Reviewer’s report

Title: Olanzapine is superior to lamotrigine in the prevention of bipolar depression: a naturalistic observational study

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Reviewer: Dimitrios Kontis

Reviewer’s report:

The paper describes the results of a naturalistic observational study comparing the preventive effects of olanzapine and lamotrigine on bipolar disorder. They found that, in terms of depressive episodes, olanzapine led to significantly lower recurrence rates and longer time to recurrence compared with lamotrigine. However the two drugs did not differ in recurrence rates of manic episodes and any bipolar episode or in the time to recurrence of any mood episode. The authors concluded that olanzapine was more effective than lamotrigine in the prevention of depressive episodes.

In general, the paper is well written and the research questions clearly defined. The methods are appropriate and their data seem sound. However, the authors should address the following issues before their paper could be publishable.

Major Compulsory Revisions

Introduction

1. The authors need to comment on the role of the comorbidity of personality disorders on the treatment of bipolar disorder, given that they present data on this comorbidity. Otherwise, they should remove these data from table 1 and the relevant comments in the discussion.

2. They also need to speak about the difference between bipolar subtypes I and II as regards the efficacy of maintenance treatment and the gender effects on treatment responsiveness (there are some comments in the Discussion which could be added here).

Methods

The authors need to answer several questions in their methods section.

1. How were the patients selected? This information is important in order to assess the generalizability of findings.

2. Who did the screening for medical disorders and how?

3. Who administered the rating scales?

4. How long have the patients been stabilized on olanzapine or lamotrigine before being recruited in the study? This is necessary in order to assess the preventive potential of each drug which expresses the time period without relapse and given that recurrence rates increase by time in bipolar disorder.

5. In the Cox proportional hazard regression model the authors should also
control for the variables reflecting the severity of the disorder which are presented in table 1. These variables (administration of antidepressants, Bipolar I or II disorder diagnosis and gender) could possibly be associated with treatment efficacy.

Results
1. What was the incidence of different definitions of recurrence given by the authors?
2. In table 1 the authors need to present YMRS and Hamilton Depression scale scores and also the polarity of previous episode.
3. What about rapid cycling? The authors need to mention whether their patients had a history of rapid cycling, which is associated with lower treatment responsiveness.
4. Was there any mixed episode recurrence?

Discussion
1. The authors need to comment more on their finding that lamotrigine-treated patients are receiving more antidepressants. This might mean that these patients had more severe depressive symptoms before achieving euthymia which could explain the superiority of olanzapine in the present study.
2. They also need to comment on the difference in bipolar I or II and gender distribution between the two groups.
3. In the second paragraph, the phrase: “However, the effect of olanzapine in preventing depressive episodes was evident by its superiority to lamotrigine in the current study, and lamotrigine was indicated for the prevention of depressive episodes” should be re-written.
4. The authors should present data on the mortality associated with anticonvulsant or lamotrigine in particular, or say that this issue needs to be explored.
5. The authors need to define the word "enriched" which has been used in the manuscript.
6. In order to compare the role of olanzapine with that of lamotrigine for the prevention of depression in bipolar disorder, new double blind studies with more subjects are needed. Therefore the present findings can be considered promising or suggestive but not definite. The authors have to acknowledge that and to be more conservative in their interpretation of their results.

Discretionary Revisions
Discussion
1. In the second paragraph (first line) the authors refer to a “novel design”. However the naturalistic design cannot be considered novel and I therefore suggest that they omit this phrase. Notably, the authors indeed later admit that this design has been adopted before (fourth paragraph).
2. The authors could include the reference of the Fountoulakis et al 2013 (Bipolar...
Disorders) which refers to the treatment of rapid cycling.

Minor Essential Revisions

Study Design and Assessment

1. Please change the word: "benzodiazepine" into "benzodiazepines" (line 4)

2. Please rephrase the next sentence of the same paragraph: “We defined recurrence as … “

Table 4

1. 0.045 is <0.05, so, it needs an asterix

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests