Bupropión and bipolar depression

Jose M. Crespo-Blanco[1]
Narcís Cardoner-Álvarez[1]
Victor Navarro-Odriozola[2]
Gemma García-Parés[3]
Josefina Pérez-Blanco[4]
Manel Sánchez-Pérez[5]
Carlos Roncero[6, 7]
Grupo EUCB

1Servicio de Psiquiatría
Hospital Universitari de Bellvitge-IDIBELL
CIBERSAM
2Programa Clínico Depresión
Servicio de Psiquiatría
Instituto Clínico de Neurociencias
Hospital Clínic de Barcelona
3Programa Clínico Depresión
Servicio de Psiquiatría
4Instituto Clínico de Neurociencias
Hospital Clínic de Barcelona
5Unitat de Psiquiatria Geriàtrica
Sagrat Cor, Serveis de Salut Mental
Martorell. Barcelona
6Servicio de Psiquiatría-CAS Vall d'Hebron
Hospital Universitario Vall d'Hebron
Agencia de Salud Pública de Barcelona (ASPB)
7Departamento de Psiquiatría
Universidad Autónoma de Barcelona

INTRODUCTION *

Bipolar depression is a complex, heterogeneous, severe clinical condition with elevated morbidity rates.[1] Specific management of depression during the course of a bipolar disorder is a crucial feature in the treatment of the disease. In spite of this importance, the drug treatment of this type of episode is one of the most controversial subjects of current psychiatry. Lithium, lamotrigine, quetiapine, electroconvulsive therapy and antidepressants are the most recommended therapeutic options in different clinical practice guidelines, but with different levels of evidence.[2]

ANTIDEPRESSANTS AND BIPOLAR DEPRESSION

Antidepressants stand out as a drug group used in bipolar disease. However, there are contradictory data regarding their efficacy and the different risks they entail, this limiting their use. These risks are related with the appearance of hyperthymic switches and the possible cycle acceleration.[3] These complications are reduced when the antidepressants are administered in combination with a mood stabilizer, this fact leading to the recommendation of always prescribing a mood stabilizer when indicating an antidepressant drug in this group of patients. Practically all antidepressants have been related with the switch phenomenon (appearance of a manic, hypomanic or mixed episode during the acute treatment of bipolar depression). The estimated rates vary greatly, although they seem to be superior for the tricyclic antidepressants and lower for the serotonin reuptake inhibitors and other non-heterocyclic antidepressants.[1] Due to all of the above, antidepressants should be used with caution in bipolar disorder and after evaluation of the risk-benefit ratio. It seems recommendable to not use them without a mood stabilizer and with precaution in specific populations as rapid cyclers, in mixed phases or in patients with previous high rate of antidepressant induced switching.[3] These controversial features require a more rigorous analysis, since bipolar depression represents a crucial aspect in the importance of bipolar disease and requires an incisive approach, although always while attempting to not negatively influence the global course of the disorder. Between the different antidepressant alterative available, bupropion represents one of them. Until recently, no significant differences were observed in the global efficacy of the different antidepressants in the treatment of major depression. However, the application of meta-analysis techniques to the combination of data from the different comparative clinical trials has made it possible to search for smaller differences in regards to specific populations or in specific symptoms.[4] From this perspective, in the following, we review the data available on bupropion in the treatment of bipolar depression.

BUPROPIÓN AND BIPOLAR DEPRESSION

Bupropion has a action mechanism that has not been totally clarified, although it seems to be related to the ability to block dopamine and norepinephrine reuptake and thus increase the availability of these neurotransmitters.[5] In other sections of this supplement, a review has been made of the different evidence about the efficacy of bupropion in major depressive disorder and in other clinical situations. The first

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Correspondence:
Narcís Cardoner Alvarez
Servicio de Psiquiatria
Hospital Universitari de Bellvitge-IDIBELL, CIBERSAM
Feixa Llarga s/n
08907
Correo electrónico: ncardoner@bellvitgehospital.cat

data on the possible efficacy of bupropion in bipolar disorder go back to the 1980's.[6-8] They were an initial observation in some uncontrolled studies that suggested a possible role of the drug in the management of bipolar patients, especially on the level of depressive symptoms. After, Sachs et al.[9] conducted a double blind comparative study in 15 bipolar patients treated with bupropion (mean dose 385 mg) or desipramine (mean dose 140 mg) for 8 weeks of treatment. Five patients in both groups responded to the treatment and these patients continued the treatment up to one year or to when they had a hyperthymic switch. Those patients who did not respond to the assigned drug were offered a switch to an alternative medication. When the switching rates were evaluated in the total group of patients treated with bupropion (initial and cross treatment), a single picture of hypomania/mania was observed. However, this change of phase was observed in five of the ten patients treated with desipramine. Therefore, and with all of the methodological limitations of this work, similar efficacy rate were suggested in bupropion and desipramine, however there was a greater risk of switching for the desipramine treated patients.

Grossman et al.[10] conducted a double blind study between idazoxan (selective alpha antagonist) and bupropion for 6 weeks in 16 patients with bipolar disorder and depressive symptoms with a score equal to or greater than 16 points on the 17-item Hamilton rating scale for depression. In those patients who took idazoxan, the dose was adjusted to 240 mg (or the maximum tolerated dose) over two weeks. No significant differences were observed between the treatments in the analysis of the last observation carried out. Two of the patients who took bupropion were withdrawn from the study after the third week. One patient was due to a seizure that required specific treatment and another due to insomnia, nausea and vomiting.

