

## Format for ANSWERING REVIEWERS

July 1, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 19946-Revised manuscript.doc )

Title: Conceptualization and Treatment of Negative Symptoms in Schizophrenia

Authors: Sonali Sarker, Kiley Hillner, Dawn I Velligan

Name of Journal: World Journal of Psychiatry

**ESPS Manuscript No: 19946**

The manuscript has been improved according to the suggestions of the reviewers:

1. Format has been updated to fit the uniform format
2. The title has been lengthened
3. An abstract was added
4. 2 key words were added in order to reach the 5-10 keyword specifications
5. Revision has been made according to the suggestions of the reviewers (all have been highlighted in the revised manuscript)
6. References and typesetting were corrected

Reviewer #1 made no recommendations for changes

Reviewer #2 suggested "The authors should expand on the etiology of negative symptoms, including both biological and psychosocial factors."

In order to address this, we expanded upon both the biological and psychosocial factors of negative symptom development in the section labeled "Mechanisms in the Development of Negative Symptoms." This includes information found in studies about the corticostriatal systems, frontal lobes, and the superior temporal gyrus.

Reviewer #3 made several suggestions. All of which have been addressed:

1. "Throughout the "Description of negative symptoms" section, the authors could report the incidence/prevalence of negative symptoms in subjects with first episode psychosis (FEP). Although it has been reported that many subjects with FEP

manifest prevalent positive symptoms as symptoms onset, there are also studies supporting the predominant role of negative symptoms in subjects at the onset of schizophrenia.”

- a. We have included a discussion of prevalence in FEP as well as data supporting negative symptoms as predictors of conversion to psychosis in at risk populations.
2. “Furthermore, the authors could report within the Types of negative symptoms” section, which are the main premorbid predictors to distinguish between primary and secondary negative symptoms in subjects of schizophrenia. This is a topic that may be further developed for the general readership.
    - a. We have described types of premorbid predictors and cognitive and neuroimaging findings that help to distinguish between primary and secondary negative symptoms under the section labeled “Types of Negative Symptoms,” and that differences may represent a separate disease or the far end of the continuum severity of one disease type.
  3. “Importantly, the “Mechanisms in the development of negative symptoms” is really too limited as presented in the current version of the manuscript and needs to be further updated. Here, possible mechanisms which have been reported underlying the emergence of negative symptoms as described by neuroimaging studies on at-risk mental states could be cited and discussed.
    - a. We have now expanded the section and included neuroimaging studies on individuals in at risk mental states as requested, although these studies were not specific to negative symptoms.
  4. “The model of Velligan and colleagues and the associated Figure which have been proposed to explain the negative symptom maintenance loop are interesting and well described. Conversely, I believe that adding a Table summarizing the main psychometric instruments with their relative cut-off scores as well as their main characteristics may be useful for the general readership.”
    - a. While instruments cited do not have cut off scores per se, we have included a description of the scales and main characteristics in a table as requested. We have further described criteria set forth for PNS using these scales.

5. "When the authors reported the main results of the recent Cochrane based review of literature indicating that antidepressant drugs may have a positive impact on negative symptoms, they should also report what may be the potential effects of these medications in the long-term period of subjects with schizophrenia. It would be interesting to understand whether mood improvement which has been initially observed in these individuals may be also maintained beyond the short-term period."
  - a. We have commented on this as no longer term studies have been done to address impact on longer term mood improvement.
6. "Finally, I suggest to summarize in a specific section at the end of the manuscript what are the main limitations concerning the current assessment, classification, and treatment of negative symptoms in the clinical practice. Unfortunately, they really represent for clinicians the most difficult and challenging symptoms to manage in the real world."
  - a. We have adjusted the summary to include these points.

Reviewer #4 commented:

1. "Page 2: Primary (deficit) negative symptoms is abbreviated as (PNS) – It can also mean persistent negative symptoms – hence suggest not to abbreviate."
  - a. We only use the abbreviation of PNS for Persistent Negative Symptoms throughout the manuscript.
2. "Page 5 : Currently, there are no approved treatment options for persistent negative symptoms that are not responsive to treatments for secondary causes. – Suggest to indicate that Amisulpride is approved in several European and Asian countries for negative symptoms."
  - a. We have added data on Amisulpride but point out that MATRICS guidelines for assessing the ability of an agent to improve negative symptoms were not followed in these studies.

Thank you again for publishing our manuscript in the World Journal of Psychiatry.

Sincerely yours,

A handwritten signature in black ink that reads "Dawn I. Velligan, Ph.D." The signature is written in a cursive, flowing style.

Dawn I. Velligan, Ph.D.

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