

Adjunctive Lamotrigine Treatment for Adolescents with Bipolar Disorder: Retrospective Report of Five Cases

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ABSTRACT

Background: Our aim was to evaluate the effectiveness, safety, and tolerability of adjunctive lamotrigine in the treatment of adolescents with bipolar disorder.

Method: We evaluated all patients under age 18 with *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) bipolar disorder in our outpatient clinic treated with lamotrigine, using the Clinical Global Impression (CGI) scale. We rated response with the CGI—Improvement (CGI-I) scale.

Results: Five patients (mean age = 15.5 ± 1.8 years; range = 14–17), 1 male and 4 females, were included. One patient (20%) had bipolar I disorder, 1 (20%) had bipolar II disorder, and 3 (60%) had bipolar disorder not otherwise specified (NOS). The polarity of the episode at baseline was depressive in all patients. The mean lamotrigine dose was 100 ± 87.5 mg/day (1.67 ± 1.39 mg/kg/day). The mean duration of treatment was 28 ± 28 weeks. CGI significantly improved from 5 at baseline to 3 ± 1 at endpoint ($p = 0.011$). Improvement was marked or moderate in 4 patients (80%) and minimal in 1 patient (20%). One patient referred to dizziness, and there were no reports of increased cycling, worsening of mania, or skin rash.

Conclusions: This open, retrospective chart review suggests that lamotrigine may be effective and well tolerated as an adjunctive treatment in adolescents with bipolar disorder. Controlled trials are needed.

BACKGROUND

LAMOTRIGINE, A PHENYLTRAZINE DERIVATIVE, is a well-established anticonvulsant agent that has shown efficacy in the prevention of mood episodes in adults with bipolar disorder (BD)

(Goldsmith et al. 2003; Fitton and Goa 1995; Culy and Goa 2000). The mechanism of action of this drug in patients with BD may be related to the inhibition of sodium and calcium channels in presynaptic neurons, which causes a stabilization of the neuronal membrane (Gold-

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smith et al. 2003; Fitton and Goa 1995; Li et al. 2002).

The efficacy of lamotrigine in the treatment of adults with BD has been investigated in 10 randomized, double-blind, placebo-controlled clinical trials (Goldsmith et al. 2003; Calabrese et al. 2003; Bowden et al. 2003; Calabrese et al. 1999; Frye et al. 2000; GlaxoSmithKline 2003). Four of these trials studied lamotrigine as a maintenance therapy for its potential to prevent mood episodes. They found that lithium and lamotrigine are effective in preventing any mood episode, increasing time between episodes. Only lamotrigine was superior to placebo in the prevention of depressive episodes, and only lithium was significantly superior to placebo in the prevention of manic/hypomanic episodes (Calabrese et al. 2003; Bowden et al. 2003). Six of these trials studied the use of lamotrigine as a short-term treatment for current mood episodes. Two studies suggested that lamotrigine was effective in patients with bipolar depression (Calabrese et al. 1999; Frye et al. 2000). However, other studies failed to show a difference between lamotrigine and placebo in the treatment of acute BD mood episodes, using the primary-endpoint Montgomery-Asberg Depression Rating Scale (MADRS) and 17-item Hamilton Depression Rating Scale (HAM-D) scores (Goldsmith et al. 2003).

Many studies about lamotrigine have been carried out in adults, but, to our knowledge, only one study has been published on adolescents. They included 9 adolescents (mean age = 16.4; range = 14–18) with mood disorders. Six of them had bipolar depression, 2 unipolar depression, and 1 a mood disorder not otherwise specified (NOS). The mean lamotrigine dose used was 141.7 mg/day (range = 25–250). Clinical Global Impression (CGI), overall illness improved in 8 of 9 patients (89%). Seven children (78%) rated as much improved, and 1 (11%) as very much improved (Caradang et al. 2003). Other open studies reported the efficacy of anticonvulsants in adolescents with BD: A study of valproate, carbamazepine, or lithium monotherapy (all three treatments were effective) (Kawatch et al. 2000) and another study of adjunctive topiramate (DelBello et al. 2002). A double-blind, placebo-controlled study doc-

umented the efficacy of lithium as a mood stabilizer in 25 adolescents with BD comorbid with substance abuse (Geller et al. 1998).

