantially decreased in the presence of hepatic or renal impairment, although age, gender and smoking do not appear to have significant impact on kinetics. Clearance is also estimated to be about 25% lower in non-Caucasians (Keck and McElroy 2002; Hahn et al 2004).

Drug interactions are generally less pronounced with newer anticonvulsants compared with older ones, but significant interactions may occur between lamotrigine and other drugs, primarily via interference with the UDP-glucuronosyltransferase enzymes (UGT), which are responsible for the hepatic microsomal glucuronidation of lamotrigine and other drugs. Interactions can occur when enzyme-inducing drugs such as phenytoin, carbamazepine, oxcarbazepine, phenobarbital and primidone are co-administered with lamotrigine, which may increase its clearance (Hachad et al 2002; Perucca 2006). Conversely, valproate is an inhibitor of UGT and may produce a two-fold increase in lamotrigine serum concentrations (Hachad et al 2002). Dose adjustments are required in both of these situations. Potential reduction of lamotrigine levels with rifampicin (Ebert et al 2000) and oral contraceptives (Sabers et al 2001), and risk of toxicity with sertraline (Kaufman and Gerner 1998), have also been documented. There has also been evidence for a modest reduction in oral contraceptive hormone levels due to lamotrigine, although the impact on contraceptive efficacy may not be affected (Sidhu et al 2006). Nevertheless, women on concurrent oral contraceptive pills and lamotrigine may benefit from cautionary advice on contraceptive dose adjustments or alternative contraceptive methods (Perucca 2006).

Studies of lamotrigine in bipolar disorder

Building on anecdotal reports of lamotrigine's psychotropic properties in epileptic and bipolar patients, Calabrese et al (Calabrese, Bowden, McElroy, et al 1999) conducted the

first study to investigate its spectrum of therapeutic activity in bipolar disorder. This 48-week, open-label, prospective trial used lamotrigine as monotherapy or adjunctive pharmacotherapy in 75 patients with refractory bipolar I or II disorder, who variously presented in depressed, hypomanic, manic or mixed phases of the illness. Their results suggested that lamotrigine was effective as both monotherapy and adjunctive therapy, and for all phases of the illness with large magnitudes of improvements. Specifically, in the 40 subjects presenting with depression, 48% showed "marked improvement", defined as a 50% or greater reduction in the 17-item Hamilton Depression Scale (HAMD); 20% showed "moderate improvement", defined as a 26%–49% reduction in HAMD; and a mean HAMD reduction of 42%. For the 31 subjects presenting with hypomania, mania or mixed state, 81% showed "marked improvement" and 3% "moderate improvement", as correspondingly defined using the mania rating scale (MRS), and a mean score reduction of 74% was achieved. These results must be interpreted with caution, given the many methodological limitations of this preliminary study, such as its treatment-refractory and heterogeneous population with regards to both bipolar type and phase, open-label non-randomized design, and lack of control for concurrent psychotropic use. Furthermore, the drop-out rate was high (51%), and largely reflected adverse events and ineffectiveness which jointly accounted for two-thirds of this figure.

Findings of such broad spectrum activity and therapeutic magnitude have more recently been reported by a retrospective chart review of 587 bipolar disorder outpatients, comprising all subtypes and in various illness phases, in a private practice setting (Ginsberg 2006). Despite obvious methodological limitations, this study had the benefit of a large sample size. Using the Clinical Global Impression-Improvement (CGI-I) scale as outcome measure, 59.5% of patients were rated as either "very much improved" or "much improved" on lamotrigine, and a further 20.4% were deemed to have "minimally improved". Response rates were comparable across bipolar disorder subtypes (ie, bipolar I, II and not otherwise specified) and index mood episode (ie, depressed, manic and mixed) for the bipolar I subset. The median time from lamotrigine initiation to observed response was 95 days, with a mean of 205 days.

There have been a number of published studies of higher-order design for lamotrigine in bipolar disorder. These have specifically examined the effects of lamotrigine on mania, bipolar depression, rapid cycling illness and bipolar disorder maintenance. These are sequentially discussed below.

