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 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]$p = 0.01$

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