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Lamotrigine and the treatment of mania in bipolar disorder

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Abstract

Anticonvulsants, including valproate and carbamazepine, have established efficacy in the treatment of mania. The anticonvulsant, lamotrigine, has been reported to have antimanic and antidepressant efficacy, and mood-stabilising effects in case reports and preliminary open trials. The efficacy and tolerability of lamotrigine has been compared with olanzapine and lithium in a randomised, prospective, controlled fashion over a period of 4 weeks' treatment in a total of 45 hospitalised patients with DSM-IV-defined mania. Significant improvements of a similar magnitude were observed for all treatment groups and lamotrigine was well tolerated. Mechanisms of action proposed to explain the antimanic activity of lamotrigine include inhibition of voltage-sensitive and use-dependent sodium channels, inhibition of glutamate release and calcium channel blockade. Platelet studies have indicated supersensitivity of glutamate receptors and increased intracellular calcium concentrations in patients with mania. Further clinical and mechanistic studies of lamotrigine use in mania are warranted. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Bipolar disorder; Lamotrigine; Mania; Controlled trial; Tolerability; Mechanisms

1. Introduction

Treatment of mania poses a number of specific management problems. During manic episodes, patients have inflated self-esteem, excess energy, increased goal-directed activity and they may be highly irritable. Their behaviour during such an episode may lead to physical harm, and difficult social and occupational situations (Bauer, 1993). However, the symptoms of mania are often not unwelcome to many patients and, as a consequence, they are reluctant to receive treatment that may reduce these feelings. This reluctance is exacerbated by the fact that the side effects of some antimanic drugs, for example lithium and valproate, are problematic and include sedation, acne and weight gain (Bauer, 1993). Improved therapies for the treatment of mania which have fewer side effects are therefore important to improve compliance and outcome, particularly in patients with type I bipolar disorder.

For many years the standard treatment for mania has been lithium, but there are limitations to its safety and efficacy (Maj et al., 1998). Lithium use is associated with tremor, blurred vision, lack of co-ordination, and may occasionally cause serious and irreversible neurotoxicity, even at therapeutic concentrations (Cookson, 1997). Other

mood stabilisers, such as valproate and carbamazepine, neuroleptics and antidepressants have become the principal alternatives (Bowden, 1998), although valproate use is associated with nausea, weight gain, and, in females, alopecia, hyperinsulinaemia, polycystic ovaries and hyperandrogenism (Isojärvi et al., 1993). Combination therapy has been common in the treatment of bipolar disorder to optimise symptom control, but poses the risk of adverse drug reactions. Preliminary data suggest that the anticonvulsant lamotrigine has antimanic and antidepressant efficacy (Walden et al., 1998). This review will concentrate on the evidence and theories presently available to support and explain the efficacy of lamotrigine in the treatment of mania in patients with bipolar disorder.

2. Evidence to support the use of lamotrigine in mania

2.1. Case reports, case series and preliminary open trials

Although the efficacy of lamotrigine in the treatment of bipolar depression is supported by data from a randomised, placebo-controlled, double-blind trial (Calabrese et al., 1999b), reports of efficacy in mania have so far been limited to case reports, case series and preliminary open

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trials. These cases and open trials have involved the use of lamotrigine as monotherapy or as augmentation therapy with other mood stabilisers. Observations in patients that relate specifically to effects of lamotrigine on mania are summarised below. Case reports/series are presented first, followed by the results of open trials.

The effects of co-administration of lamotrigine and valproate have been documented in a 39-year-old man with refractory bipolar disorder who had been treated previously with lithium, neuroleptics and antidepressants (Walden et al., 1996). Whilst hospitalised during a manic episode, the patient received valproate (2700 mg/day) for a few weeks and showed slight improvement prior to addition of lamotrigine. The dose of lamotrigine was titrated slowly from 25 mg twice daily to 150 mg twice daily. Steady improvement in the patient's condition occurred over the following weeks and the dose of lamotrigine was reduced to 100 mg twice daily. The patient remained stable over the follow-up period of more than 1 year following the start of lamotrigine administration, confirming that the improvement seen was attributable to lamotrigine (Walden, 1998). The patient exhibited no side effects of drug therapy (Walden et al., 1996).