Studies in acute mania

In the first double-blind, randomized controlled trial of lamotrigine in mania, Ichim and colleagues (Ichim et al 2000) allocated 30 hospital inpatients meeting the DSM-IV criteria for bipolar I disorder, manic phase, to treatment with either lamotrigine or lithium over 4 weeks. Other psychotropic agents were discontinued for at least a day prior to commencing the trial. Both treatment arms produced comparable response rates and extent of improvement, as measured by the MRS, brief psychiatric rating scale (BPRS), CGI severity (CGI-S) and improvement (CGI-I) scales, and the Global assessment of functioning (GAF) scale. Additionally, there were no significant differences between the treatment arms over the course of the study period, notable given the slow dose titration for lamotrigine. This study had several limitations, the strongest of which being its insufficient power arising from the small sample size. The use of a relatively low dose of lamotrigine (100 mg/day) and a fixed lithium dose (800 mg/day) may also have confounded the results. Such encouraging findings have not been replicated by other double-blind trials, although these have been few in number and their comparability compromised by differing methodologies that were likewise imperfect.

Three such studies were described in a review by Yatham (2004). One was an 8-week study of 16 lithium-refractory manic and hypomanic patients, which found lamotrigine to be no more useful than placebo. Conclusions of efficacy are difficult to make considering the small sample size and refractory population. In the other two cited studies, neither found lamotrigine to be superior to placebo in the treatment of acute mania. In the 3-week monotherapy study, lamotrigine at 50 mg/day (N = 84)

was compared against lithium, given to reach serum levels of 0.8 to 1.3 (N = 36), and placebo (N = 95). The second study compared lamotrigine at 200 mg/day (N = 74) with lithium (N = 78) and placebo (N = 77) as adjunctive therapy to antipsychotics over 6 weeks. The low lamotrigine dose used in the first study, and the adjunctive design of the second, are confounding factors that preclude direct comparisons.

Studies in acute bipolar depression Monotherapy trials

Several studies have investigated the efficacy of lamotrigine monotherapy with findings relevant to bipolar depression (Table 1). Calabrese and colleagues (Calabrese, Bowden, Sachs, et al 1999) reported the first double-blind placebo-controlled trial of lamotrigine monotherapy in the treatment of bipolar I depression. They recruited 195 subjects meeting the DSM-IV diagnostic criteria for bipolar I disorder who were in a major depressive episode. These patients were randomized into 3 monotherapy treatment arms of equal size (N = 66), consisting of 50 mg/day lamotrigine, 200 mg/day lamotrigine and placebo, given over 7 weeks. All psychoactive agents except sedatives had been ceased prior to randomization, at durations equivalent to 5 half-lives of the drugs. Both lamotrigine groups showed moderately larger margins of improvement than placebo as measured by HAMD, montgomery-åberg depression rating scale (MADRS), CGI-S and CGI-I, although only differences on MADRS, CGI-S and CGI-I for the lamotrigine 200 mg/day group reached statistical significance at the $p < 0.05$ level. The 200 mg/day group showed an earlier response compared with the 50 mg/day group, with significant differentiation of the trajectories between the

Table 1 Randomized, controlled trials of lamotrigine monotherapy in acute bipolar depression

Trial	Study arms	N	Sample	Trial length in weeks	Response rate in percentage ^a		
					HAMD	MADRS	CGI-I
Calabrese, Bowden, Sachs et al 1999	LTG 50 mg/day	66	Bipolar I major depressive episode,	7	45	48 ^b	41
	LTG 200 mg/day	66	outpatients		51	54 ^b	51 ^b
	Placebo	66			37	29	26
Brown EB et al 2006	LTG	205	Bipolar I major	7	MADRS 59.7		CGI-S 64.4
	OFC	205	depressive episode		68.8		71.8

Abbreviation: N, sample size; HAMD, 17-item hamilton rating scale for depression; MADRS, montgomery-åberg depression rating scale; CGI-I, clinical global impressions scale for improvement; CGI-S, clinical global impressions scale for severity; LTG, lamotrigine; OFC, olanzapine/fluoxetine combination

^aNote that definitions of response vary with different studies: HAMD and MADRS definitions of response are $\geq 50\%$ reduction from baseline scores for the respective scales; CGI-I definition of response is a rating of much improved or very much improved; CGI-S definition of response is a rating of ≤ 3

^b $p < 0.05$ vs placebo

lamotrigine and placebo groups after Week 3. No significant treatment-emergent polarity switch was found.