The initial dose of lamotrigine in adolescents and adults who are not taking valproic acid is 25 mg/day during the first 2 weeks, followed by 50 mg/day, given in 2 divided doses in the next 2 weeks. The usual maintenance dose is 100–400 mg/day, given in 2 divided doses. Patients who take valproic acid start with 25 mg every other day for the first 2 weeks, then 25 mg/day for the next 2 weeks, and, from then on, we should increase the dose 25–50 mg/day every 1 or 2 weeks. The final dose is 100–200 mg/day, given twice-daily.

Lamotrigine can interact with other psychotropics used as mood stabilizers. Valproic acid inhibits the metabolism of lamotrigine when lamotrigine is begun in patients already receiving valproic acid, so when a patient is taking valproic acid and begins treatment with lamotrigine, valproate levels can decrease and lamotrigine levels can increase. This could result in a greater risk of skin rash and tremor. Carbamazepine and other cytochrome P450 inducers (phenytoin, phenobarbital, and primidone) induce the metabolism of lamotrigine, and there could be a higher risk for dizziness, as well as double and blurred vision, in these patients.

The aim of this report was to evaluate the effectiveness, safety, and tolerability of adjunctive lamotrigine in the treatment of adolescents with bipolar disorder.

METHOD

We included all patients (age <18) with *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association 2000) BD evaluated at the University Clinic, University of Navarra (Pamplona, Spain), Department of Psychiatry and Medical Psychology, Child and Adolescent Psychiatry outpatient clinic treated with lamotrigine using the Clinical Global Impression—Severity scale (CGI-S). We retrospectively rated the response with the CGI—Improvement scale as: 1 = very much improved, 2 = much improved, 3 = minimally

TABLE 1. CLINICAL CHARACTERISTICS OF FIVE ADOLESCENTS WITH BIPOLAR DISORDER TREATED WITH ADJUNCTIVE LAMOTRIGINE

Patient	Age/gender/ Race	Primary diagnosis	Comorbid diagnoses	Prior medication	Baseline medication	Current medication	Lamotrigine dose mg/day mg/kg/day	Duration (weeks)	Response (CGI-I)	Side effects
1	16.2/F/W	BD-NOS, D	ED-NOS	Fluoxetine Sertraline	Valproate Quetiapine	Valproate Quetiapine	75 0.75	56	Very much improved (1)	None
2	17.5/F/W	BD-NOS, D	Marijuana abuse	Olanzapine Paroxetine Lorazepam	Valproate Lithium Quetiapine	Valproate Quetiapine	100 1.67	32	Very much improved (1)	Dizziness (transient)
3	15.5/F/W	BD-II, D	Marijuana, alcohol, and cocaine abuse	Paroxetine Fluoxetine Lorazepam Thioridazine	Quetiapine Valproate	Valproate	150 2.67	24	Minimally improved (3)	None
4	15.1/M/A	BD-I, D	None	Carbamazepine Haloperidol Sertraline	Carbamazepine Risperidone	Carbamazepine Risperidone	200 3.5	28	Very much improved (1)	None
5	15.3/F/W	BD-NOS, D	None	Risperidone Sertraline Zolpidem	Valproate Olanzapine	Valproate Olanzapine	100 0.96	8	Much improved (2)	None

CGI-I = Clinical Global Impression—Improvement; F = female, M = male, W = white, A = African; BD = bipolar disorder, D = depressive episode, Mix = mixed episode, ED = eating disorder; NOS = not otherwise specified.

Note. Baseline medications = treatment regimen when lamotrigine was added. Prior medications = medications used that were discontinued before starting lamotrigine.

improved, 4 = no change, 5 = minimally worse, 6 = much worse, or 7 = very much worse.

We identified all patients under age 18 treated with lamotrigine—a total of 9. We excluded 4 patients for different reasons: 1 patient had a mood disorder and comorbid mental retardation, and 3 patients because they did not have a mood disorder, despite having significant depressive symptoms (depression and irritability), 2 patients had anxiety disorder, and 1 had a somatoform/conversion disorder.

