Author's response to reviews

Title: Clinical management and burden of bipolar disorder: a multinational longitudinal study (WAVE-bd Study)

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Author's response to reviews: see over
Dear Dr Norton,

Thank you for sending the comments on our manuscript entitled, ‘Clinical management and burden of bipolar disorder: a multinational longitudinal study (WAVE-bd Study)’ that we submitted last month for consideration for publication in *BMC Psychiatry* as a Study Protocol. We found the review to be objective and fair, and agree with all of the points made by the reviewer.

An item-by-item commentary on the points raised by the reviewer is included overleaf and the manuscript text has been revised as described. We have pleasure in resubmitting the amended manuscript as requested.

All of the authors have contributed to, and approved the revised manuscript and we confirm that no other manuscripts related to the study have been submitted or published, nor has this manuscript been submitted elsewhere.

Yours sincerely,

Dr Esteban Medina
Responses to specific reviewer comments

Vieta et al, Study Protocol: Clinical management and burden of bipolar disorder: a multinational longitudinal study (WAVE-bd Study).

Comments

This paper describes a study protocol for a prospective, observational study of patients with bipolar disorder. The topic is important, as large scale naturalistic studies are necessary to confirm findings from more tightly controlled studies. The protocol has a number of strengths including the multinational perspective, simplicity of data gathering, longitudinal follow up, attention to representative sampling of “usual care settings,” and focus on caregiver burden.

There are some issues with the paper. The primary advantage of publishing study protocols, especially in on-line journals with no page limits, is that the methodology can be described fully, with detailed rationale given for the various design decisions that cannot be done in a final results paper, which usually needs to be very succinct. The authors have no doubt carefully thought about some of their methodology choices, but there is not enough detail in the paper to allow the reader to fully appreciate them. Hence, more information is needed for the following issues:

• A major issue in the field is the reliability of diagnosis, especially for BD II. There are likely going to be regional, as well as national, differences in the threshold for diagnosis of BD II (less so for BD I). Given the large number of investigators, how will the authors ensure that patients actually have a bipolar disorder?

The focus of this study is to evaluate how bipolar patients are managed in real-life practice. We fully agree that some patients, especially those with BD II, could be incorrectly diagnosed and may be treated for MDD or even schizophrenia, rather than bipolar disorder. These patients will not have been included in the study. We have modified the text to make this point in the Discussion.

• Should they stratify recruitment for BD I and BD II, so that one subtype is not overrepresented?

Patients were selected at random from the whole bipolar disorder population recorded by each investigator. This methodology, in combination with the large sample size, ensured that the numbers of patients with BD I and BD II were representative of the actual population diagnosed in real life. We have modified the text to make this point in the Discussion.

• The inclusion criteria are unclear because of inconsistencies in the description. The authors state on p.8 that patients are included if they had one index mood episode within the 12 months prior to Time 0, but it appears that there is a maximum of 12 months and a minimum of 3 months prior to Time 0 (although the 3-month minimum is not mentioned at other places in the protocol). Does that mean that patients who are in an active episode are not eligible?

Patients with active episodes may be eligible. The inclusion criteria make reference to the mood event start time, and patients starting the index mood event less than 3 months before Time 0 were not eligible for inclusion. However, patients starting the index mood event 3–12 months before
Time 0 were eligible even if the index event had not resolved, or if the index event had resolved and another event had subsequently initiated. We have clarified the text in the Methods section.

• There is no description of what happens in the Inclusion period vs. the Follow Up period.

There are no major differences in data collection between the Inclusion and Follow-up periods, except that all retrospective information (from index event to inclusion) was recorded at the first visit. Data for prospective analysis are collected as described at all visits (starting with the inclusion visit). We have clarified the text in the Methods section.

• Have the various outcome instruments been validated in the different languages?

All instruments have been validated before the study start, including linguistic validation in some countries where necessary. In all cases, the scales were psychometrically validated, at least in the original language. We have added text to this effect in the Methods section.

• Table 1 notes that no recruitment is to be carried out in Spain and that patients will be recruited in Romania and Ukraine. If true, then this table needs to be revised to reflect the actual sites used.

This has been modified appropriately.

• Medication use will be captured in the CRFs, but will they also capture psychosocial treatments (psychotherapy, psychoeducation, rehabilitation or occupational therapy)?

We are collecting data on whether the patient received psychologist or group therapy and have added text to the Methods section.

• The statistical analysis section is very vague. What will be the meaning of survival curves when patients do not start in the same state at Time 0? Will it reflect time from the last mood episode?

The information collected will cover the period from the index mood event to the end of the study. Therefore, we will have sufficient information on patient status to enable us to analyse data, relative to the time of index mood event initiation. We have added text to this effect.

• In the discussion section, the detailed description of the breast cancer study does not appear relevant.

This paragraph and associated references has been removed.

• On p.9, where does the 93% patient acceptance rate come from?

A total of 3188 randomly selected patients were invited to participate. Of these, 93% accepted the invitation and provided written informed consent, giving a total study population of 2965 patients. The remaining 7% of patients declined to participate and will not be included in the analysis. We have inserted this information to support the discussion point that the study aims to be as near to ‘all inclusive’ as possible.