Treatment of bipolar II disorder with lamotrigine

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Tratamiento del trastorno bipolar II con lamotrigina

Summary

Introduction. *This study analyzes the effectiveness and safety of lamotrigine in the treatment of bipolar II disorder.*

Patients and methods. *Seventeen patients with DSM-IV bipolar II disorder with a history of poor response to lithium or other mood-stabilizers gave their consent to be treated with lamotrigine. They were followed-up for 6 months and assessed with the Young Mania Scale (YMRS), Hamilton Depression Rating Scale (HDRS-17) and the modified version of the Global Clinic Impresion Scale for Bipolar Disorder (CGI-BP-M).*

Results. *Twelve patients completed the study. Three patients dropped out due to side effects (two because of mild rash, which vanished after treatment was discontinued and one because of vomiting) and two due to lack of efficacy. The mean dose of lamotrigine for patients completing the study was 202.1 ± 64.4 mg/day. There was a significant improvement in HDRS-17 scores (p = 0.004) and the depressive (p = 0.002) and overall (p = 0.002) subscales of the CGI-BP-M.*

Conclusions. *This study confirms previous findings concerning the antidepressant profile of lamotrigine and its potential effectiveness in bipolar II disorder.*

Key words: *Bipolar II disorder. Lamotrigine. Depression. Clinical trial.*

Resumen

Introducción. *Se analiza la efectividad y seguridad de la lamotrigina en el tratamiento de pacientes bipolares de tipo II.*

Pacientes y métodos. *Un total de 17 pacientes con trastorno bipolar II según criterios DSM-IV con antecedentes de respuesta insuficiente al tratamiento con litio u otros eutimizantes dieron su consentimiento para recibir lamotrigina para el tratamiento de su enfermedad. La respuesta se evaluó con la Escala de Manía de Young (YMRS), Escala de Hamilton para la Depresión (HDRS-17) y la versión modificada de la Escala de Impresión Clínica Global para el Trastorno Bipolar (CGI-BP-M) a lo largo de 6 meses.*

Resultados. *Completaron los 6 meses de seguimiento 12 pacientes. Hubo tres abandonos por efectos secundarios (dos por exantema de escasa gravedad que desapareció al interrumpir el tratamiento y uno por vómitos) y dos por falta de eficacia. La dosis media de lamotrigina de los pacientes que completaron el estudio fue de 202,1 ± 64,4 mg/día. Se produjo una mejoría significativa en las escalas HDRS-17 (p = 0,004) y las subescalas de depresión (p = 0,002) y general (p = 0,002) de la CGI-BP-M.*

Conclusiones. *Este estudio confirma los hallazgos de estudios previos respecto al perfil predominantemente antidepresivo de la lamotrigina y su potencial terapéutico en el trastorno bipolar II.*

Palabras clave: *Trastorno bipolar II. Lamotrigina. Depresión. Ensayo clínico.*

INTRODUCTION

On the contrary to the generalized opinion that type II bipolar disorder is simply an attenuated or mild form of the classical maniac-depressive psychosis or type I bipolar disorder, several studies have demonstrated that its longitudinal course is characterized by a greater number of episodes[1], particularly depressive[2], greater percentage of rapid cyclers[3] and of associated psychiatric disease[4] and greater risk of suicide[5]. Consequently, the limited number of studies focusing on the treatment of this disorder is surprising. A two year follow-up demonstrated that appropriate treatment can radically change the prognosis[6], reducing the number of relapses significantly. The key would be the use of mood stabilizers and antidepressives, avoiding the use of tricyclics as much as possible[7].

Lamotrigine is a drug indicated in the treatment of partial and generalized epilepsy in both adults and children[8]. Its fundamental action mechanism is that it blocks the sodium channels of the neuronal membrane, reducing the release of excitatory amino acids such as glutamate, although other mechanisms could also be

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involved in both its anti-epileptic activity as well as in its effects on the mood status. Based on the accumulated experience with other anti-epileptic drugs that have been demonstrated to possess mood stabilizing properties, such as carbamazepine and valproate, several groups of investigators have studied the efficacy of lamotrigine in bipolar disorder. One study demonstrated that lamotrigine was effective in the treatment of the depressive phase of the disease[9], and another that it had prophylactic properties in rapid cycling bipolar disorder[3]. This last study suggests that lamotrigine could be especially effective in the long term treatment of bipolar II disorder. To verify this hypothesis, the present study analyzed the response of a series of patients diagnosed of bipolar II disorder after treatment with lamotrigine during a 6 month period.

