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LETTER TO THE EDITOR

Levetiracetam in bipolar spectrum disorders: first evidence of efficacy in an open, add- on study

Dear Editor

Levetiracetam (LEV) is a new antiepileptic drug (AED) providing wide clinical efficacy in partial as well as in generalized epilepsy (Menachement and Gilland, 2003). Its mechanism of action is not completely known so far, but might include an atypical GABAergic effect (Patsalos, 2000).

For other AEDs, such as valproate, carbamazepine and, more recently, gabapentin and lamotrigine, an antimanic effect is well established, as well as an effect on emotional and behavioural features commonly associated with manic syndrome (Grunze and Walden, 2002). So some effects on the clinical components of mania can be hypothesized for LEV, also based on the first results in animal models (Lamberty *et al.*, 2001).

To date, only preliminary clinical observations reported an antimanic effect of LEV in single cases or small samples of bipolar patients (Goldberg and Burdick, 2002; Braunig and Kruger, 2003). An open on-off-on study reported an amelioration in 10 patients with bipolar disorder I, who received LEV as add-on therapy to haloperidol (Grunze and Walden, 2003).

We aimed to investigate the potential efficacy of LEV in outpatients affected by bipolar spectrum disorders, as an add-on therapy to previous, not mood stabilizing, pharmacological treatments.

Twenty outpatients, 13 males and 7 females, affected by bipolar disorder (4 bipolar disorder I, 6 bipolar disorder II) or related disorders (4 cyclothymic disorder, 2 mixed mania, 4 with mood and conduct abnormalities in subjects with borderline personality disorder), received oral LEV 500 mg twice a day, for 60 days, in an open design study as add-on to previous treatments (neuroleptics and benzodiazepines), that had been unable to induce a complete recovery of the excitement state and that were not modified during the study period.

The severity of mania and related symptoms was assessed at baseline (T0) and after 15 (T1), 30 (T2) and 60 (T3) days of treatment, by the Bech-Raphaelsen scale of mania (BRSM) and the brief psychiatric rating scale (BPRS), 18 items version. The tolerability was assessed by the dosage record and treatment emergent symptom scale (DOTES).

The Wilcoxon test was used to evaluate statistical differences between baseline and last visit item and total scores.

Five patients dropped out during the study, one due to worsening at day 30, the other for reasons independent of treatment response.

For the 15 patients that completed the study, all BRSM total and item scores showed a rapid decrease following LEV add-on, that was clearly significant at day 60.

Also BPRS total and specific excitement items (hostility, etc) scores showed a similar decrease during the study, with a significant level at day 60. More frequent side effects were mild blurred vision, nausea, dizziness and headache.

The results provide a first indication of a positive effect of LEV in manic syndrome, including mood as well as behavioural symptoms. Such an overall efficacy appeared to extend to bipolar spectrum patients, suggesting an action of LEV on both mood and emotional aspects of the disorders.

To our knowledge this is the first pilot study with LEV in a population of outpatients, but its open design clearly limits the clinical relevance of the results. Double-blind studies in large samples of patients vs other mood stabilizers (AEDs and lithium) and placebo, both as add-on treatment as well as in monotherapy, are required before the antimanic properties of LEV can be fully accepted.

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