Author's response to reviews

Title: Factors associated with chronic pain in patients with bipolar depression: a cross-sectional study

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

First of all, we would like to thank you for your comments on our manuscript, and for offering us the opportunity to revise and resubmit our article "Factors associated with chronic pain in patients with bipolar depression: a cross-sectional study" to BMC Psychiatry. We also appreciate the suggestions and comments made by the Reviewer.

We include in this letter our detailed responses to the issues raised (see below), indicating the modifications we have made to the manuscript in the light of these suggestions. We hope that having addressed all these issues and modified the manuscript accordingly, you will now find our article suitable for publication.

We thank you once again for your kind attention and we look forward to hearing from you in the near future.

Yours Faithfully,

EDITOR's COMMENTS:

**Introduction:**

1. A broad statement is made regarding analgesic agents and the association with mania. Can the authors be more specific?

Response:

Typical opiate analgesics (such as morphine or oxycodone) and atypical opiates (such as tramadol) are prescribed for the treatment of chronic pain (e.g., for Diabetic Peripheral Neuropathic Pain - DPNP: Smith HS, 2012). There is known co-morbidity of diabetes in patients with bipolar disorders (Kemp et al., 2010) and according to some studies (e.g., Schaffer et al., 2007), opioid analgesics can have important mood-altering
effect on patients with bipolar disorder. The same might be true for antidepressants, which are sometimes used to treat chronic pain and more specifically, DPNP (Micó et al., 2006). Thus, we believe that these two types of analgesics (typical and atypical opiates) could precipitate manic bouts if they are prescribed as analgesics (or co-analgesics) to patients with bipolar depression that also suffer from DPNP (as an example of a chronic pain syndrome). To clarify this association between analgesics and mania, we have extended the last paragraph on page 3.


2. One of the references cites tramadol. Is there reason to believe this agent poses more of a risk given its serotonergic properties than other analgesics, such as morphine, oxycodone, codeine, etc.?

Response:

While there are many reports of mania induced by opiates (John et al., 2007; Jagadheesan et al., 2004; Gonzalez-Pinto et al., 2001; Orr et al., 1998; Watts et al., 1997), the case of tramadol is special. Tramadol is an atypical opiate, with properties of serotonergic and noradrenergic reuptake inhibitors, both in vitro and in vivo (Raffa et al., 1992). Furthermore, it has been reported that tramadol has intrinsic antidepressant-like properties, an effect that has been demonstrated in various preclinical models of
depression (Rojas-Corrales et al., 1998, 2002, 2004), as well as in refractory depressed patients (for a review see Berrocoso et al., 2009). Tramadol is widely dispensed to patients with DPNP (Attal et al., 2010) and some patients with bipolar depression are probably among these (given that there is a known co-morbidity of BD with diabetes, see above). Thus, it would be reasonable to think that (in comparison with other opiates) the risk of inducing mania would be higher with tramadol due to its serotonergic properties. For example, there have been reports of cases where mania is induced in patients treated with Selective Serotonin Reuptake Inhibitors (SSRIs) and tramadol (Gonzalez-Pinto et al., 2001; John and Koloth, 2007; Watts and Grady, 1997). By contrast, there are very few cases of serotonergic syndrome as a consequence of the association of classical opiates with SSRIs. Nevertheless, in our opinion the potential role of noradrenaline cannot be ruled out as tramadol also inhibits the reuptake of this monoamine. The administration of tramadol with SSRIs is specifically contraindicated, as with other antidepressants with noradrenergic reuptake blocking properties, although the dose of tramadol is important in this regard.

This information has now been added to the introduction in paragraph 2 on page 4.


3. A statement is made regarding Implications of NSAIDs and lithium, but NSAIDs have also been linked to antidepressant effects given their anti-inflammatory properties. Can the potential risks/benefits of NSAIDs be described more thoroughly?:

Response:

We cite the potential risk of an interaction between NSAIDs and lithium (Ragheb et al., 1990) as one possibility that could account for chronic pain in patients with bipolar depression, and to illustrate the importance of recognizing this problem in patients with this co-morbidity. There are indeed important studies about the use of NSAIDs as potential antidepressants due to their anti-inflammatory properties and in the context of the possible inflammatory hypothesis of depression (Gallagher et al., 2012). The potential risks/benefits of NSAIDs due to their antidepressant-like effects (as anti-inflammatory: we assume that the question refers to bipolar depression) is difficult to define due to the lack of appropriate studies. However, precaution should be exercised in the use of NSAIDs with lithium due to the possible pharmacokinetic interactions.
To address this issue in more detail, we have added some information in first paragraph on page 4 of the manuscript.


**Methods**

4.- It is not clear how the 121 patients diagnosed with bipolar disorder were selected. Please clarify.

Response:

At the beginning of the methodology a paragraph has been added (page 5) and this section has been rewritten to clarify the selection procedure for the 121 patients analyzed.

5.- Were there any additional inclusion criteria?

Were there any specific exclusion criteria?

Response:

It is stated in the text that the depressed bipolar patients that visited the psychiatrist for the first time were included in the study using the diagnostic criteria of the DSM IV-R. The age, capacity and consent to participate in the study were criteria already included in the original version of the manuscript.
Results

6.- What are the specific pain etiologies?