In the second monotherapy study (Frye et al 2000) (Table 2), lamotrigine was compared with gabapentin and placebo in a double-blind, randomized, crossover trial on 31 patients with refractory unipolar and bipolar affective illness requiring hospitalization. The diagnostic distribution of these patients was 6 unipolar illness, 11 bipolar I and 14 bipolar II disorder, the majority of the bipolar group (23 out of 25) had a rapid cycling course. Patients were randomized, with stratification by diagnostic classification, to receive sequential 6-week trials of each of the 3 treatment arms. Maximum tolerated doses of lamotrigine and gabapentin were used with mean daily doses being 274 mg and 3987 mg, respectively. Using the CGI for bipolar illness as primary outcome measure, 52% of the lamotrigine group had a rating of "much improved" or "very much improved", compared with 26% of the gabapentin and 23% of the placebo groups ($p = 0.031$). When response rates were analysed by affective episode types, both mania (lamotrigine 44%, gabapentin 20%, placebo 32%) and depression (lamotrigine 45%, gabapentin 26%, placebo 19%) showed similar non-significant trends. In an extension to this study with a bigger sample size ($N = 45$), of which there were 35 bipolar and 10 unipolar treatment-refractory patients, response rates of 53% for lamotrigine, 28% for gabapentin and 22% for placebo ($p = 0.01$), were reported (Obrocea et al 2002). Response to lamotrigine monotherapy was significantly correlated with a diagnosis of bipolar disorder, the male gender, exposure to fewer prior medication trials and a history of fewer prior hospitalizations

for depression, although only the last two survived logistic regression. These studies lend further support for the efficacy of lamotrigine in bipolar depression, but their generalizability is restricted by their highly-refractory and diagnostically heterogeneous populations.

Brown and colleagues conducted a double-blind, randomized trial comparing the efficacy of olanzapine/fluoxetine combination (OFC) ($N = 205$) to lamotrigine ($N = 205$) as acute treatments in bipolar depression (Brown EB et al 2006) (Table 1). They found that OFC showed significantly greater improvement than lamotrigine across the 7-week study period, as measured by CGI-S, MADRS and the Young Mania Rating Scale (YMRS), as well as a significantly shorter time to response. However, the prolonged dose titration of lamotrigine (over 5 weeks) relative to the study period could have influenced the results. Lamotrigine, however, was associated with less adverse effects and showed comparable response and remission rates as OFC.

Adjunctive trials

Data also exists for the adjunctive use of lamotrigine in treatment-resistant bipolar depression. One such report stemmed from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (Nierenberg et al 2006). Patients ($N = 66$) in a major depressive episode who had not responded to combination mood stabilizer and antidepressant, were randomized, with equipose stratification, to up to 16 weeks of open-label adjunctive treatment with lamotrigine, inositol or risperidone. No significant inter-group differences were found on primary outcome measure, which

Table 2 Controlled trials of lamotrigine monotherapy in refractory bipolar disorder

Trial	Study arms	N	Sample	Trial length in weeks	Response rate in percentage ^a		
Frye et al 2000		31	Refractory disorder: 6 unipolar; 11 bipolar I; 14 bipolar II	6 (sequential crossover design)	CGI-I overall ^b	CGI-I mania	CGI-I depression
	LTG				52	44	45
	Gabapentin				26	20	26
	Placebo				23	32	19
Obrocea et al 2002		45	Refractory disorder: 10 unipolar; 15 bipolar I; 20 bipolar II	6 (sequential crossover design)	CGI-I ^c		
	LTG				53		
	Gabapentin				28		
	Placebo				22		

