Author's response to reviews

Title: Pharmacotherapy for Bipolar Disorder and concordance with treatment guideline: survey of a general population sample referred to a tertiary care service.

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Author's response to reviews: see over
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Dear Editor,

Please find enclosed the new version of the paper “Pharmacotherapy for Bipolar Disorder and concordance with treatment guideline: survey of a general population sample referred to a tertiary care service”, after revision. The English has been revised by Edanz editing services.

You will find enclosed the description of the changes made in the paper.

Sincerely yours,

Dr S. Paterniti

Reviewer 1 – Mark Bauer

1) The individuals were classed as guideline-concordant or not on criteria chosen “a priori”, based on the type and dosage of medications, following a “Boolean” program. The longitudinal history and resistance of treatment was not available, so second and third line treatments were considered concordant with guidelines, independently if the first line recommendations had been already prescribed. (see Discussion, Concordance with treatment guidelines, pag 15)

2) In this new version we have integrated the serum levels of lithium and the dosage of treatments (anticonvulsivants and atypical antipsychotics) to classify a treatment as concordant with guidelines or not. As the serum levels of anticonvulsivants were not available, we considered the dosage, rather than the serum levels. (See Methods, Criteria: adherence to treatment guidelines, pag 8-9)

   We have also showed the minimum-maximum daily dosage of the different treatments in Table 2. The results of concordance changed for seven patients, decreasing the total percentage of concordance from 74% to 68%. Details are given in the section Results.

3) The patients taking methylphenidate and trazodone, showed in Table 4 of the first version, were not taking any other treatment recommended by the guidelines, and for this last reason they were considered as “non concordant”. As the previous table could cause confusion, we have split the table in two different tables. The first one (Table 4) considers three main groups: the first two groups have at least one treatment concordant with guidelines and the third one has no treatment concordant. The second table (Table 5) considers the different reasons of non concordance, considering only the patients who were prescribed no treatments concordant with guidelines. In our sample, one patient was prescribed a stimulant (see table 2); this patient was not prescribed with any other psychotrophic, so there was no conflict in classifying such patient.
4) Benzodiazepines and hypnotics were not considered in the classification of concordance, as they are not included in CANMAT recommendations. As we wished to focus on Bipolar Disorder, we didn’t consider the concordance of treatment prescribed for the Anxiety disorders.

5) Gabapentin, topiramate and levetiracetam were included in Table 2, which included all the psychotropics prescribed in the sample, for a descriptive goal. Only the anticonvulsivants valproate, lamotrigine and carbamazepine were considered in classifying a treatment as concordant, as mentioned in the Methods section (pag 8-9). To make the classification process clearer to the reader, we have explicitly mentioned the reference tables, which defined the concordance with guidelines, and which were drawn from the reference 18, Yatham et al *Bipolar Disord* 2009; 11:225-55. (see Methods)

6) Second and third line treatments were considered concordant to guidelines as the patients of our sample were referred to a tertiary care structure. The selection process of the sample included the criteria of being resistant-to-treatment, or having a chronic, severe and highly recurrent disorder. In these cases, it is likely that the patients had already been prescribed with at least a first line treatment. (see discussion pag 16)

7) Primary and secondary analyses: the section “Statistical analysis” (pag. 9) gives the details about the primary and secondary analyses.

Additional issues

8) The title was changed in *Pharmacotherapy for Bipolar Disorder and concordance with treatment guideline: a survey in a general population sample referred to a tertiary care service.*

9) The 20% of the referrals were assessed by the psychosocial team. A standardized diagnosis by SCID and semi-structured interview collecting information about the treatment was available only for these patients. The other 80% referrals received a consultation by the psychiatrist only, who made recommendations for further pharmacological treatment by the GP or followed the patient in short-term. (see Methods page 7)

10) ROMHC acronym was written out (Abstract, page 2 and abbreviation list)

11) “Association” was changed to “combinations” (page 9)

12) Table 3. NS was eliminated.

Reviewer 2. – Ellen Dennehy

1) We agree about the uncertainty to handle hypomania, especially in bipolar II patients, in the current scientific literature. We have tried to address this issue in the discussion, referring to the inconsistencies in the scientific literature and difficulty to find a final agreement. Following the suggestion of Dr Dennehy, we have added a paragraph in the Discussion (pag 18):
It is noteworthy that the CANMAT guidelines do not make explicit recommendations for BD-II hypomania, leaving some potential confusion for the reader whether recommendations for acute mania have to be adopted.

Dr Dennehy suggests a “different approach” for Bipolar Disorder type I and II. We indeed treated separately BD type I and II, being quite descriptive, and following the specific recommendation of CANMAT guidelines for the two types of Bipolar Disorder.

2) We have split the table 4 in two different tables, where the Table 5 considers the different reasons of non concordance, considering only the patients prescribed with no treatments concordant with guidelines. We discuss the reasons of non-concordance in the two types of BD.

3) The specific recommendations of CANMAT by type of disorder and nature of the episode were in fact used in classifying the treatment as concordant or not. We referred more explicitly to the criteria of classification in Methods, referring to the table published in Yatham et al 2009.

4) Table 3 was broken in bipolar I and II.

5) The percentage of patients declining the assessment after being contacted was not known.

6) Added in the discussion: Although the study focused on patients seen between the end of 2006 and beginning of 2009, we decided to use the 2009 guidelines rather than 2007, as some of the recommendations adopted in 2009 were already suggested in the previous version. For example, the possibility to use antidepressant monotherapy in bipolar II patients in depressive phase was already described in 2007, and more explicitly formulated in 2009. Other new recommendations adopted in the 2009 CANMAT version, which could potentially affect the percentage of concordance with guidelines in our sample, concerned with the use of quetiapine monotherapy as first line recommendation of BD-II depression and in BD-I maintenance; the use of divalproex monotherapy as second line recommendation in BD-I and BD-II depression; and the use of quetiapine in combination with lithium or divalproex in BD-I maintenance. In our sample, only two treatments would have been classified in a different way if we had adopted the 2007 guidelines: two BD-II depressive patients taking divalproex monotherapy would have been classified as “doesn’t follow guidelines”, instead of “second line treatment”.

Discretionary revisions

7) Patients “took” a medication was changed into “were prescribed”.

8) The English was revised.