_I do not understand what is meant by bipolar depression and other depressive disorders in Table 1 (this is used throughout the paper). Please add a couple sentences describing exactly what other depressive disorders entails._

Response:

On page 8 in paragraph 2 the information regarding the diagnoses included in the study as "other depressive disorders" has been introduced, specifically indicating that of the 36 patients that have been diagnosed with another depressive disorder, 30 patients suffer major depression, 3 depression induced by physical disorders, 1 depression induced by illegal drugs and 2 dysthymia.

Discussion

7.- Please develop more thoroughly the text regarding the delay in diagnosis of bipolar depression in association with pain.

Response:

A paragraph (paragraph 3) has been included on page 10 to explain the relationship described previously between other forms of depression (especially Major Depression) and the delay in diagnosis, explaining the possible role that the presence of pain may have in the delayed diagnosis of BD.

8.- Can the authors address the association with suicide?

Response:

As now indicated in the discussion (page 9 paragraph 3 and page 10) we did not find any association between suicidal ideation and the presence of chronic pain in BD.
patients, probably due to the small size of the sample. Nevertheless, it is known that increased co-morbidity with depression is a risk factor contributing to higher rates of suicidal behaviour in chronic pain (Fishbain, 1999), highlighting the need for routine evaluation and monitoring of suicidal behaviour in patients with chronic pain (Smith MT et al, Pain 2004). Because patients with bipolar disorder are also at risk of experiencing suicide ideation, we think that the sum of the two risk factors could enhance the possibility of a suicide attempt. However, to our knowledge no large clinical studies have been addressed to explore this possibility.

This information has now been added to paragraph 3 on page 9.


9.- How do the results compare with a general population of patients? In its present form, it is difficult to put the results in perspective of whether there are differences in comparison to patients with other non-mental health conditions.

Response:

The prevalence of chronic pain in the general population has been addressed in distinct studies (Breivik et al., 2006), presenting a lower prevalence than that which we found. However, this comparison was not the objective of our study and as such, we have not included this in the manuscript.

**REVIEWER’S COMMENTS:**

1.- *If I understand the manuscript correctly, patients selected are bipolar patients who are currently depressed, thus “bipolar depressed (BD) patients”. I think it would be more appropriate to use this phrase rather than just “bipolar patients”, particularly in the research aims.*

Response:

Where reference is made to "bipolar patients" who are currently depressed, we have now used the term "bipolar depressed patients" in the text.

2.- *The subsample of 121 participants is rather small. The reason why this particular subset of participants was chosen is not clearly stated. If I interpret the whole section, the participants are first time visitors of a psychiatrist with bipolar disorder and a current depressive disorder.*

Response:

Yes, your interpretation is correct. As indicated above, the section referring to the "Patient sample" has been modified to clarify this issue. The text has also been modified to clarify where the subjects that participated in the study came from and their characteristics.

3.- *Why are borderline results mentioned in the results section for factors associated with pain? Mention: Table 3 includes all factors with p<.10. All in all the sample size is small and the findings are not very convincing due to borderline significant results.*

Response.

It is certainly true that the p values found are not particularly small, yet the adjusted OR values are > 1. Although this may not be conclusive, these values would suggest that in a larger sample, a significant result might be obtained and demonstrate a statistically relevant association.
4. The Discussion section could be more structured and focused on the findings. Page 10, line 20 the finding for delayed bipolar diagnosis could be more explored as it is mentioned as a crucial finding. Page 12, line 1 suicidal ideation was not associated with pain in Table 2.

Response:

As indicated above, various paragraphs have been introduced into the discussion to better explain the relationship between pain and a delayed diagnosis of bipolar disorder, and the higher risk of suicide in depressed bipolar patients suffering pain.

Minor essential revisions:

-The writing could be improved; for instance the last sentence of Methods section in the Abstract and the long sentence in the Conclusions section of the Abstract is not clear to me.

Response:

This part of the abstract has been modified to make it clearer.

- Headings and paragraphs in the Methods section could be improved.

Response:

We have replaced: Patients with “Patient sample”; Measurements with “Instruments and variables”, and the information provided has been reordered to clarify the process of patient selection.

- How were missing data or inconsistencies corrected (page 7, line 8)?

Response:

The co-ordinator of the study was responsible for verifying the inconsistencies and the missing values, and of correcting them through contact with the patient’s doctor. However, there were a few cases, such as that indicated by the reviewer, that were not identified at the appropriate time and that could not be subsequently corrected.
- Page 9, line 9 old age should be older age, similar to line 16. Page 9, line 10 (and page 8, second paragraph);

Response:

The manuscript has been revised by a native English bilingual scientist in order to correct the errors indicated by the reviewer and to make the article easier to understand.

- “delayed bipolar disorder” was not a measure reported as such in the Methods section. What is the rationale for this measure?

Response:

In fact, this variable was not directly measured in the study. However, consistent with previously published studies in which delayed diagnosis of BD or its misdiagnosis was related with prior Major Depression, we believe that the patients in the study with other depressive syndromes, mainly Major Depression, could be patients with bipolar disorder and depression in whom the diagnosis has been delayed.

- The lay out of the Tables could be improved. How come there are missings on measures like gender and age?

Response:

The layout of the tables, especially tables 1 and 2, has been improved. The missing data regarding gender and age was due to the fact that this information was not collected in the study and it was not possible to obtain this information in the control phase.