Ref: JAD\_2016\_1190

Title: A Clinically Relevant and Simple Measure of Global Inflammation Is Related to Symptom Burden in Bipolar Disorder

**Abstract**

Introduction Immunological theories may explain mood disorder psychopathology. However, no studies have investigated the association between overall immune system markers with specific psychopathology. Methods Two similar clinical trials, the Lithium Treatment Moderate-Dose Use Study (LiTMUS) and the Clinical and Health Outcomes Initiatives in Comparative Effectiveness for Bipolar Disorder Study (Bipolar CHOICE), enrolled 765 participants with bipolar disorder. At baseline, white blood cell (WBC) count was measured and psychopathology assessed with the Montgomery-Aasberg Depression Rating Scale (MADRS). We performed gender-specific adjusted ANOVA and linear regression analyses to investigate the relationship between the deviation from the median WBC, and multinomial regression analysis between different WBC levels. Results The overall MADRS-score increased significantly for each 1.0x109/L deviation from the median WBC among 322 men (coefficient=1.10; 95%-CI=0.32-1.89; p=0.006), but not among 443 women (coefficient=0.56; 95%-CI=-0.19-1.31; p=0.14). Among men, WBC-deviations were associated with increased severity of sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, inability to feel, and suicidal thoughts. Among women, WBC-deviations were associated with increased severity of reduced appetite, concentration difficulties, lassitude, inability to feel, and pessimistic thoughts. Both higher and lower WBC levels were associated with increased severity of several specific symptoms. Limitations We had only one WBC measure. Discussion Immune system alterations correlated with increased severity of specific mood symptoms, particularly among men. Our results support the sickness syndrome theory, but furthermore emphasize the importance of a well-balanced immune system in bipolar disorder. Studies investigating whether WBC-levels may predict gender- and/or symptom-specific treatment response are warranted.

**Comment:** the authors aim to investigate the link between immunological markers, in this case WBC, and clinical markers of psychopathology (MADRS, BISS, sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, inability to feel, and suicidal thoughts) in a sample of BD patients. The authors find an interaction between WBC and gender and report that both higher and lower WBC levels are associated with increased severity of several specific symptoms. The findings highlight the role of the immune system in BD. Further, the reported gender-related differences may help individualize therapy for males and females with BD. This topic has clinical relevance and deserves to be investigated. However, the use of a single measure of immunological response, with no reference to other possible immune/inflammatory measures and the selection of a single clinical population are debatable choices that limit the generalizability of these findings. Further, these choices are not clearly addressed or explained in the manuscript. Further, the authors should explicitly explain the differences between the current findings and those previously published by the same authors in ANZJP earlier this year. I noticed that some of the current results were included in this previous manuscript and I have therefore strong concerns about a potential overlap between these manuscripts. I would be happy to review this manuscript again if the authors addressed this concern. I have a few more comments here below that I think may improve the quality of this paper.

Please explain why the authors selected bipolar disorder. No proper link between inflammation, psychopathology and mood disorders is provided. Please address this in the abstract and introduction.

Tables: please provide statistics relative to regression analyses, betas, R2, p values

Provide references to explain your choice of WBC vs cytokines for instance. Highlight potential differences related to gender or age in healthy populations, and previous evidence in mood disorder patients. Add this in intro/discussion where necessary

Please explain how the population was recruited, inclusion and exclusion criteria, comorbidities and medication status (besides lithium and quietapine), BD subtypes, course of illness (e.g. hospitalizations, number of mood episodes)

Clarify how you extracted MADRS scores from BISS

Provide explanation for symptom severity ranges (1-2, 3-4 etc.) included in the analyses.

Explain why diabetes, hypertension and hyperlipidemia were included as covariates. were they scored dichotomously (1=yes, 0=no?)

Provide statistical threshold and explanation for correcting for both Bonferroni, sheffe, sidak. Which results did you provide?

Provide a post-hoc power analysis or reference to ideal sample size

When discussing infection etc. the authors could refer to [Kapczinski](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kapczinski%20F%5BAuthor%5D&cauthor=true&cauthor_uid=20541770) et al. (2011) who compared inflammatory measures between BD and septic patients

Given the limitations in terms of populations, infection and immunological measures I would encourage the authors to be more cautious in their interpretation of their findings. Words such as preliminary, caution and suggest should be used when interpreting these findings.