

Lamotrigine in bipolar affective disorder

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Aims and method The study aimed to assess the available data on the use of lamotrigine as a mood stabilising agent. We reviewed all published and unpublished data available to us through a Medline search from 1987–1998 and from our own files, which include reference materials presented at conferences as well as published reports.

Results Most of the data found were derived from case reports or open trials. We could find no published double-blind, placebo-controlled studies. The data from initial open trials suggest that lamotrigine may be effective in bipolar disorder, but further data are required before specific treatment recommendations can be made.

Clinical implications At this early stage, there are too few data to recommend lamotrigine for first or second line therapy in bipolar disorder. However, initial reports are very promising and this agent may eventually be unequivocally shown to be useful in treating mania, hypomania, depression, rapid cycling and mixed affective states in people with bipolar disorder.

Lamotrigine, an anticonvulsant, is licensed in the UK as monotherapy for the treatment of partial seizures and primary and secondary generalised tonic-clonic seizures. It is believed to act by inhibiting the release of excitatory neurotransmitters (glutamate and aspartate) by blocking voltage-dependent sodium channels and by stabilising presynaptic neuronal membranes (McKee & Brodie, 1996). It may also have effects on calcium channels. As well as being useful in the treatment of epilepsy, lamotrigine, like other anticonvulsants, has also been reported to be useful in the treatment of refractory bipolar disorder and rapid-cycling bipolar disorder. A few reports of improvement in quality of life measures when used in people with epilepsy prompted the use of this drug in patients with psychiatric illness. Data about its psychotropic effects are, however, largely reported as case histories and open trials and are discussed below.

Clinical studies and case reports

In the first published case report, a 49-year-old man with a long-standing history of rapid cycling

disorder presented while in the depressed phase of his illness (Calabrese *et al.* 1996). The patient had previously not responded to lithium and was unable to tolerate carbamazepine. Lamotrigine was started at 25 mg/day for two weeks and increased to 200 mg/day over five weeks. Over a 20-week period the patient's Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960) score fell from 46 to nine and his Global Assessment Scale (GAS; Endicott, 1976) score increased from 32 to 69. Eleven months later the patient remained euthymic. The authors postulated that lamotrigine has antidepressant effects and will not induce mania in patients with rapid-cycling bipolar disorder.

In a case report where lamotrigine was added to valproate therapy (Walden *et al.* 1996), a 39-year-old man presented while in the manic phase of bipolar affective disorder. He had previously been treated with various neuroleptics, antidepressants and lithium. He was admitted and initially treated with neuroleptics, benzodiazepines and carbamazepine (1500 mg/day). This regimen proved to be ineffective and so the carbamazepine was changed to valproate (up to 2700 mg/day). Some improvement was noted, although a mixed dysmorphic manic state persisted. The patient was discharged on valproate and 10 weeks later lamotrigine was added at 25 mg twice a day which was slowly increased to 150 mg/day. The patient responded well.

In the following year, Kusumaker & Yatham (1997a) described seven patients with rapid-cycling bipolar disorder who were also treated with lamotrigine. Six of these patients were newly diagnosed and started on lamotrigine 25 mg twice a day. This was increased to 50 mg twice a day one week later and to 75 mg twice a day three weeks later if required. Four patients responded; all by the third week. The seventh patient (an elderly woman) had an eight-year history and had previously been treated with lithium, carbamazepine and valproate (divalproex). She was most recently taking valproate which controlled her hypomania but not her depressive symptoms. During a depressive episode lamotrigine was started and symptoms resolved in a week. The dose was not stated but the patient developed a

rash four weeks later. Lamotrigine was discontinued but recommenced four days later and the patient has remained well.

In the same year these same authors (Kusumaker & Yatham, 1997b) also reported on 22 patients with bipolar depression who had lamotrigine added to their valproate therapy in an open naturalistic setting. Sixteen of these patients had a 50% or greater reduction in their HAM-D score by week 6 and no patient switched to mania.

Fogelson & Sternbach (1997), have further reported an open trial of lamotrigine in refractory patients. Six patients had treatment-refractory bipolar I disorder (four with rapid cycling) and one patient had bipolar schizoaffective disorder. All patients had failed an adequate trial of at least six antidepressants, mood stabilisers or other combinations. Lamotrigine was given in maintenance doses between 50 mg and 400 mg/day, in addition to various other therapies (carbamazepine, lithium, acetazolamide, risperidone, dexamphetamine and trazodone). At eight-week follow-up, three of the four rapid-cycling patients had marked improvement (complete remission of symptoms) and one showed no improvement and discontinued at eight weeks because of nausea. The bipolar schizoaffective patient did not respond and the other two bipolar I patients had a moderate response (significant amelioration of symptoms). The longer-term outcome (i.e. between 14 and 65 weeks) was less promising with only two of the rapid-cycling patients sustaining a marked improvement. One now showed a moderate response and only one of the bipolar I patients still showed a moderate response.

