The role of lamotrigine in the management of bipolar disorder

Felicity Ng[1]
Karen Hallam[2]
Nellie Lucas[3]
Michael Berk[1]

[1]Department of Clinical and Biomedical Sciences: Barwon Health, University of Melbourne, Geelong, Victoria, Australia; [2]Department of Psychiatry, The University of Melbourne, Melbourne, Victoria, Australia; [3]ORYGEN Research Centre, Melbourne, Victoria, Australia

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.

Correspondence: Felicity Ng
Department of Clinical and Biomedical Sciences: Barwon Health, University of Melbourne, PO Box 281, Geelong, Victoria 3220, Australia
Tel +61 3 5260 3154
Fax +61 3 5246 5165
Email felicitn@barwonhealth.org.au

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 perhipheral 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 metabolization 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 Remmel 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-åsberg 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]		
Calabrese,			Bipolar I	7	HAMD	MADRS	CGI-I
Bowden, Sachs	LTG	66	major		45	48[b]	41
et al 1999	50 mg/day		depressive				
	LTG	66	episode,		51	54[b]	51[b]
	200 mg/day		outpatients				
	Placebo	66			37	29	26
Brown EB			Bipolar I	7	MADRS		CGI-S
et al 2006	LTG	205	major		59.7		64.4
	OFC	205	depressive episode		68.8		71.8

Abbreviation: N, sample size; HAMD, 17-item hamilton rating scale for depression; MADRS, montgomery-åsberg 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

[a]Note that definitions of response vary with different studies: HAMD and MADRS definitions of response are ≥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 equipoise 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
[a]CGI-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, equipoise 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]		
Barbosa et al 2003	LTG + fluoxetine	13	Treatment-resistant major depression: 15 unipolar; 8 bipolar II	6	HAMD 76.9	MADRS 76.9	CGI-I 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

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

[b]$p = 0.013$.

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	6	No intervention	Survival time
	LTG	93	bipolar I or II		50	18 weeks
	Placebo	89	patients		44	12 weeks
Calabrese et al 2003			Stabilized bipolar I	18	No intervention	Survival time
	LTG	221	patients with		18	200 days[a]
	Lithium	121	index		17	170 days[a]
	Placebo	121	depressive episode		10	93 days
Bowden et al 2003			Stabilized bipolar I	18	No intervention	Survival time
	LTG	59	patients with		53	141 days[b]
	Lithium	46	index mania		61	292 days[b]
	Placebo	70	or hypomania		30	85 days

Abbreviation: N, sample size; LTG, lamotrigine

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

[a]$p = 0.029$ for LTG vs placebo, $p = 0.029$ for lithium vs placebo, with no significant difference between LTG and lithium

[b]$p = 0.02$ 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 exceedingly 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.

Disclosure

No funding assistance was received for the preparation of this manuscript.

Professor Berk has received grant/research support from Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Mayne Pharma, Novartis, Organon, Stanley Medical Research Institute, Medical Benefits Fund of Australia Limited, National Health and Medical Research Council, and Beyond Blue; has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, and Pfizer; and has been a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay, and Wyeth.

Dr Ng, Dr Hallam and Ms Lucas report no funding or financial relationships that may constitute conflicts of interest with regards to the subject of this manuscript.

References

American Psychiatric Association. 2002. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry*, 159:1–50.

Angst J, Sellaro R. 2000. Historical perspectives and natural history of bipolar disorder. *Biol Psychiatry*, 48:445–57.

Baldessarini RJ, Tondo L, Hennen J. 2003. Lithium treatment and suicide risk in major affective disorders: update and new findings. *J Clin Psychiatry*, 64(Suppl 5):44–52.

Barbosa L, Berk M, Vorster M. 2003. A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *J Clin Psychiatry*, 64:403–7.

Bauer MS, Mitchner L. 2004. What is a "mood stabilizer"? An evidence-based response. *Am J Psychiatry*, 161:3–18.

Berk M, Ichim L, Brook S. 1999. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *Int Clin Psychopharmacol*, 14:339–43.

Berk M, Plein H, Belsham B. 2000. The specificity of platelet glutamate receptor supersensitivity in psychotic disorders. *Life Sci*, 66:2427–32.

Besag FM, Ng GY, Pool F. 2000. Successful re-introduction of lamotrigine after initial rash. *Seizure*, 9:282–6.

Blum D, Meador K, Biton V, et al. 2006. Cognitive effects of lamotrigine compared with topiramate in patients with epilepsy. *Neurology*, 67:400–6.

Bourin M, Masse F, Hascoet M. 2005. Evidence for the activity of lamotrigine at 5-HT(1A) receptors in the mouse forced swimming test. *J Psychiatry Neurosci*, 30:275–82.

