Author's response to reviews

**Title:** Treatment and outcomes of an Australian cohort of outpatients with bipolar I or schizoaffective disorder over twenty-four months: implications for clinical practice

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**Author's response to reviews:** see over
Dear Editorial Board of BMC Psychiatry,

Thank you for considering our manuscript “Treatment and outcomes of an Australian cohort of outpatients with bipolar I or schizoaffective disorder over twenty-four months: implications for clinical practice,” by Jayashri Kulkarni, et al.

The manuscript has been revised to address all the reviewers’ comments, as detailed in our responses below; all revisions are visible as tracked changes in the revised manuscript re-submitted today. In addition, the affiliations of some authors have changed and we discovered an error in the references; all these corrections also appear as tracked changes.

**Reviewer 1: Rafael T de Sousa**

**Reviewer's report:**
Even though the most important data analyzed are negative findings, the study brings interesting clinical information in a very large sample.

I suggest only minor essential revisions:

1) Criteria for exclusion and ineligibility should be better described in the methods.

**Response:** Thank you for bringing this to our attention. The methods section (p8) has been revised to provide additional information as per the extract below.

“In order to obtain a representative sample of participants, exclusion criteria were minimal, only those participants: with a DSM-IV-TR diagnosis of schizophrenia, organic psychosis or dementia; involved in a controlled clinical trial 30 days prior to the study or at any time during the study; who did not meet all of the inclusion criteria; were considered ineligible.”

2) Also, the authors should cite the source of the criteria for syndrome remission used.

**Response:** Thank you, the methods section (p10) has been revised to include the sources for both symptomatic and syndromal remission as per the extract below.

“Symptomatic remission from a manic state was defined as a YMRS total score of ≤12 (Lam, Michalak and Swinson, 2005) and HAMD21 total score of ≤8; from a depressive state, remission was defined as a HAMD21 total score of ≤8 (based on the consensus definition proposed by the International Society for Bipolar Disorders task force, assuming the
equivalence of HAMD$_{21}$$\leq$8 and HAMD$_{17}$$<5$ or $<7$ [Tohen et al, 2009]). ….Definitions of syndromal remission were modified from those used in the McLean first-episode psychosis project [Tohen et al, 1992].

3) Was median time for relapse compared between PT-olanzapine and PT-CMS groups? This result should be presented.

**Response:** We agree, this information appears in the Results section, p15, final paragraph of the ‘Symptomatic relapse’ subsection, as per the extract below.

“The median time (calculated from the Cox model) to relapse was 286 days (182 to 624 days) for the PT-olanzapine cohort compared with 230 days (182 to 357 days) for the PT-CMS cohort.”

4) Figure 3 is not clear. Does it include the whole sample? Does it include CMS and olanzapine? The authors should make it more clear.

**Response:** Thank you for pointing this out. The footnote for figure 3 specifies that olanzapine is included as a mood stabilizer for the purposes of this figure (footnote shown below, it appears separate to the figure in the current draft paper, as per the submission instructions). In order to make this clearer, the following has been added to the results section (p 16): “Please note that, in figures 3 and 4, olanzapine is grouped with CMS in a broader ‘mood stabilizer’ grouping, which differs from the CMS grouping used in other analyses.”

Footnote 1 Psychotropic medications included are: atypical antipsychotics (AA), antidepressants (AD), benzodiazepines (B), mood stabilizers (MS; olanzapine, lithium, valporate, and carbemazepine), and other (i.e., anticonvulsants, anticholinergics, anxiolytics, and hypnotics).

5) Figure 5 would be more informative including data on PT-olanzapine and PT-CMS mental and physical health assessment.

**Response:** Figure 5 forms part of the descriptive information based on the participant cohort as a whole. While the authors agree that the PT data would be of interest, we didn’t include all the measures for the PT cohorts (these groupings were used only for remission and relapse), as given the complex treatment patterns observed, we wanted to describe the participant cohort irrespective of treatment.

**Reviewer 2:** Richard H Weisler

**Reviewer's report:**
The well written article provides important information from a useful real world study of patients with bipolar I and schizoaffective disorder. As the authors noted the patterns of prescribing seen in the study differed from that found in many of the prevailing treatment guidelines. Most clinical trials do not allow for commonly seen psychiatric co-morbidities which often impact clinician treatment choices.

Many of the guidelines are significantly influenced by these more restrictive trials without significant co-morbidities used primarily for regulatory approval.


Response: Thank you for bringing this work to our attention. We have included it in the discussion (p 19), citing the study as follows: “Polypharmacy is also prevalent in other countries; a large US study of patients with BD (n=7406), revealed that, although 33% of patients received an initial prescription for more than one psychotropic agent, 12 months later, the polypharmacy rate among those still receiving treatment had risen to 50% (Baldessarini et al, 2008).”

2) Additionally, if reasonable it would be very interesting to look at dosages of Olanzapine used by smokers versus non-smokers. Smoking induces CYP 1a2 enzymes that can significantly lower olanzapine levels in some studies. Did smoking appear to impact clinical treatment and/or outcomes in this study? Also, were the subjects with multiple hospitalizations overrepresented by smokers. Many hospitals have no smoking policies, but most psychiatric patients resume smoking after discharge potentially significantly lowering Olanzapine blood levels because of the enzyme induction. If so it would be useful to remind clinicians of the need to to consider readjusting the dosing of Olanzapine when patients start or stop smoking.

Response: Thank you for your interest. We agree wholeheartedly, but felt that it was out of the scope of this publication, so we have published a separate manuscript examining smoking in this study population, please see: Dodd S, Brnabic AJ, Berk L, Fitzgerald PB, de Castella AR, Filia S, Filia K, Kelin K, Smith M, Montgomery W, Kulkarni J, Berk M. A prospective study of the impact of smoking on outcomes in bipolar and schizoaffective disorder. Compr Psychiatry. 2010 Sep-Oct;51(5):504-9.

Yours sincerely,
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