We used the DSM-IV-TR symptom checklist to diagnose BD, in which a manic episode consists in: Elevated, expansive, or irritable mood during a minimum of 1 week, in association with at least three of the following: Grandiosity, decreased sleep, increased talkativeness, racing thoughts, distractibility, psychomotor agitation, and participation in pleasurable activities with painful consequences. If symptoms last 4–6 days, and the patient has presented depressive episodes in the past, DSM-IV-TR classifies the type as bipolar II disorder.

RESULTS

Five patients (mean age 15.5 ± 1.8 ; range = 14–17 years), 1 male and 4 females, were included in the analysis. Demographic and clinical characteristics of these patients are shown in Table 1. One patient (20%) had bipolar I disorder, 1 (20%) had bipolar II disorder, and 3 (60%) had BD-NOS. The polarity of the episode at baseline was depressive in all the patients. The mean lamotrigine dose was 100 ± 87.5 mg/day (range = 75–200 mg/day) or 1.67 ± 1.39 mg/kg/day (range = 0.75–3.5 mg/kg/day), and the mean duration of treatment was 28 ± 28 weeks (range = 8–56 weeks). All 5 patients displayed persistent affective symptoms that impaired their functioning. Before adding lamotrigine, all patients were following a treatment with a mood stabilizer (lithium, carbamazepine, and/or valproate) and an antipsychotic (olanzapine, risperidone, or quetiapine). We increased the lamotrigine dose gradually, as we described in the Introduction. No serious adverse events were re-

ported. Lamotrigine was well tolerated. Only 1 patient reported dizziness, and none referred to serious adverse events, such as skin rash. There were no reports of increased cycling or worsening of mania. CGI significantly improved from 5 (markedly ill) at baseline to 3 ± 1 (mildly ill) at endpoint ($p = 0.011$). Three patients (60%) showed marked improvement, 1 (20%) moderate, and 1 (20%) showed minimal improvement.

CASE REPORTS

Patient 1

Patient 1 (Table 1) was a 16-year-old female with a 6-year history of depressed mood, irritability, feelings of worthlessness, and decreased sleep. Her brother had major depressive disorder, and an aunt had committed suicide. Over the last 3 years, she had presented with physical aggressiveness, sexual disinhibition, increased appetite, binge episodes, and obsessive thoughts about her weight. She had been taking fluoxetine 20 mg/day for the last 3 years. We first made a diagnosis of major depression, oppositional-defiant disorder, and eating disorder (binge-eating disorder) and gradually increased the fluoxetine dose up to 60 mg/day. However, the patient showed increased irritability and aggressiveness. After 5 months, we changed it to sertraline (50 mg/day) and associated clonazepam (1.5 mg/day). In 2 months, she had a hypomanic episode (extreme irritability, psychomotor agitation, decreased need for sleep, rapid thoughts, and hypersexual behavior), so sertraline was discontinued and we then changed the diagnosis to BD-NOS. The patient started treatment with sodium valproate (1,500 mg/day; serum levels = 77 μ g/mL) and olanzapine (10 mg/day), which turned her slightly less aggressive. Because of side effects (she had a weight gain of 8 kg and sedation), olanzapine was discontinued after 6 months. One year after her first visit, she was started on quetiapine (200 mg/day).

Because the patient still showed depressive symptoms 6 months later, we added lamotrigine to her previous treatment regimen of val-

proate sodium (decreasing the dose to 1,250 mg/day; serum levels = 108 µg/mL), quetiapine (200 mg/day), and clonazepam (1.5 mg/day). The lamotrigine dose was increased to 75 mg/day at 6 weeks. After 6 months of lamotrigine treatment, she continued having irritability and oppositionality, and we increased the lamotrigine dose to 100 mg/day. She then showed a marked response within 6 weeks and presented with euthymic mood, good academic performance, improvement of social relationships, and better sleep. She did not refer to side effects and lost 6 kg in 2 months. She has not presented with any mood episode after 13 months.