After, McIntyre et al.[11] conducted a simple blind study during 8 weeks in 36 patients with type I and II bipolar disorder who had scores equal to or greater than 16 on the 17-item Hamilton rating scale for depression. The patients received treatment with bupropion or topiramate. Both drugs are used as add-on treatment to a mood stabilizer that the patient was already taking. The mean doses of bupropion were 250 mg/day (interval between 100 and 400 mg) and those of topiramate were 176 mg/day with a range between 50 and 300 mg. The principal measurement of efficacy was the response rate defined as a reduction equal to or superior to 50% of the scores on the scales used, specifically the 17-item Hamilton rating scale for depression, the global clinical impression scale and the Young mania rating scale. Two patients were withdrawn from the study due to lack of efficacy and ten due to adverse effects (four in the bupropion group and six in all of the patients treatment with topiramate).

More recently, G. Sachs et al.,[12] using the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), performed a double blind randomized and placebo controlled study during 26 weeks in 366 patients with bipolar depression. The objective of the study was to determine the effectiveness of adding on an antidepressive treatment to a mood stabilizing drug in bipolar disorder. After the patients were stabilized with a mood stabilizer (any FDA-approved antimanic drug), they were assigned to bupropion (mean dose of 300 mg), paroxetine (mean dose of 30 mg) or placebo as coadjuvant treatment. After performing different analysis, no significant differences were observed in the principal variable of the study that was defined as the durable effectiveness rate that implied an euthymic state that was maintained for more than 8 consecutive weeks between the different treatment groups. The different efficacy measurements used were not significantly different between the patients taking bupropion or paroxetine. Another datum of the study suggested that the hyperthymic switching risk was similar to the placebo for both drug groups. The adverse events rate, including mania, and the number of patients who interrupted treatment was similar between the patients who received antidepressants as coadjuvant strategy and those who did not receive it. More recently, Nierenberg verified favorable results on adding low dose of bupropion to the stabilizer treatment in treatment-resistant bipolar depression.[13] Other data from the literature have suggested the appearance of hyperthymic switchings in bupropion treated depressive patients.[14]

The pharmacokinetic characteristics, tolerability and drug interactions profile do not present important limitations to the use of bupropion.[15] In relation to the bipolar treatment, carbamazepine and phenobarbital reduce bupropion serum levels while valproate increase the concentration of hydroxymetabolite.

CONCLUSIONS

Bupropion is a therapeutic option to consider in the management of bipolar depression in combination with different alternatives with different grades of recommendation. We have observed different data that suggest its possible utility in bipolar depression, both in type I as well as type II bipolar disorder. The efficacy data focus on its efficacy as add-on treatment to the usual mood stabilizer treatment. It seems clear that initial doses of 150 mg with close control for the possible appearance of phase changes is recommended. In the situations of absence of response to this dose and good tolerability, the dose can be optimized up to 300 mg/day. Bupropion has a favorable profile of side effects, above all regarding weight gain and sexual dysfunction. It can also be considered in bipolar depression and comorbid situations in which it has demonstrated efficacy as, for example, the attention deficit hyperactivity disorder. In summary, bupropion is an

antidepressant that should be considered as a possible coadjuvant treatment of bipolar depression and as one of the antidepressants of choice.

REFERENCES

1. Schwartz PJ. Bipolar Disorder: a focus on depresión. N Engl J Med. 2011;364(16):1581-2.
2. Nivoli AM, Colom F, Murru A, et al. New treatment guidelines for acute bipolar depression: a systematic review. J Affective Disorder. 2011;129(1-3):14-26.
3. Crespo JM, Colom F. Tratamieto de los trastornos bipolares. En Vallejo J, Leal C (editores). Tratado de Psiquiatría, 2 Edición. Barcelona: Ars Medica, 2010 pp 1390-406.
4. Papakostas GI, Bousoño M, Martin Carrasco M. Eficacia comparada de los antidepresivos actuales: el papel de bupropion. Actas Esp Psiquiatr. 2009;37(suppl 1):3-10.
5. Ascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanisms of antidepressant activity. J Clin Psychiatry. 1995;56:395-40.
6. Shosin B. Bupropion´s prophylactic efficacy in bipolar affective illness. J Clin Psychiatry. 1983;44(5):163-9.
7. Haykal RF, Akiskal HS. Bupropion as a promising approach to rapid cycling bipolar II patients. J Clin Psychiatry. 1990;51:450-5.
8. Wright G, Galloway L, Kim J, et al. Bupropion in the long term treatment of cyclic mood disorders: mood stabilizing effects. J Clin Psychiatry. 1985;46:22-5.
9. Sachs GS, Lafer B, Stoll AL, et al. A double blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry. 1994;55:391-3.
10. Grossman F, Potter WZ, Brown EA, et al. A double blind study comparing idazoxan and bupropion in bipolar depressed patients. J Affect Disord. 1999;56: 237-43.
11. McIntyre RS, Mancini DA, McCann SM et al. Topiramate versus bupropion SR when added to mood stabilizer therapy for depressive phase of bipolar disorder. A preliminare single blind study. Bipolar Disord. 2002;4:207-13.
12. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med. 2007;356(17):1711-22.
13. Nierenberg AA. Low dose buspirone, melantonin and low dose bupropion added to mood stabilizers for severe treatment resistant bipolar depression. Psychother Psychosom. 2009;78(6):391-3.
14. Aggarwal A, Sharma RC. Bupropion induced mania and hypomania: a report of two cases. J Neuropsychiatry Clin Neurosci. 2011;23(2):51-2.
15. Jefferson J, Aguera L, Menchón JM. Bupropión, farmacología e interacciones. Actas Esp Psiquiatr 2009;37(suppl 1):11-5.