Abbreviation: N, sample size; CGI-I, clinical global impressions scale for improvement; LTG, lamotrigine

^aCGI-I definition of response is a rating of much improved or very much improved

^b $p = 0.031$

^c $p = 0.01$

was defined using the DSM-IV criteria for full remission. However, remission rate was highest for lamotrigine (23.8% compared with 17.4% for inositol and 4.6% for risperidone), suggesting some superiority of adjunctive lamotrigine although the differences did not reach statistical significance. These results encourage further exploration of the adjunctive role of lamotrigine in treatment-resistant bipolar depression, but this trial on its own was hindered by low statistical power, equiprobable randomization and open-label design.

Another trial studied the adjunctive use of lamotrigine in treatment-resistant depression, including a subset with bipolar II depression (N = 8) although the majority had unipolar depression (N = 15) (Barbosa et al 2003) (Table 3). The 23 patients were in a major depressive episode that had not responded to at least one antidepressant trial, which did not include fluoxetine. They were randomized to receive 100 mg/day lamotrigine (N = 13) or placebo (N = 10), in addition to 20 mg/day of fluoxetine, for a period of 6 weeks. All other psychotropic medications were ceased. The groups did not significantly differ on HAMD, but the lamotrigine group was significantly superior to placebo in terms of improvement in CGI-S scores and response rate as measured by the CGI-I. There was no difference between the unipolar and bipolar II groups.

A few negative unpublished randomized, placebo-controlled trials of lamotrigine in bipolar depression have been conducted (Data on file 1999, 2002, 2006). A pooled meta-analysis of these trials has shown an efficacy signal for lamotrigine (Geddes, unpublished data). There are also small studies comparing lamotrigine to venlafaxine (McIntyre et al 2004) and to citalopram (Schaffer et al 2006) for bipolar depression, neither showing any advantage with lamotrigine.

Studies in rapid cycling

There is only a single reported double-blind, placebo-controlled study of lamotrigine in rapid cycling bipolar

disorder (Calabrese et al 2000) (Table 4). This trial recruited 324 patients in various mood states (euthymia or active mood episode), but all meeting the DSM-IV criteria for rapid cycling bipolar disorder, into the preliminary stabilization phase. In this phase, lamotrigine was introduced and when the patient became affectively well, existing psychotropic agents were withdrawn. At the end of this phase, 182 patients emerged eligible to participate in the randomization phase, during which they were allocated to lamotrigine or placebo monotherapy for 6 months, using flexible lamotrigine dosing from 100 to 500 mg per day. Time to additional pharmacotherapy to treat emergent mood symptoms was the primary outcome measure, and this did not differ between the lamotrigine and placebo groups. Neither did the groups differ on secondary outcome measures such as changes in CGI-S and the global assessment scale (GAS). However, the two groups statistically diverged in their survival in study figures in favor of lamotrigine, a difference that retained statistical significance in the bipolar II population when the subtypes were analyzed. 41% of the lamotrigine group completed the 6-month randomization phase without illness relapse, compared with 26% of the placebo group. This significant difference was again only observed for bipolar II disorder on subtype analysis.

A small (N = 14), open-label study also reported on the prophylactic efficacy of lamotrigine monotherapy in rapid cycling bipolar disorder (Walden et al 2000). This cohort of bipolar I disorder patients was treated with either lithium or lamotrigine monotherapy for one year, and found that 43% of the lithium group no longer met the criteria for rapid cycling (ie, more than four mood episodes in a year) compared with 86% of the lamotrigine group, with 43% of the latter having no episodes. Despite many methodological weaknesses, this study demonstrated positive findings in a literature-poor area, and observed that possibly greater benefits could be associated with

Table 3 Randomized, controlled trials of adjunctive lamotrigine in bipolar disorder

Trial	Study arms	N	Sample	Trial length in weeks	Response rate in percentage ^a		
					HAMD	MADRS	CGI-I
Barbosa et al 2003	LTG + fluoxetine	13	Treatment-resistant major depression: 15 unipolar; 8 bipolar II	6	76.9	76.9	84.6 ^b
	Placebo + fluoxetine	10			50.0	40.0	30.0

Abbreviation: N, sample size; CGI-I, clinical global impressions scale for improvement; LTG, lamotrigine

^aNote that definitions of response vary with different studies: HAMD and MADRS definitions of response are $\geq 50\%$ reduction from baseline scores for the respective scales; CGI-I definition of response is a rating of much improved or very much improved.