METHODOLOGY

A total of 17 patients who complied with the diagnostic criteria of the DSM-IV for type II bipolar disorder gave their consent to participate in the study. Mostly (n = 13) the response to lithium or to other anti-epileptic agents had been unsatisfactory; in other cases, lamotrigine was chosen due to contraindications to other drugs or patient preference. The study design was open, observational, and prospective over 6 months. Response to treatment was evaluated by the Spanish version of the Young Mania Scale (YMRS)[10], the Hamilton Depression Rating Scale (HDRS)[11] and the modified version of the Global Clinical Impression Scale for Bipolar Disorder (CGI-BP-M)[12]. In each visit, appearance of adverse effects and use of concomitant medication were also evaluated. In every case, lamotrigine was introduced in a stepwise way at a dose increase rhythm of 25 mg/week given that it has been demonstrated that this reduces the risk of the appearance of exanthema[8]. The final dose was individualized for each patient, considering efficacy and tolerability criteria, and the dose of 200 mg/day as target dose based on that observed in the controlled studies was maintained as a reference[13]. During treatment with lamotrigine, it was attempted to maintain the concomitant medication received by the patients unchanged. An analysis for intention to treat was performed with last observation carried forward analysis to strictly compare the status of the patients before and after the treatment. The statistical analysis was performed with non-parametric tests (Wilcoxon).

RESULTS

The sample composition was made up of 17 bipolar II patients with depressive symptoms and signs (n = 13), hypomaniac (n = 2) or in partial remission (n = 2) who demonstrated unsatisfactory response from any point of view (inefficacy, intolerability, personal rejection) to the conventional treatments. Concomitant treatment is shown in table 1. Mean age of the patients was 41.1 ± 10.7. There was a predominance of women (12.71%).

TABLE 1. Concomitant medication taken by the patients during the study

	N	*%*
Lithium	6	35.3
Loracepam	6	35.3
Valproate	4	23.5
Carbamazepine	2	11.8
Clonacepam	2	11.8
Topiramate	1	5.9
Paroxetine	1	5.9
Venlaxafine	1	5.9
Quetiapine	1	5.9
None	5	29.4

Twelve patients (71%) completed the 6 months of follow-up. There were three drop outs due to secondary effects (two due to exanthema, that disappeared when the treatment was discontinued, and one due to vomiting) and two due to lack of efficacy. The mean dose of lamotrigine at 6 months was 160.3 ± 86.6 mg/day for all the sample and 202.1 ± 64.4 mg/day for the patients who completed the study.

To evaluate the treatment efficacy, the scores of the HDRS and YMRS scales with the subscales of the CGI-BP-M (mania, depression, and longitudinal course) were compared between the baseline and final visit, carrying forward the values of the patients who dropped out. This analysis was also performed in the subgroup of patients who initiated the treatment during a depressive episode, these being the majority.

For all the sample, statistically significant differences were obtained between the initial and final scores of the HDRS scale (p = 0.004) and the subscales of the CGI-BP-M of depression (p = 0.002) and longitudinal course (p = 0.002) as is shown in figure 1. There were no differences in the YMRS scale and the CGI-BP-M mania subscale. Ten of the 13 patients who initiated the treatment during a depressive phase showed improvements superior to 50% of the baseline score in the HDRS scale, which implies a 76.9 % percentage of responders. However, since one of the responder patients really presented a shift towards hypomania, with a score of 17

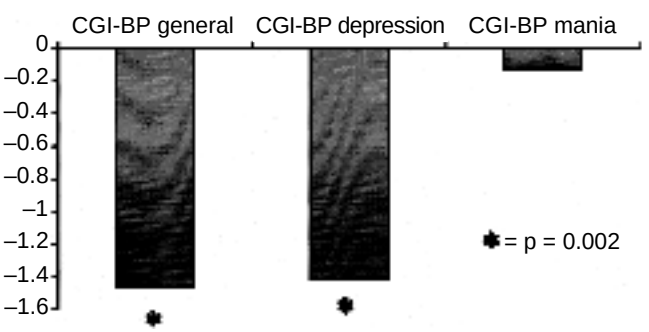

Figure 1. Average reduction of scores of the CGI-BP-M after the administration of lamotrigine.

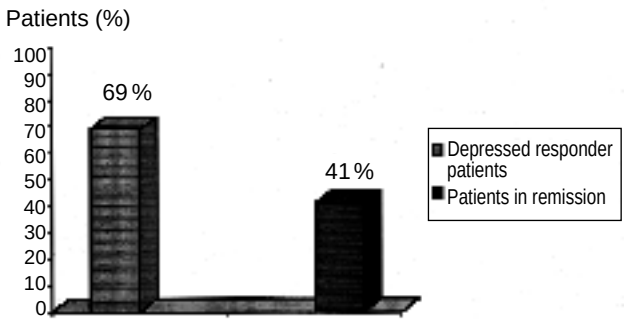

Figure 2. Percentage of response and remission at 6 months by intent to treat of the patient who initiated the study in the depressive phase.

points in the YMRS, the real value of responders would be 9/13, that is 69.2%. Applying the strict remission criterion of presenting a score of 8 points or less on both the YMRS and HDRS, there were 7 patients in remission (41.2%) at the end of the follow-up, 6 of whom had initiated the treatment during a depressive phase and 1 while euthymic. Figure 2 shows these data.

The adverse effects occurring during the study are shown in table 2. Ten patients (58.8%) showed some side effect, the most frequent being headache. Two patients presented exanthema that was resolved without complications when the treatment was discontinued. Besides these two interruptions, a third patient discontinued the medication due to intolerability related with nausea and vomiting. One patient presented a shift towards hypomania and was withdrawn from the study, although this was considered as lack of response to treatment. The shift, however, has been added to the table as a possible side effect or as drug related.