Bowden CL, Asnis GM, Ginsberg LD, et al. 2004. Safety and tolerability of lamotrigine for bipolar disorder. *Drug Saf*, 27:173–84.

Bowden CL, Calabrese JR, Sachs G, et al. 2003. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry*, 60:392–400.

Bowden CL, Karren NU. 2006. Anticonvulsants in bipolar disorder. *Aust N Z J Psychiatry*, 40:386–93.

Bowden CL, Singh V. 2005. Valproate in bipolar disorder: 2000 onwards. *Acta Psychiatr Scand,* Suppl:13–20.

Brown E, Nejtak V, Perantie D, et al. 2003. Lamotrigine in patients with bipolar disorder and cocaine dependence. *J Clin Psychiatry*, 64:197–201.

Brown E, Perantie D, Dhanani N, et al. 2006. Lamotrigine for bipolar disorder and comorbid cocaine dependence: a replication and extension study. *Journal of Affective Disorders*, 93:219–2.

Brown EB, McElroy SL, Keck PE Jr, et al. 2006. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry*, 67:1025–33.

Calabrese JR, Bowden CL, McElroy SL, et al. 1999. Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. *Am J Psychiatry*, 156:1019–23.

Calabrese JR, Bowden CL, Sachs G, et al. 2003. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*, 64:1013–24.

Calabrese JR, Bowden CL, Sachs GS, et al. 1999. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry*, 60:79–8.

Calabrese JR, Kasper S, Johnson G, et al. 2004. International consensus group on bipolar I depression treatment guidelines. *J Clin Psychiatry*, 65:571–9.

Calabrese JR, Keck PE Jr, Macfadden W, et al. 2005. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*, 162:1351–60.

Calabrese JR, Suppes T, Bowden CL, et al. 2000. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry*, 61:841–50.

Calabrese JR, Woyshville MJ. 1995. Lithium therapy: limitations and alternatives in the treatment of bipolar disorders. *Ann Clin Psychiatry*, 7:103–12.

Chosidow O, Stern R, Wintroub B. 2005. Part 2. cardinal manifestations and presentations of diseases. Section 9. Alterations in the skin. Chapter 50. Cutaneous drug reactions. Harrison's principles of internal medicine 16th.

Cunnington M, Tennis P. 2005. Lamotrigine and the risk of malformations in pregnancy. *Neurology*, 64:955–60.

Daban C, Martinez-Aran A, Torrent C, et al. 2006. Cognitive functioning in bipolar patients receiving lamotrigine: preliminary results. *J Clin Psychopharmacol*, 26:178–81.

Data on file, Lamictal, RM1997/00712/00, Study Synopsis of SCAA2010 (603), 1999.

Data on file, Lamictal, RM2002/00129/00, Clinical Study Report for SCA40910, 2002, p 2–4, 58–59.

Data on file, Lamictal, RM2004/00533/00, Study Synopsis of SCA100223, 2006.

Ebert U, Thong NQ, Oertel R, et al. 2000. Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects. *Eur J Clin Pharmacol*, 56:299–304.

Fagiolini A, Frank E, Scott JA, et al. 2005. Metabolic syndrome in bipolar disorder: findings from the bipolar disorder center for pennsylvanians. *Bipolar Disord*, 7:424–30.

French LE, Trent JT, Kerdel FA. 2006. Use of intravenous immunoglobulin in toxic epidermal necrolysis and Stevens-Johnson syndrome: our current understanding. *Int Immunopharmacol*, 6:543–9.

Frye MA, Ketter TA, Kimbrell TA, et al. 2000. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol*, 20:607–14.

Ginsberg LD. 2006. Efficacy and safety of lamotrigine for adults with bipolar disorder in a private practice setting. *CNS Spectr*, 11:376–82.

Goldberg JF, Truman CJ. 2003. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disord*, 5:407–20.

Goodwin GM, Bowden CL, Calabrese JR, et al. 2004. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *J Clin Psychiatry*, 65:432–41.

Greil W, Kleindienst N, Erazo N, et al. 1998. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. *J Clin Psychopharmacol*, 18:455–60.

Grunze H, Kasper S, Goodwin G, et al. 2002. World federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders. Part I: Treatment of bipolar depression. *World J Biol Psychiatry*, 3:115–24.

Grunze H, Kasper S, Goodwin G, et al. 2004. The world federation of societies of biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment. *World J Biol Psychiatry*, 5:120–35.

Hachad H, Ragueneau-Majlessi I, Levy RH. 2002. New antiepileptic drugs: review on drug interactions. *Ther Drug Monit*, 24:91–103.

Hahn CG, Gyulai L, Baldassano CF, et al. 2004. The current understanding of lamotrigine as a mood stabilizer. *J Clin Psychiatry*, 65:791–804.

