

# Use of bupropion in elderly patients

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Mood state disorders are, together with anxiety, the most common psychiatric disorder in the elderly. They are generally associated to multiple conditions that are frequent in elderly age, such as pain, somatic disease or cognitive deterioration and to psychosocial factors (loneliness, impoverishment, discapacity or mourning). Depression in the elderly has an important impact on the quality of life and general health in this age and noticeably casts a shadow over the functional prognosis or survival related with the concomitant medical diseases. It also contributes, in a large degree, to the stress of the caregiver. In the daily clinical practice, depression in the elderly is underdetected and undertreated in spite of the effectiveness of the treatments available. In the antidepressive drug treatment in the elderly, it is important to achieve its effectiveness without jeopardizing safety. The experience in the use of bupropion as an antidepressant in elderly patients is presented.

## INTRODUCTION

The availability of studies on the effectiveness of new treatments with psychopharmaceuticals in the elderly is usually limited. In practice, aspects such as multiple diseases commonly present in the elderly age, multiple drug treatment or difficulties for the follow-up of fragile patients condition the scarcity of these works in relationship with the adult.

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Even so, as bupropion has been available on the market for more than 15 years, it is possible, in this case, to find several publications and results on efficacy and safety in elderly patients.

## Studies with therapeutic doses of up to 300 mg/day

The efficacy and tolerability of bupropion (150-300 mg once a day) in patients over 65 years with major depression were investigated in a 10-week placebo-controlled study.<sup>1</sup> The improvements observed in most of the final results of the secondary variables were statistically significant in comparison with placebo, including health, as a measure of the result of the motivation, and satisfaction and happiness. The adverse events were generally mild to moderate and were similar between the treatment groups. This study demonstrated that bupropion is an effective drug, which is well tolerated for the treatment of major depression in the elderly. It included efficacy measures evaluated with the Montgomery-Asberg Depression Rating Scale (MADRS), a more reliable instrument for the measurement of depressive symptoms in the elderly.

## Studies with therapeutic doses superior to 300 mg/day

In a double-blind placebo-controlled study, 63 patients with depression (age range 55 to 80 years) were randomly assigned to one of the four treatment groups: bupropion 150 mg/day; bupropion 300 to 450 mg/day; imipramine 25 to 150 mg/day or placebo.<sup>2</sup> Fifty patients were evaluated at the end of the seven weeks of the study period. In comparison with the placebo, all of the groups treated with active

ingredient showed a statistically significant reduction in their depressive symptoms, according to their measurement for improvement on the Hamilton Rating Scale for Depression (HDRS-21), Hamilton Rating Scale for Anxiety (HARS) and Clinical Global Impression Scale (CGI). The patients who received the highest doses of bupropion seemed to respond faster than the other treatment groups. Adverse reactions reported with bupropion were similar to those reported with the placebo. On the contrary, the incidences of mouth dryness and constipation were significantly greater in the imipramine group.

Kane et al. informed on the preliminary results of a 4-week trial in 44 elderly patients (age 55 to 77 years)<sup>3</sup> who took doses of bupropion ranging from 150 to 450 mg/day. The study design was similar to that previous mentioned. Improvement of depression was greater in the bupropion and imipramine groups than in the placebo group. However, these differences did not reach statistical significance. Bupropion was well-tolerated, however, imipramine was associated to a greater incidence of orthostatic hypotension and mouth dryness than with bupropion.

## SAFETY IN THE ELDERLY: CARDIOVASCULAR DISEASE

Two published reports have described bupropion as a safe drug in elderly patients with heart disease.<sup>4,5</sup> In the first trial, 10 patients with congestive heart failure (mean age 69 years) received bupropion (dose of 444 mg/day) for 3 weeks and 3 weeks of treatment with imipramine (dose 17 mg/day) in a randomized and crossover design study.<sup>4</sup> Orthostatic hypotension was reported in 5 patients during the treatment with imipramine. On the contrary, no patient developed orthostatic hypotension during treatment with bupropion. No cases of ventricular dysfunction were registered with any of the drugs.

In the second study, this being a continuation study, patients with left ventricle deterioration (n = 15, including the 10 previously-mentioned patients), ventricular arrhythmias (n = 15), and/or conduction defects (n = 21) were included.<sup>5</sup> All the patients received bupropion (doses 442 mg/day) for 3 weeks. Heart function was evaluated by blood pressure, heart rate, ECG, 24 hour ECG, and angiography. Bupropion did not have any significant effects on the ejection fraction in patients with left ventricular dysfunction. A premature decrease in the ventricular contraction frequency was observed in 14 of the 15 patients with pre-existing ventricular arrhythmias. Although treatment with bupropion was associated with an increase in supine position blood pressure, it would not significantly affect heart conduction and it was associated with a low rate of orthostatic hypotension (1 patient). Two patients

interrupted treatment due to the exacerbation of the hypertension and one patient was withdrawn from the study after developing a change in angina pattern.