Patient 2

Patient 2 (Table 1) was a 17-year-old female with a 6-month history of disorganized behavior, extreme irritability, euphoric mood, grandiosity, hypersexual behavior, and money theft at home. She had been using marijuana for the previous 4 months. For the last 3 months, she took paroxetine (20 mg/day), which worsened her symptoms. At the age of 3 years, she presented with a period of temper tantrums and insomnia. On her first visit to our clinic, we diagnosed her with BD-NOS. We discontinued paroxetine and started treatment with sodium valproate 500 mg/day. She refused to take any medication and was agitated and irritable (she ran away from home at 3 a.m. and required police intervention to return), so she was hospitalized. We started treatment with sodium valproate (titrating up to 1,200 mg/day; serum levels = 98 µg/mL). Two months later, once in home, she presented with manic symptoms, so we added lithium (800 mg/day; blood levels = 0.7 mEq/L). Five months after her first visit, she showed a moderate response but still had mixed symptoms (grandiosity, decreased sleep, apathy, and suicidal ideation) and had quit school. We then added olanzapine (5 mg/day) but had to stop it after 15 days of treatment because of excessive sedation. We started treatment with quetiapine (up to 1,200 mg/day), to which she had a moderate response.

She continued showing anhedonia, apathy, hypersonnia, and social isolation. She was

sleeping until 3 p.m., not going to school nor working, and spending most of the day at home. Occasionally, she would run away from home to have sex with a casual boyfriend and would return the next day. We added lamotrigine 25 mg/day to her regimen of valproate, lithium, and quetiapine and titrated it over 8 weeks to 100 mg/day. Two weeks later, lithium was gradually tapered because it caused subclinical hypothyroidism and tachycardia. Within four weeks of treatment, she got involved in social activities, attended a professional school, and was euthymic. Initially, she referred to dizziness, which disappeared in a few days. Six months later, we increased the lamotrigine dose (150 mg/day). On lamotrigine (150 mg/day), quetiapine (600 mg/day), and sodium valproate (1,000 mg/day; serum level = 81 µg/mL), she remained euthymic for the following 8 months.

Patient 3

Patient 3 (Table 1) is a 14-year-old girl with a 7-month history of depressed mood, daytime sleepiness, academic failure, oppositional behavior (ran away from home), and suicidal gestures. She had previously received treatment with selective serotonin reuptake inhibitors (SSRIs) (paroxetine and fluoxetine). This medication resulted in elated mood, grandiosity, increased energy, and decreased need of sleep. At age 12 years, after moving to another school, she had been using substances (alcohol, cannabis, and cocaine) for a year. Many family members suffered mood disorders. We diagnosed bipolar II disorder, current depressive episode, and cannabis and cocaine abuse. In her first visit, we took her off the medication she was taking (thioridazine = 30 mg/day and lorazepam = 2 mg/day), and she received valproate (1,000 mg/day) instead. In 2 weeks, she improved her oppositional behavior, aggressiveness, and impulsiveness.

However, she continued having depressive symptoms, so 3 months later we added lamotrigine, titrating up in 4 weeks to 50 mg/day. This change improved her mood (less lability and irritability) but did not modify her school avoidance, defiance, oppositionality, and social isolation. We hospitalized her in order to

increase the lamotrigine dose to 150 mg/day and the valproate dose to 2,000 mg/day (serum level = 80 mEq/L). She showed less irritability and defiance but continued with social isolation and school avoidance after 2 months on this treatment. She referred to mild daytime sedation and distal tremor.

Patient 4

Patient 4 (Table 1) was a 15-year-old boy from an equatorial African country who came to our clinic because, a year ago, after a dental extraction, he suddenly presented with his first manic episode, which consisted of: Decreased need for sleep (awake for the whole night drawing and reading), talkativeness, increased energy, irritability, grandiosity, visual hallucinations, and paranoid delusions. A psychiatrist prescribed haloperidol (which dose could not be specified by the family) 10 days later. Although he did not have to be hospitalized, he could not attend school for a month. Treatment with haloperidol eliminated most manic symptoms but caused mild sedation, so it was stopped 2 months later. In the next 15 days, mixed symptoms reappeared, and he was treated with sertraline (20 mg/day), with partial clinical improvement. After 3 months, sertraline was discontinued, because the patient had a hypomanic episode, as well as extrapyramidal symptoms of the tongue. At this point, he started treatment with risperidone (4 mg/day), which improved his irritability and aggressiveness, so they decreased the dose gradually to 1 mg/day. However, for the last 5 months, he presented with sadness, asthenia, lack of energy, feelings of guilt and worthlessness, diminished concentration, doubtfulness, and social isolation. Appetite and sleep were preserved, and he denied suicidal ideas. He had always been an introverted child with very good academic performance, but in the last term, he had failed his exams. He had been taking carbamazepine owing to epilepsy since 15 days after his birth. A recent electroencephalograph (EEG) was normal. The day he came to our clinic he was on risperidone (1 mg/day) and carbamazepine (400 mg/day; serum levels = 5 µg/mL).

