MS 42625
Comorbidity of bipolar and anxiety disorders: an overview of trends in research

Reply to reviewer's comments

This is a very well written, very long and detailed (perhaps too long and detailed - very hard on the reader's attention span) report attempting to summarize 103 reviews of the comorbidity of bipolar disorder and anxiety disorders. I would recommend sharply reducing the wealth of unnecessary detail in this article and instead focussing on the interesting question or what is special about the conjunction of anxiety with bipolar disorder.

The length of the revised manuscript has been reduced by 1050 words without compromising on its essential content. Results regarding features of anxiety disorder comorbidity in bipolar disorder (BD) have been summarized to cut down on the length. Additionally, subheadings have been used for all sections to make the manuscript more readable.

The authors underline the fact that this is an important co-morbidity because it sheds light on mechanisms of illness and also on treatment strategies. This claim of importance is not, however, convincing. The reader is no further ahead having read the article.

There appears to have been some misunderstanding here. Throughout the article it has been repeatedly stressed that data on aetiology and management of anxiety disorder comorbidity in BD is limited. Thus, the expectation that examination of this comorbidity would reveal causal mechanisms of BD has not been realized. This has been re-emphasized by the following statements of the revision:

Abstract - Despite the extensive body of research **there is paucity of data on aetiology and treatment of anxiety disorder comorbidity in BD**.

Introduction - The increased awareness of the substantial burden of comorbid bipolar and anxiety disorders over the years has propelled research in this area [5, 26]. Moreover, **it gave rise to the hope** that examination of anxiety disorder comorbidity in BD could provide clues to underlying aetiopathogenetic mechanisms of BD [3, 6, 9].

Results -

Treatment of anxiety comorbidity in BD- Despite the reasonably comprehensive exploration of rates, correlates and impact of anxiety comorbidity in BD, **research on the efficacy of different modalities of treatment for comorbid anxiety disorders in BD has been rather scarce.**

Aetiology of anxiety comorbidity in BD - Though **there is no clarity regarding the aetiology of anxiety disorder comorbidity in BD**, several lines of evidence have suggested that family-genetics, neurobiology, trauma and other psychosocial factors may be involved in the genesis of anxiety disorders in BD [6, 20].

Discussion - Then again, the findings of the current review also showed that the majority of the research pertains to rates, correlates and impact of comorbid anxiety disorders in BD, while **research on treatment and aetiological processes is relatively limited**.

Lacunae in existing research - *Treatment and aetiological research:* Although anxiety comorbidity has important implications for management of BD, evidence on this aspect was scarce. Additionally, the lack of research on aetiology of comorbid bipolar and anxiety disorders was also evident. **The expectation that examination of this comorbidity would reveal the aetiopathogenetic processes underlying BD has thus not been fully realized.**

We agree with the reviewer that the lack of research about aetiology is disappointing, but such is the nature of the current evidence.

The question that would be interesting to address is whether the presence of anxiety disorders are any more common with bipolar disorder than they are in everyday life. If so, are people made anxious by the illness, by the consequences of illness, by the treatment of illness or is it possible that anxiety disorders by some unknown mechanism lead to depression and/or mania?

Anxiety disorders are co-morbid with all physical and mental health disease - which is not surprising given the stress of disease.

This review focuses only on comorbidity of anxiety disorders in BD. The studies on anxiety symptoms in BD have not been included. One reason is that true anxiety comorbidity, by definition has to consist of at least two comorbid disorders which are independent and distinct. In this case, true anxiety comorbidity can only mean the coexistence of a diagnosable anxiety disorder (and not just anxiety symptoms) and a co-occurring bipolar disorder. This has been stated in the discussion (**Lacunae in existing research -** *Conceptual issues).*

Ideally, true comorbidity presupposes that the comorbid disorders will be independent and distinct disorders and that there will be minimal overlap between the content of symptoms of the two disorders [1, 3]. However, **certain studies have moved beyond these precise definitions by including sub-threshold anxiety disorders or symptoms of anxiety as a part of the overall comorbidity of BD.** This often leads to over-diagnosis and over-inflated rates of comorbidity [3, 13].

To make this distinction clearer the phrase 'anxiety disorder comorbidity in BD' has been used uniformly throughout the text.

It has been mentioned that rates of anxiety disorders in BD are severalfold higher than rates of anxiety disorders in general population, unipolar depression and schizophrenia. The high rates of anxiety disorders in BD cannot be explained simply by the stress of the disease. The possibility that anxiety disorders could serve as

prodromes of BD has also been mentioned but the mechanisms by which anxiety disorders could lead to BD are not clear.

This article, while very comprehensive, fails to specify what is special about this particular comorbidity. I would recommend sharply reducing the wealth of unnecessary detail in this article and instead focussing on the interesting question or what is special about the conjunction of anxiety with bipolar disorder.

The revision now contains a section on the unique features of anxiety disorder comorbidity in BD as a part of the discussion.

Reply to editor's comments

The language of the manuscript is not so good. A Non-Native Speakers of English Editing Certificate from an editing company is required.
Otherwise, the manuscript can't be accepted.
We strongly recommend that authors use language editing services provided by the following biomedical editing companies, based on their good reputation and reliable quality.

Final decision on this matter communicated by e-mail on 30 October:

Dear Dr. Chakrabarti,
I just get a reply from the editor-in-chief. You don't need to send your manuscript to any editing company.
Jin-Lei Wang, Vice General Manager
Baishideng Publishing Group Inc

Please shorten the words of the abstract. It should be around 200 words.

Abstract has been reduced to 200 words

The main text should be shortened.

Length of main text has been reduced by 1050 words.

Other changes

Reference numbers 137 and 186 changed

ORCID numbers of all authors included

All changes highlighted using red coloured font