^bp = 0.013.

Table 4 Randomized, controlled trials of lamotrigine monotherapy in prophylaxis of bipolar disorder

Trial	Study arms	N	Sample	Trial length in months	Efficacy ^a	
Calabrese et al 2000			Stabilized, rapid-cycling bipolar I or II patients	6	No intervention	Survival time
	LTG	93			50	18 weeks
	Placebo	89			44	12 weeks
Calabrese et al 2003			Stabilized bipolar I patients with index depressive episode	18	No intervention	Survival time
	LTG	221			18	200 days ^a
	Lithium	121			17	170 days ^a
	Placebo	121			10	93 days
Bowden et al 2003			Stabilized bipolar I patients with index mania or hypomania	18	No intervention	Survival time
	LTG	59			53	141 days ^b
	Lithium	46			61	292 days ^b
	Placebo	70			30	85 days

Abbreviation: N, sample size; LTG, lamotrigine

^aEfficacy outcome definitions: No intervention refers to the proportion (in percentage) of patients who did not require treatment for an emergent mood episode; Survival time refers to the median time until treatment was required for an emergent mood episode

^{*}p = 0.029 for LTG vs placebo, p = 0.029 for lithium vs placebo, with no significant difference between LTG and lithium

^bp = 0.02 for LTG vs placebo, p = 0.003 for lithium vs placebo

the higher plasma lamotrigine levels (above 5 mg/L) that were recommended in epileptology.

Studies in maintenance treatment

In a continuation study to the afore-mentioned 7-week, double-blind, placebo-controlled trial of lamotrigine monotherapy in the treatment of bipolar I depression (Calabrese, Bowden, Sachs, et al 1999), 92% of those who had completed the controlled trial (N = 124) entered the 1-year open-label lamotrigine continuation phase, although only 69 (56%) completed it with a mean duration of exposure of 10.4 months (McElroy et al 2004). Those who had received placebo in the controlled trial showed significant reduction in MADRS scores as early as Week 4 (maximum mean decrease of 9.7 points), and all participants maintained their improved MADRS scores throughout the continuation phase. Furthermore, the proportion of patients reporting manic, hypomanic or mixed episodes during the one year of lamotrigine continuation was half that of the year before (31% versus 62%). Study design limitations including the allowance of concomitant psychotropic medications, notably with a third of the group receiving antidepressants and a minority on additional mood stabilizers, should be borne in mind. Nevertheless, this study provided support for the mood stabilizing in addition to antidepressant properties of lamotrigine.

Two 18-month placebo-controlled trials compared lamotrigine and lithium as maintenance monotherapy in

bipolar I disorder, each focusing on a single pole of the illness at entry (Table 4). In one study (Calabrese et al 2003), patients currently or recently in a major depressive episode were first stabilized on lamotrigine in an 8- to 16-week open-label phase, before being randomized to receive lamotrigine (N = 221), lithium (N = 121) or placebo (N = 121) monotherapy for up to 18 months. Using time from randomization to intervention for any emergent mood episode as outcome measure, lamotrigine and lithium did not differ from one another, but both were superior to placebo. Depressive episodes outnumbered mania by a ratio of 3:1 as cause for intervention. When time to intervention was examined according to the polarity of the emergent mood episode, lamotrigine but not lithium was superior to placebo for depression, whereas the reverse held true for manic, hypomanic and mixed episodes. Of interest, out of the three daily lamotrigine doses studied (50 mg, 200 mg and 400 mg), only patients on 200 mg showed significant advantage over placebo in time to intervention for both overall mood episodes and depressive episodes. The second study (Bowden et al 2003) used a similar design on a smaller sample (N = 175) of bipolar I disorder patients with recent manic or hypomanic episodes, and produced matching results, which were the superiority of lamotrigine and lithium to placebo on survival time to intervention, and the differential superiority of lamotrigine and lithium with regards to depression and mood elevation, respectively.