A case series of patients with refractory bipolar disorder provides evidence that lamotrigine, either as monotherapy or in combination with lithium or carbamazepine, leads to improvement in mania (Fogelson and Sternbach, 1997). Four females with type I bipolar disorder presenting in a manic or hypomanic state received varying doses of lamotrigine (200–400 mg daily). Three of these patients showed improvement in condition after 4 weeks of lamotrigine therapy and this improvement increased or was maintained during a further 4 weeks of lamotrigine therapy. Long-term follow-up (5.5–16 months) showed that the patients' improved condition was maintained in all but one patient with continued lamotrigine treatment.

Data on the treatment of refractory bipolar disorder with lamotrigine in combination with valproate have been obtained from a retrospective study of ten children and adolescents who were resistant to commonly used anti-manic agents such as lithium, carbamazepine and valproate (Mandoki, 1997). Improvements on the Clinical Global Impression (CGI) scale were observed when lamotrigine was added to valproate. Doses of lamotrigine ranged from 50 to 200 mg daily and doses of valproate ranged from 500 to 1500 mg daily.

In a 12-month open study, patients with bipolar disorder received lamotrigine as monotherapy or augmentation therapy (Calabrese et al., 1999a). The Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia (MRS from SADS-C) was used to estimate the efficacy of lamotrigine in treating mania. Thirty-one patients presented with hypomanic ($n=6$), manic ($n=14$) or mixed ($n=11$) states; twenty-five patients received lamotrigine as augmentation therapy to other psychotropic drugs and six patients received lamotrigine as monotherapy. Clinically

significant improvement was observed after as little as 1 week of treatment and was maintained over the 48-week treatment period. The mean MRS from SADS-C scores for these patients are presented in Table 1. At the last study observation, 25 patients (81%) showed marked improvement in the MRS from SADS-C score and one patient showed moderate improvement. Six of the thirty-one patients who entered this trial during a hypomanic, manic or mixed manic episode received lamotrigine as monotherapy, with short-term use of chloral hydrate or lorazepam being permissible as required. These patients showed similar improvement in condition over the 48-week treatment period (Calabrese et al., 1997). The mean MRS from SADS-C scores for these patients are also presented in Table 1. At the last study observation, five of these six patients showed marked improvement.

2.2. Randomised, controlled data

The efficacy and tolerability of lamotrigine ($n=15$) compared with olanzapine ($n=15$) or lithium ($n=15$) in hospitalised patients with DSM-IV-defined mania have recently been reported (Berk, 1999). The 4-week treatment regimens were compared in a double-blind, randomised, parallel-group, exploratory fashion with patients recruited from a single site. The age range was 20–59 years and similar numbers of males and females were recruited. The use of psychotropic agents, depot neuroleptics and fluoxetine was prohibited within 1 day, 1 month or 5 weeks, respectively, prior to the start of treatment with study drugs. Patients meeting DSM-IV criteria for alcohol or drug abuse were excluded.

The dosing schedule for lamotrigine was 25 mg daily during week 1, 50 mg daily during week 2 and 100 mg daily during weeks 3 and 4. This was a more rapid titration schedule than recommended to minimise the risk of skin rash, but was necessary due to the short treatment period. Lithium was maintained at a constant dose of 400 mg

Table 1
Efficacy of lamotrigine in patients presenting with hypomania, mania or mixed mania

Time point	MRS from SADS-C score			
	Entire sample ($n=31$)		Monotherapy sample ($n=6$)	
	Mean	<i>P</i> value*	Mean	<i>P</i> value*
Baseline	20.9	–	22.5	
Week 1	13.1	<0.001	11.7	<0.05
Week 24	5.2	ns	7.0	ns
Week 48	2.2	ns	0.5	ns
LOCF	5.4	<0.01	5.0	<0.05

LOCF; Last observation carried forward.

MRS; Mania Rating Scale.

SADS-C; Schedule for Affective Disorders and Schizophrenia.

ns; Not significant.

*Compared with baseline.

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