We diagnosed bipolar disorder type I, current episode depressive, and decided to add lamotrigine (tapering up to 200 mg/day in 4 weeks) to his regimen. The dose of carbamazepine was increased to 600 mg/day because of low blood levels. In 7 months, he was euthymic and his academic results and peer relationships improved. He developed hyperprolactinemia (serum prolactin levels: 19.2 ng/mL) caused by risperidone, and in a magnetic resonance imaging (MRI), we found an enlargement of the anterior pituitary gland, so risperidone was gradually tapered and discontinued. He remained stable after 3 months.

Patient 5

Patient 5 (Table 1) was a 15-year-old girl who came to our clinic because she had presented with sadness associated with malaise, academic failure, lack of initiative, feelings of worthlessness, anxiety, and insomnia for the last 2 years. She had bingeing episodes without purging, so she had developed obesity (body mass index [BMI] = 28.5 kg/m²). The patient attributed these symptoms to problems with classmates. At birth, she presented with perinatal stress, but her subsequent development was normal. Her mother had dysthymia. We diagnosed a mood disorder NOS and recommended treatment with sertraline (50 mg/day) and zolpidem. After 1 month of treatment, symptoms had mildly improved, so we increased the antidepressant dose (100 mg/day). Within days, she presented with elated mood, irritability, oppositional behavior (she ran away from home and quit school), talkativeness, racing thoughts, and motor agitation. We then diagnosed BD-NOS and recommended to stop sertraline and start treatment with valproate (titration up to 1,500 mg/day; serum levels = 72 µg/mL) and olanzapine (titration up to 15 mg/day). In the following visits, she had a moderate response, but she was still sad, labile, and irritable.

Five months after her first visit, we started treatment with lamotrigine, gradually increasing the dose up to 100 mg/day at 8 weeks. At the same time, we decreased the olanzapine dose to 10 mg/day and the val-

proate dose to 900 mg/day (serum levels = 79 µg/mL). She was still apathetic and oppositional, but as lamotrigine had been added, she showed more emotional stability and less irritability. Because she persistently gained weight (25 kg since her first visit), we progressively stopped olanzapine and increased lamotrigine (300 mg/day). During the next 6 months, she was euthymic, she attended professional school, which she passed with excellent grades, and showed better control of her impulses.

DISCUSSION

This study, as it was only a preliminary observation, had several methodological limitations. Most importantly, these are nonblinded, noncontrolled case reports. The lack of a randomized, double-blind, placebo-controlled design and the use of concomitant medications do not allow to attribute the observed antidepressant and possible mood-stabilizing effects entirely to lamotrigine. Also, we cannot exclude the possibility of placebo response, rater or patient bias, or spontaneous remission. Lamotrigine was added to the ongoing psychotropic regimen in all 5 patients; it is, therefore, uncertain whether the observed positive response after adding lamotrigine was a result of lamotrigine alone, a late response to the prior drug regimen, or a synergistic response with lamotrigine. Although these findings must, therefore, be regarded as provisional, pending substantiation in controlled trials, this retrospective study suggests that adjunctive lamotrigine may be effective and is well tolerated in the treatment of adolescents with bipolar disorder.

CONCLUSIONS

Despite the limitations of this retrospective study, all 5 patients had received adequate mood stabilizer and antipsychotic medication trials and had failed to respond to combination treatments. The fact that they responded to lamotrigine is important, because these pa-

tients had shown a poor or partial response or lack of tolerance owing to adverse events to other mood-stabilizing medications. Controlled trials are needed to evaluate the efficacy, safety, and tolerability of lamotrigine in adolescents with bipolar disorder.

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