When data from both studies were pooled, lamotrigine again emerged superior to placebo and lithium in the

prolongation of time to intervention for depression. Both lamotrigine and lithium were superior to placebo at prolonging the time to intervention for manic, hypomanic and mixed episodes, but only lithium remained superior after adjusting for index mood type. It was also apparent that the index episode was strongly predictive of the polarity of the subsequent episode, which could potentially inform treatment decisions in bipolar maintenance (Goodwin et al 2004).

Studies in comorbid disorders

Lamotrigine has been suggested as effective in the treatment of comorbid bipolar and borderline personality disorder (Preston et al 2004), comorbid bipolar disorder and alcohol dependence (Rubio et al 2006), and comorbid bipolar disorder and cocaine dependence (Brown et al 2003; Brown E et al 2006). However, these studies all have limited methodological rigor that impact on the validity of their findings.

Safety and tolerability of lamotrigine

Placebo-controlled trials of lamotrigine in bipolar disorder, including the 18-month studies, suggest it to be well-tolerated with a comparable adverse event profile to placebo, without appearing to have significant impact on laboratory parameters, body weight and sexual functioning or to have mood destabilizing effects (Bowden et al 2004). The most common treatment-emergent adverse event is headache, which was found to occur statistically more frequently than placebo in one study (Calabrese, Bowden, Sachs et al 1999).

The most worrying adverse effect of lamotrigine is the rare but potentially lethal Stevens-Johnson syndrome (SJS) or toxic epidermal necrosis (TEN). These syndromes are understood to be fundamentally the same drug-induced cutaneous reaction characterized by blistering and epidermal detachment resulting from keratinocytic apoptosis, but denote differing severity with SJS defined as <10% body surface area epidermal detachment, SJS/TEN 10% to 30% detachment and TEN >30% detachment. Mortality increases from 1%–5% for SJS to 25%–35% for TEN. Despite the promising therapeutic outcome of intravenous immunoglobulins, prevention and early diagnosis with discontinuation of the causative drug remain the best strategy (Chosidow et al 2005; French et al 2006). The occurrence of rash is common in both lamotrigine- and placebo-exposed groups in bipolar trials, but the incidence of serious rash, defined as that requiring hospitalization and lamotrigine discontinuation or reported as SJS or TEN, is low at approximately 0.1% (Bowden et al 2004). These have typically occurred in the first 8 weeks

of drug initiation (Messenheimer et al 1998). A three-fold, albeit still low, incidence was found in earlier lamotrigine trials for epilepsy, a difference that was attributed to higher initial doses, rapid dose escalation and concurrent valproate use (Messenheimer 1998). The use of additional precautions aimed at reducing antigen exposure, above the standard product information precautions, has not been found to lower the risk of non-serious rash in a randomized trial (N = 1175), and no serious rash was reported to allow comparison (Ketter et al 2006). There have been case reports of successful slow-titration rechallenge with lamotrigine after the occurrence of serious rash (Tavernor et al 1995; Besag et al 2000; Manfredi et al 2004).

There are reports of tics (Sotero de Menezes et al 2000; Seemuller et al 2006), mania (Raskin et al 2006), hallucinations (Uher and Jones 2006) and hyponatraemia (Mewasingh et al 2000) being associated with lamotrigine.