Ichim L, Berk M, Brook S. 2000. Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry*, 12:5–10.

Judd LL, Akiskal HS, Schettler PJ, et al. 2003. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry*, 60:261–9.

Judd LL, Akiskal HS, Schettler PJ, et al. 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*, 59:530–7.

Kaufman KR, Gerner R. 1998. Lamotrigine toxicity secondary to sertraline. *Seizure*, 7:163–5.

Keck PE Jr, Marcus R, Tourkodimitris S, et al. 2003. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*, 160:1651–8.

Keck PE Jr, McElroy SL. 2002. Clinical pharmacodynamics and pharmacokinetics of antimanic and mood-stabilizing medications. *J Clin Psychiatry*, 63(Suppl 4):3–1.

Keck PE Jr, McElroy SL, Strakowski SM, et al. 1997. Compliance with maintenance treatment in bipolar disorder. *Psychopharmacol Bull*, 33:87–91.

Ketter TA. 2004. Sustained remission/euthymia with quetiapine monotherapy for bipolar manic states. Collegium internationale neuropsychopharmacologicum, Paris, France.

Ketter TA, Calabrese JR. 2002. Stabilization of mood from below versus above baseline in bipolar disorder: a new nomenclature. *J Clin Psychiatry*, 63:146–51.

Ketter TA, Greist JH, Graham JA, et al. 2006. The effect of dermatologic precautions on the incidence of rash with addition of lamotrigine in the treatment of bipolar I disorder: a randomized trial. *J Clin Psychiatry*, 67:400–6.

Ketter TA, Manji HK, Post RM. 2003. Potential mechanisms of action of lamotrigine in the treatment of bipolar disorders. *J Clin Psychopharmacol*, 23:484–95.

Khan A, Ginsberg LD, Asnis GM, et al. 2004. Effect of lamotrigine on cognitive complaints in patients with bipolar I disorder. *J Clin Psychiatry*, 65:1483–90.

Kraepelin E. 2002. Manic depressive insanity and paranoia. Barclay M, translator. Bristol: Thoemmes Press. Reprint of 1921 edition.

Liporace J, Kao A, D'Abreu A. 2004. Concerns regarding lamotrigine and breast-feeding. *Epilepsy Behav*, 5:102–5.

Maj M. 2003. The effect of lithium in bipolar disorder: a review of recent research evidence. *Bipolar Disord*, 5:180–8.

Manfredi G, Pacchiarotti I, Kotzalidis GD, et al. 2004. Successful rechallenge with slowly titrated lamotrigine after rash. *Bipolar Disord*, 6:338–9.

McElroy SL, Zarate CA, Cookson J, et al. 2004. A 52-week, open-label continuation study of lamotrigine in the treatment of bipolar depression. *J Clin Psychiatry*, 65:204–10.

McIntyre R, Mancini D, Fulton K. 2004. Double-blind acute depression study comparing venlafaxine XR and lamotrigine when added to a mood stabilizer in the treatment of bipolar depression. *Int J Neuropsychopharmacol*, 7(Suppl 2):S154.

Messenheimer J, Mullens EL, Giorgi L, et al. 1998. Safety review of adult clinical trial experience with lamotrigine. *Drug Saf*, 18:281–96.

Messenheimer JA. 1998. Rash in adult and pediatric patients treated with lamotrigine. *Can J Neurol Sci*, 25:S14–18.

Mewasingh L, Aylett S, Kirkham F, et al. 2000. Hyponatraemia associated with lamotrigine in cranial diabetes insipidus. *Lancet*, 356:656.

Mitchell PB, Slade T, Andrews G. 2004. Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. *Psychol Med*, 34:777–85.

Morrow J, Russell A, Guthrie E, et al. 2006. Malformation risks of antiepileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry*, 77:193–8.

Narasimhan M, Buckley PF. 2006. Predictors of response to pharmacological treatments in bipolar disorder. *Clinical Approaches in Bipolar Disorders*, 5:36–44.

Nierenberg AA, Ostacher MJ, Calabrese JR, et al. 2006. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry*, 163:210–16.

Obrocea G, Dunn R, Frye MA, et al. 2002. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry*, 51:253–60.

Ohman I, Vitols S, Tomson T. 2000. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia*, 41:709–13.

Paykel ES, Abbott R, Morriss R, et al. 2006. Sub-syndromal and syndromal symptoms in the longitudinal course of bipolar disorder. *Br J Psychiatry*, 189:118–23.

Peck AW. 1991. Clinical pharmacology of lamotrigine. *Epilepsia*, 32(Suppl 2):S9–12.