Fatemi *et al* (1997) also studied the use of lamotrigine, in a naturalistic setting, in five patients with treatment-resistant rapid-cycling bipolar disorder. Lamotrigine was given for a mean of 225.8 days, either as monotherapy or as add-on therapy (mean dose=185 mg/day). Data were analysed using a random regression model. Depressive symptoms and social functioning improved in a dose- and time-dependent manner.

A retrospective study also recently reported the outcome of 16 patients with bipolar disorder (13 bipolar I, three bipolar II) not satisfactorily controlled by standard mood stabilisers, who had been treated with lamotrigine for a period of 2–6 weeks (mean five weeks) (Sporn & Sachs, 1997). At the beginning of treatment, nine patients were depressed, six were in a mixed state and one was diagnosed with mania. Eight patients were considered to be responders (Clinical Global Impressions scale (CGI; Guy, 1976) ≤ 2). Those who responded were either in the depressed or mixed phase; all had an improvement in their depressive symptoms. Unfortunately, two of the people with depression

who did not respond switched to either mania or a mixed state and one responder switched from a mixed state to hypomania. The maximum dose of lamotrigine reached was between 50 and 250 mg/day with a mean dose of 141 mg/day for responders.

In the most recent case report (Labbate & Rubey, 1997), lamotrigine was given to a 48-year-old gentleman with treatment refractory bipolar disorder (depressed phase). While remaining on various psychotropics, he was started on 25 mg/day which was increased to 500 mg/day over six weeks. Treatment was considered successful with improvement in his mood and allowing the discontinuation of most of his psychotropics.

Preliminary data on two unpublished trials have recently been presented. Bowden *et al* (at the American Psychiatric Association 151st Annual Meeting, 1998; further details available from the author upon request) has outlined the results of a placebo-controlled open trial. He recruited from 21 centres in the US and Europe, 192 out-patients with bipolar I disorder who were depressed on entry into the study. Lamotrigine (200 mg/day) showed clear evidence of antidepressant efficacy as assessed by the HAM-D; with a lesser effect seen with 50 mg/day thus suggesting a dose-related response. Calabrese (at the American Psychiatric Association 151st Annual Meeting, 1998; further details available from the author upon request) also reported on his unpublished 48-week open-label, prospective trial of 75 treatment-refractory patients. Of 41 people with depression in this study, 68% showed significant improvement. Of 31 presenting with a manic, mixed or hypomanic presentation, 84% improved.

Adverse effects

Alongside these reports of the positive psychotropic effects, lamotrigine has also been associated with adverse psychiatric effects. Delirium has been described in one case report of a 39-year-old woman when the lamotrigine dose was increased to 150 mg/day, resolving when the dose was lowered to 100 mg/day (Sporn & Sachs, 1997). She had been given lamotrigine in combination with lithium because of a history of mood elevation and depression which had previously not responded well to lithium, carbamazepine, clonazepam and valproate. Encephalopathy has also been described in another recent case report (Hennessey & Wiles, 1996). Apart from 'switching' into mania (described above), other adverse psychiatric effects reported in people with epilepsy include aggression, confusion, depression and psychosis, although a causal effect has not been established (McKee & Brodie, 1996).

The rash associated with lamotrigine has received a great deal of media attention in recent months because of the potential of developing Stevens–Johnson syndrome, toxic epidermal necrolysis and angioedema. Predisposing factors include age (more common in childhood), concomitant valproate therapy and rapid titration. Other common adverse effects include headache, nausea, vomiting, diplopia and dizziness. Hepatic dysfunction and blood dyscrasias may also occur less commonly.

At this early stage it appears that lamotrigine may be useful in bipolar patients with depressive symptoms as well as those with hypomania, mania, mixed states or rapid cycling. More formalised, randomised controlled trials are needed. If lamotrigine is to be used, it should be started at doses recommended in epilepsy by the manufacturer and increased according to instructions. It should be noted that these recommendations are more cautious than many of the regimens described here.

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