Available data on the teratogenicity of lamotrigine comes from epileptic patients. From the United Kingdom epilepsy and pregnancy register, which prospectively collects data on women with epilepsy who become pregnant, lamotrigine has been associated with a rate of major congenital malformations of 3.2%, compared with 3.5% for epileptic women not on anticonvulsants during pregnancy and 4.2% for those on anticonvulsants. Specifically, there was a trend towards fewer major malformations for pregnancies exposed only to lamotrigine than to valproate, and a significant dose-dependent relationship was found for lamotrigine, with major malformation rates of 1.3% for daily doses under 100 mg, 1.9% for 100–200 mg and 5.4% for doses exceeding 200 mg. This latter figure was comparable with that for valproate daily doses of 1000 mg or less (5.1%) and lower than that for valproate daily doses over 1000 mg (9.1%) (Morrow et al 2006). Data from the international lamotrigine pregnancy Register provided a major malformation rate of 2.9% in first trimester monotherapy exposure (N = 414) (Cunnington and Tennis 2005).

The potential neonatal adverse effects of breastfeeding while on lamotrigine are unclear. Studies indicate a relatively high level of drug transmission in the breast-milk, with neonatal plasma lamotrigine levels gauged to be approximately 25%–30% that of the mother's (Tomson et al 1997; Ohman et al 2000; Liporace et al 2004), although the clinical implications of such levels on the infant remain speculative.

Patient-focused perspectives

Quality of life is an important consideration for any treatment decision, and encompasses the aspects of treatment

efficacy, safety and tolerability, including the evaluation of seemingly trivial drug effects that may cause enduring functional impairment. Lamotrigine's tolerability, especially in comparison with lithium and other mood stabilizers, is a factor conducive to adherence, which is a confronting issue in bipolar disorder with an estimated 51% of patients unable to adhere to prescribed medications in a 1-year follow-up study (Keck et al 1997).

Lamotrigine appears to hold two specific advantages among the bipolar pharmacotherapies in tolerability terms, namely its apparent lack of adverse effects on weight (Sachs et al 2006) and cognitive functions. These are desirable properties considering the higher prevalence of obesity (Simon et al 2006) and metabolic syndrome (Fagiolini et al 2005) in bipolar patients, and the evidence for marked cognitive dysfunction in this population (Robinson et al 2006). There is preliminary support for improved cognitive functioning on lamotrigine monotherapy or adjunctive therapy in bipolar patients (Khan et al 2004), and for its superior neurocognitive profile over other anticonvulsants, such as carbamazepine, valproate (Daban et al 2006) and topiramate (Blum et al 2006; Smith et al 2006). There are also suggestions that lamotrigine may exert a neuroprotective effect (Wiard et al 1995; Trojnar et al 2002), although confirmatory evidence is wanting. In a double-blind, randomized crossover study comparing patient preference of lamotrigine and topiramate using healthy subjects, the majority (70%) preferred lamotrigine (Werz et al 2006), which lends support for its acceptability to patients.

Conclusion

Despite a broad spectrum of effect and large magnitudes of improvement in uncontrolled studies, the available randomized controlled trials of lamotrigine in the treatment of bipolar disorder have only demonstrated convincing efficacy in the prophylaxis of bipolar depression. There is weaker support for its efficacy in acute bipolar I depression, refractory unipolar and bipolar depression, and rapid cycling illness. The timeframe of response seems to be several weeks, perhaps as early as three, and a daily lamotrigine dose of 200 mg appears to be effective for its bipolar indications with lowered risks of teratogenicity and serious rash. The utilization of slow titration methods has proven a useful mechanism for avoiding serious side effects but may impede the acute efficacy of the drug.

It must be borne in mind, however, that the total number of clinical trials in this area is small. There are four randomized controlled trials in mania producing inconclusive results due to