Perucca E. 2006. Clinically relevant drug interactions with antiepileptic drugs. *Br J Clin Pharmacol*, 61:246–55.

Preston G, Marchant B, Reimherr F, et al. 2004. Borderline personality disorder in patients with bipolar disorder and response to lamotrigine. *Journal of Affective Disorders*, 79:297–303.

Raskin S, Teitelbaum A, Zislin J, et al. 2006. Adjunctive lamotrigine as a possible mania inducer in bipolar patients. *Am J Psychiatry*, 163:159–60.

Rihmer Z, Kiss K. 2002. Bipolar disorders and suicidal behaviour. *Bipolar Disord*, 4(Suppl 1):21–5.

Robinson LJ, Thompson JM, Gallagher P, et al. 2006. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord*, 93:105–15.

Rubio G, Lopez-Munoz F, Alamo C. 2006. Effects of lamotrigine in patients with bipolar disorder and alcohol dependence. *Bipolar Disord*, 8:289–93.

Sabers A, Buchholt JM, Uldall P, et al. 2001. Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Res*, 47:151–4.

Sachs G, Bowden C, Calabrese JR, et al. 2006. Effects of lamotrigine and lithium on body weight during maintenance treatment of bipolar I disorder. *Bipolar Disord*, 8:175–81.

Schaffer A, Zuker P, Levitt A. 2006. Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression. 159th Annual Meeting, American Psychiatrifc Association., Toronto, Ontario, Canada.

Seemuller F, Dehning S, Grunze H, et al. 2006. Tourette's symptoms provoked by lamotrigine in a bipolar patient. *Am J Psychiatry*, 163:159.

Segal J, Berk M, Brooks S. 1998. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clinical Neuropsychopharmacology*, 21:176–80.

Sidhu J, Job S, Singh S, et al. 2006. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *Br J Clin Pharmacol*, 61:191–9.

Simon GE, Von Korff M, Saunders K, et al. 2006. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry*, 63:824–30.

Sinz MW, Remmel RP. 1991. Isolation and characterization of a novel quaternary ammonium-linked glucuronide of lamotrigine. *Drug Metab Dispos*, 19:149–53.

Smith ME, Gevins A, McEvoy LK, et al. 2006. Distinct cognitive neurophysiologic profiles for lamotrigine and topiramate. *Epilepsia*, 47:695–703.

Sotero de Menezes MA, Rho JM, Murphy P, et al. 2000. Lamotrigine-induced tic disorder: report of five pediatric cases. *Epilepsia*, 41:862–7.

Suppes T, Dennehy EB, Hirschfeld RM, et al. 2005. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry*, 66:870–86.

Tavernor SJ, Wong IC, Newton R, et al. 1995. Rechallenge with lamotrigine after initial rash. *Seizure*, 4:67–71.

The Royal Australian and New Zealand College of Psychiatrists. 2004. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder. *Aust N Z J Psychiatry*, 38:280–305.

Tohen M, Vieta E, Calabrese J, et al. 2003. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*, 60:1079–8.

Tomson T, Ohman I, Vitols S. 1997. Lamotrigine in pregnancy and lactation: a case report. *Epilepsia*, 38:1039–41.

Tondo L, Baldessarini RJ, Hennen J, et al. 1998. Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. *Am J Psychiatry*, 155:638–45.

Trojnar MK, Malek R, Chroscinska M, et al. 2002. Neuroprotective effects of antiepileptic drugs. *Pol J Pharmacol*, 54:557–6.

Uher R, Jones HM. 2006. Hallucinations during lamotrigine treatment of bipolar disorder. *Am J Psychiatry*, 163:749–50.

Walden J, Schaerer L, Schloesser S, et al. 2000. An open longitudinal study of patients with bipolar rapid cycling treated with lithium or lamotrigine for mood stabilization. *Bipolar Disord*, 2:336–9.

Weissman MM, Bland RC, Canino GJ, et al. 1996. Cross-national epidemiology of major depression and bipolar disorder. *Jama*, 276:293–9.

Werz MA, Schoenberg MR, Meador KJ, et al. 2006. Subjective preference for lamotrigine or topiramate in healthy volunteers: relationship to cognitive and behavioral functioning. *Epilepsy Behav*, 8:181–91.

Wiard RP, Dickerson MC, Beek O, et al. 1995. Neuroprotective properties of the novel antiepileptic lamotrigine in a gerbil model of global cerebral ischemia. *Stroke*, 26:466–72.

Yatham LN. 2004. Newer anticonvulsants in the treatment of bipolar disorder. *J Clin Psychiatry*, 65(Suppl 10):28–35.

Yatham LN, Kennedy SH, O'Donovan C, et al. 2005. Canadian network for mood and anxiety treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord*, 7(Suppl 3):5–69.