## Expert's opinion

The opinion on bupropion in the treatment of depression in elderly patients could be based on three aspects. The first one includes some general considerations on the information provided by clinical trials in elderly patients. The second one is based on that published up to now and the third on the criterion focused on the experience in the clinical use.

In regards to point one, it is useful to add that commented above about the difficulty of having clinical trials designed exclusively for the elderly, and that depression as a clinical syndrome has elevated heterogeneity in the elderly patient. Aspects such as grade of cognitive deterioration, cerebrovascular involved present, including the role of the microvascular lesions in the so-called *vascular depression* or the frequent comorbidity with other somatic diseases may significantly condition the interpretation of the results of patients treated for a depressive syndrome. Together with these data, it must be remembered that the response times to antidepressants are generally longer at an older age. This characteristic may especially affect the subpopulations of patients obtained from older, not elderly, samples, which generally establish the times in the study in periods of eight weeks or less.

In regards to the evidence, product of the studies published up to now on the use of bupropion in the elderly, these have focused on the comparability of efficacy versus placebo or other antidepressants, fundamentally imipramine<sup>2,4</sup> and paroxetine<sup>6</sup> and the most important aspects of these studies have already been discussed above. It could be well at this point to mention the contribution of the more recently published study of Hewitt et al.<sup>1</sup> which had a specific design for elderly patients. In that work, they evaluated a dose of 150-300 mg/day of bupropion (mean dose 179 mg/day) versus placebo in 211 patients over 65 years diagnosed of major depression. They found an improvement of affective symptoms and other general health measures (energy and motivation) and quality of life.

In the third place, in regards to the experience of the clinical use in our setting, the information of its management with elderly patients in the medical office shows a positive impression in the resolution of depressive condition, although extensive series of patients treated are still unavailable.

The absence of anticholinergic effects may be an aspect to consider in this group of patients, frequently

vulnerable to cognitive deterioration. This characteristic is useful not only for the patients with some cognitive deterioration already initiated at the time of having the depressive episode, but in those depressions that evolve with important secondary cognitive affectation. It must be remembered that overlapping between depression and cognitive deterioration is important in the elderly with affective disorders and any treatment *that does not worsen things* at this point should be taken into consideration.

Furthermore, the activator effect may be useful, especially in the pictures that occur with more anergy and psychomotor inhibition, which are more frequent in the depression of the more elderly. This last circumstance is of interest in this group of patients, since the immobility associated to depressive pictures in the fragile elderly subjects is a very common source of somatic complications. In the depressions that evolve with more anxiety, on the contrary, this effect could increase it.

The presence of diabetes is frequent with increase of age and requires greater monitoring, especially in the poorly-controlled patient. If bupropion is administered, thus, it is possible that hypoglycemia or electrolytic alterations may occur and could potentially decrease the seizure threshold.

Although bupropion may cause tremor and Parkinsonism (both very rare), there are no data that it has caused deterioration of the patients in patients with Parkinson's disease already treated with it.<sup>7</sup> However, on the other hand, there have been improvements in some patients with tremor, although not for the stiffness.

In spite of the significant individual differences, renal function is generally reduced in the elderly and an indication is generally made to limit the dose to 150 mg/day. The existence of mild or moderate hepatic insufficiency also requires limiting this dosage.<sup>8</sup>

Interactions with platelet antiaggregants (ticlopidine, clopidogrel) may increase the levels of bupropion, although the clinical significance is unknown.<sup>9</sup>

In practice, restlessness/insomnia and constipation have been the most significant adverse effects in the elderly treated with bupropion in relationship to the placebo while headache, dry mouth and nausea occurred similarly to that occurring with the placebo.

## OPINION OF THE EXPERTS OF THE WORK GROUP

Bupropion is an antidepressant that acts by inhibiting the reuptake of dopamine and norepinephrine of demonstrated antidepressive potency

The studies performed in populations over 65 years show their effectiveness in the treatment of depression at these ages

Its absence of anticholinergic effects allows it to be used safely in patients with cognitive deterioration.

The activator effect can be useful in depressions of the elderly who have psychomotor inhibition

Attention should be paid to the elderly being treated with bupropion having diabetes, arterial hypertension, hepatic or renal insufficiency or who are under treatment with anti-platelet drugs.

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