marred methodologies, several published randomized trials in bipolar depression of varying designs, lamotrigine utilization and sample characteristics, and only one randomized controlled trial in rapid cycling illness. This limited evidence base stands favorably in the area of bipolar depression treatment, which is marked by a paucity of safe and efficacious treatment options. As the evidence stands at present, lamotrigine seems to be a generally well-tolerated and, providing that dose titration and concurrent valproate precautions are followed, a safe treatment option whose main disadvantage is a restricted efficacy repertoire in mania, compared with the best-available standard of lithium. Its advantages are primarily a favorable adverse effect profile and evidence of its superior efficacy in the prophylaxis of bipolar depression, which should be its main first-line indication. Consideration of bipolar subtype and index polarity in acute episodes may be helpful, as it may provide evidence-based guidance on the selection of the maintenance agent. More specifically, bipolar disorder presenting in manic phase would suggest lithium as the preferred maintenance, whereas bipolar II disorder or an index bipolar depressive episode may indicate lamotrigine as a suitable option, in monotherapy or combination treatment, especially if lithium is relatively contraindicated. Predictors of lamotrigine response include atypical depression, comorbid anxiety and substance use, failure to respond to lithium, valproate or carbamazepine, and a family history of substance use or anxiety (Narasimhan and Buckley 2006).

Practice guidelines vary in their recommendations, but lamotrigine is generally placed as first-line treatment for both acute bipolar depression and bipolar maintenance (American Psychiatric Association 2002; Grunze et al 2002; The Royal Australian and New Zealand College of Psychiatrists 2004; Calabrese et al 2004; Grunze et al 2004; Suppes et al 2005; Yatham et al 2005). The Canadian network for mood and anxiety treatments (CANMAT) guidelines are perhaps the most encompassing in their bipolar indications for lamotrigine, as they additionally include first-line treatment for rapid cycling bipolar disorder, first-line maintenance for bipolar II disorder, and second-line treatment for bipolar II depression (with no first-line treatment options) (Yatham et al 2005). These recommendatory variations seem to arise from different expectations of evidence base standards, and given the limited quantity and quality of clinical trials, the incorporation of lamotrigine for first-line indications beyond bipolar depression maintenance would seem to reflect clinical need and the paucity of alternatives.

However, the role definition of lamotrigine in the treatment of bipolar disorder may yet expand. In particular,

its usefulness in refractory affective disorders and bipolar subsets, including the soft bipolar spectrum, is encouraging and may become better understood. Timeframes for optimal response may differ in certain subsets of affective disorders, which may possibly explain the lengthy mean time to onset of response reported by one study (Ginsberg 2006). This suggests that an adequate trial of lamotrigine may need to be correspondingly lengthy in order not to miss this delayed onset of action.

Disorders of the bipolar spectrum are aetiologically and phenotypically heterogeneous and complex, and the likelihood of monotherapy succeeding in the treatment and maintenance of all illness phases is low. A mood stabilizer, when most stringently defined, is an agent that is efficacious in the treatment of both acute mania and bipolar depression, and in the prophylaxis of both poles of the illness. Only lithium can fully satisfy this criteria (Bauer and Mitchner 2004), and yet it is not unsurpassable in its efficacy in individual aspects of bipolar management, as exemplified by lamotrigine's comparative superiority in depression prophylaxis. Therefore, rather than seeking for the ultimate single agent mood stabilizer, targeting therapy to individual clinical needs and the use of mood stabilizing cocktails may be more strategic approaches to tailor for the illness characteristics of patients with bipolar disorder, and better reflect the modern conceptualization of bipolarity and clinical practice. The role of lamotrigine in this future is yet to be fully defined.

Practical summary points

- Lamotrigine has demonstrated its efficacy most convincingly in the prophylaxis of bipolar depression.
- Weaker efficacy data are available in the treatment of acute bipolar I depression, refractory unipolar and bipolar depression, and rapid cycling illness.
- The timeframe to response with lamotrigine is lengthy, and seems to lie in the range of several weeks.
- The therapeutic daily dose range appears to lie between 200 to 400 mg, with the majority of studies demonstrating efficacy at the lower end of this range.
- A standard initiation and titration practice involves the initiation of lamotrigine at a daily dose of 25 mg, and increasing this to 50 mg per day after one to two weeks, then doubling the dose every one to two weeks until a dose of 200 mg per day is reached.
- A more cautious initiation and dose titration schedule should be undertaken if either valproate or sertraline is concurrently administered, due to potential drug interactions that may increase the risk of toxicity and skin rash.

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