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Title: Decreased High Mobility Group Box1 (HMGB1) Level in the Patients with Bipolar Disorder During the Euthymic Period

**Background:** Previous reports have examined the relationship between neurotrophic factors and inflammatory markers and the euthymic period of bipolar disorder (BD). High mobility group box1 (HMGB1), was reported to be a late-mediator of inflammation and its role in DNA reconstruction and cell differentiation has been shown. Our aim in the present study was to evaluate the levels of HMGB1 in BD patients during the euthymic state, and to determine the relationship between inflammatory markers and neurotrophic factors in the pathophysiology of euthymic state BD. Methods: The study groups included 40 cases with BD in the euthymic state and 40 health subjects. CGI-SI, YMRS, and HAM-D were completed and assessed after the participants had signed the informed volunteer consent forms. Blood was collected for biochemical analyses. Results: The HMGB1 level in the patient group was determined to be significantly lower compared with the control group (p < 0.05). Limitations: The study being a cross-sectional one, the lack of an evaluation of the patients in the manic and depressive states, and lack of evaluation of the relation between HMGB1 levels and the drugs that the patients use. Conclusion: The HMGB1 levels were found to be lower in BD in the euthymic state when compared with the healthy controls. Collectively, this may be an indicator of the disorder existing at the biochemical level in the euthymic state of BD. We also suggest that the low HMGB1 levels in the euthymic period of BPD may be a gauge of improper healing in the disease.

Feedback to the editor: The topic of this manuscript is interesting but there are a few flaws in the study design (e.g. poorly formulated research question, poor conceptualization of the approach to answering the research question). Further the authors have focused their manuscript entirely on HMGB1 without linking these biological mechanisms to important clinical and cognitive variables in the field of bipolar disorder. Thus the clinical relevance of this paper is I therefore think that this topic would be of interest to a very narrow or specialized audience that the journal does not cater to specifically.

Alternatively I would recommend that the authors consider revising and resubmit this paper by addressing the following issues:

1. Improve explanation of the rationale for the study with better literature review
2. Attempt to place the study in a broad context e.g. clinical relevance of studying inflammatory markers
3. Improve formulation of the research question
4. Improve conceptualization of the approach to answering the research question
5. Provide additional measures that may have been collected during this study. Such as clinical/cognitive measures.