CONCLUSIONS

The results of this study confirm the observation of Calabrese et al. (1999a and 2000) that lamotrigine could have antidepressive and mood stabilizer properties in bipolar patients, although these studies specifically observe an antidepressive effect in depressed bipolar I patients and a preventive effect on the depressive phases in bipolar II patients with rapid cycling, respectively. Thus, our study provides data on the efficacy and safety of lamotrigine in an indication that has still not been studied strictly, although the results are clearly concordant with those of the previous study.

TABLE 2. Adverse effects appearing during the treatment with lamotrigine

	N	*%*
None	7	41.2
Headache	4	23.5
Nausea	3	17.6
Dizziness	2	11.8
Somnolence	2	11.8
Asthenia	2	11.8
Exanthema	2	11.8
Vomiting	1	5.9
Anxiety	1	5.9
Blurred vision	1	5.9
Hypomaniac change	1	5.9

However, there are important limitations that make it necessary to be extremely cautious in the conclusions that can be made from our study. The first and fundamental one is the open and non-controlled design that prevents intra-trial sensitivity from being known and opens the door to a possible placebo effect. The second, and no less important, one is simultaneity with other treatments, which, although they were practically not modified during the study, could contribute to the results. The third obvious limitation is the sample size, with more manifestation in patients who initiated the study during a hypomaniac phase or in partial remission. Finally, compliance with the medication was not verified by any laboratory technique, but rather was based on the information provided by the patient and their family.

In spite of the limitations mentioned, we consider that our study provides relevant information from the clinical point of view. Although drug efficacy is shown much better when compared with a placebo, the simple existence of the placebo in the design of a study automatically biases the study population, indirectly selecting the patients with the most predisposition and generally, the least serious. Controlled clinical trials also systematically exclude patients with a risk of suicide, with comorbid disorders or polymedicated. In this sense, our study is closer to the clinical reality and its results may possibly be more generalized.

It seems that two conclusions regarding the efficacy of lamotrigine in bipolar II patients can be deduced in our study: lamotrigine seems to improve the depressive symptoms of patients who initiated the treatment during a depressive phase and the benefits of treatment seem to extend beyond the acute phase with an improvement of the disease course evaluated by the specific subscale CGI-BP-M at 6 months. Our data are insufficient to draw any conclusion in hypomaniac patients, given their limited number. It can be deduced that the investigators were more prone to enroll depressed patients than hypomaniacs, probably as a consequence of the previous negative data on the efficacy of lamotrigine in mania, that have not been published, and the positive data in depression[9]. One piece of data which, from our point of view, instills certain optimism, is the finding of 41.2% of the patients who are in remission at 6 months. Considering that the patients enrolled were mostly resistant or intolerant to the conventional treatment, this value seems to be quite promising.

The mean dose of lamotrigine was 202 mg/day, in relationship with the mean dose used in previous studies[3,13]. Slow titration of 25 mg/week was performed in most of the cases to avoid or reduce the risk of exanthematic

reactions as much as possible. After the titration period, most of the patients took lamotrigine as a single morning dose of 200 mg/day. The dose range used with 25 to 325 mg if the patients who prematurely withdrew from the study are included and from 100 to 325 if we refer exclusively to those who reached 6 months of follow-up.

Lamotrigine was shown to be a well tolerated drug, although three drop outs occurred due to side effects. In two cases, interruption occurred due to the appearance of a cutaneous exanthema that spontaneously abated at 48 hours of withdrawing the drug, and which, in both cases, had limited seriousness. Although appearance of exanthema has been described in approximately 10% of the patients treated with lamotrigine (which coincides with our study), this result of extreme seriousness rarely occurs[8]. The cases of serious exanthema are extremely rare and have been related with high and sudden doses, combinations with valproate, and more frequently in children. In any case, in our study, we follow the guideline of discontinuing treatment when any form of skin reaction appears. Regarding other side effects, their incidence was also comparable to that observed in samples of epileptic[8] and bipolar[3,13] patients. Another relevant question in the treatment of depressed bipolar patients is the risk of hypomaniac change associated to the treatment. This risk has been associated with certain antidepressant treatments[14], but it was not superior to that of the placebo in the Calabrese et al. (1999) study. In our sample, there was only one case (5.9%), which means a value similar to that observed in the mentioned study, which was 8% of the patients treated with 200 mg/day.

As a conclusion, we believe that, in spite of its limitations, this study provides sufficient data on short and long term efficacy of lamotrigine in bipolar II patients, especially for those who initiate treatment during a depressive phase. Up to the present date, few studies have focused on analyzing the treatment of the bipolar II disorder[15]. If verified in randomized clinical trials, the results of our study would indicate that lamotrigine is a very interesting alternative in short and long term treatment of bipolar II disorder. Other features that should be studied are up to what point a combined treatment (with lithium, for example) would be convenient and up to what point the efficacy of lamotrigine in bipolar depression extends to the prevention of the suicide behavior as seems to occur in the case of lithium[16].

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