Author's response to reviews

Title: The longitudinal interplay between negative and positive symptom trajectories in patients under antipsychotic treatment: a post hoc analysis of data from a 1-year study

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Author's response to reviews: see over
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Mr. Carlo Rye Chua  
Journal Editorial Office  
BioMed Central

Dear Carlo:

Thank you for the opportunity to respond to the reviewers’ comments pertaining to our manuscript entitled, “The longitudinal interplay between negative and positive symptom trajectories in patients under antipsychotic treatment: a post hoc analysis of data from a 1-year study” currently under consideration for publication in *BMC Psychiatry*.

In particular, we would like to thank all three reviewers for their detailed, thoughtful, and pertinent comments. We feel the suggested changes in response to those comments improve the manuscript. You will find suggested amendments and detailed responses within both the revised manuscript and the summary document below.

Thank you for your further consideration of this manuscript, and we look forward to hearing from you regarding possible publication. Please address correspondence to me at (phone) 317-600-6579; (email) chen_lei_lc@lilly.com

Sincerely,

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Referee 1
This is an interesting article, well-written and reasonably analyzed. Prior to acceptance, a few points are appropriate to incorporate.

Major Compulsory Revisions
1. The literature review is incomplete. The below citations are missing that must be cited and noted-

Data from randomized controlled trials has shown that treatment response is heterogeneous and is typically captured by 4 or 5 symptom severity trajectory groups [1-4] (examine these papers on positive and negative symptoms – esp. #3). This finding is complemented by epidemiological data showing X trajectories of hospitalization based data (a symptom proxy) with over 30 years showing [5].

Response: Thank you for your recommendation. We have added citations of the suggested references in the introduction section.

Minor Essential Revisions
2. Statistical analysis – directions for future study – dual trajectory modeling, and ability to account for systematic dropout common in RCTs, in some software.

Response: Thank you for the recommendation. Actually, we have done investigations on simultaneous/dual trajectory modeling and have also attempted to account for missing data (using the statistical software of MPlus, under the assumptions of data missing at random and different patterns of non-ignorable missing data [Rabinowitz and Davidov 2008]); the results are not conclusive. Considering the target audience of this paper is mainly non-statisticians, we decided not to introduce in the paper the sophisticated statistical methodology research.


3. Present BICs with posterior odds / neither.
Response: This study has presented model statistics BIC, aBIC and BLRT. We feel the model statistics are consistent with the literature, when using the technique of GMM.

4. Typos – there are a few. E.g., “The psychometric property of” – should be properties. Response: Thank you. We have corrected the typos in the text.

References in this document that should have been included in the manuscript

Referee 2
The study investigates the relation between positive and negative symptoms in schizophrenia and the effects of antipsychotic treatment on these domains. The paper is well presented, the methods are clear and the topic is of interest. However a number of points have to be clarified and revised.

Major Revisions
1) Clinical dimensions of schizophrenic illness are not limited to positive and negative ones. Cognitive symptoms, disorganization and severity should have been considered. As disorganization and cognitive symptoms are related to negative dimension, perhaps
the observed improvement in negative symptoms is the result of the change in other dimensions.

Response: We fully agree with the reviewer’s insightful comment. Further research would be required to evaluate the other symptom dimensions and the relationship among those dimensions, especially the relationship between negative symptoms and cognitive symptoms. Considering this study is the first attempt to model two (major) symptom domains in a longitudinal manner and modeling multiple symptom domains is not free of methodological challenges, we feel it best to focus the current study to the relationship between positive and negative symptoms.

2) It is established that atypical antipsychotics can improve negative symptoms, but, after treatment with atypical agents, a number of patients present residual negative symptoms as well as cognitive impairment that have a strong impact on social functioning and quality of life.

Response: We agree with this observation. Participants in this study were chronically ill schizophrenia patients who may have likely shown residual negative symptoms, which have likely impacted their social functioning and quality of life. This topic was, however, not the focus of the present analysis.

3) The presented neurotransmitter model of schizophrenia is partial. Glutamatergic system is thought to be involved both in negative and positive symptoms of schizophrenia.

Response: We agree with these comments. Glutamate is clearly involved in the mediation of both positive and negative symptoms of schizophrenia, although the data are inferential. The inference is based upon 2 main tenets. First, phencyclidine, an antagonist at the NMDA glutamate receptor, provokes both positive and negative symptoms de novo in healthy volunteers as well as in patients with schizophrenia. Second, drugs which modulate glutamate activity in the brain can improve the positive and negative symptoms of schizophrenia including mGlu2/3 receptor agonists, glycine transport inhibitors, and glycine receptor agonists. We added this information in the introduction section.
4) Two variables can be correlated but independent. Of note none of the reported Pearson coefficients indicate a strong correlation between negative and positive symptoms (>0.7)

Response: We agree that two variables could be correlated but independent. However, besides the positive and moderate Pearson correlation coefficients between positive and negative symptoms, the longitudinal interplay between them (Figure 3) shows the consistent and robust concordance between the positive and negative trajectories. Though there is no single statistic (to our knowledge) to summarize this phenomenon, we feel it suggest some dependency between these two symptom domains.

5) The sample is not homogenous. The patients probably have different duration of illness (schizophreniform patients in comparison with schizophrenic ones) with clearly implication in term of treatment response. In addition schizoaffective patients have a different treatment response and outcome respect to schizophrenics and they had not to be included in the sample.

Response: Yes, the sample is heterogeneous, and the study sample included patients diagnosed with schizophrenia, schizophreniform, and schizoaffective disorders. There were very few participants (less than 1%) with schizophreniform disorder (Tunis et al. 2006, reference 24). To help address the heterogeneity of the sample, we used growth mixture modeling, a statistical method that allows for modeling of heterogeneity.

Minor Revisions

1) Most of patients were previously treated with first generation antipsychotics that can have modified clinical presentation

Response: That is correct. Most study participants were chronically ill schizophrenia patients who were previously treated with antipsychotic medications. Current findings may not be generalizable to patients in an early stage of the illness. This limitation is noted in the discussion section of the manuscript (page 13).
2) PANSS baseline total scores indicate a moderate severity of illness. The rate of severity is predictive of treatment response so that in case of more severe patients the results could have been different.
Response: Yes, the mean PANSS baseline total scores indicate a moderately severe disease severity level. In a follow-up analysis, we found that the DSI (dramatic and sustained early improvement) and NI (no improvement) subgroups had mean PANSS total scores of 96.4 and 97.1 respectively, which suggest severe illness severity. Thus, we feel this study represents population with moderate to severe disease severity.

3) Comorbid psychiatric diagnoses were cross-sectional or life-time? If cross sectional, what type of mood disorder was comorbid in 21.6% of patients? Was psychotic bipolar disorder accurately excluded?
Response: Comorbid psychiatric diagnosis is life-time, based on a comprehensive clinical assessment with documentation of psychiatric diagnoses using the Structured Clinical Interview for DSM-IV Axis I Disorders and treatment history (Tunis et al. 2006, reference #24).

Referee 3

The authors examined the longitudinal pattern of positive and negative symptom domains and the interplay between them using the data from a multicenter, randomized, open-label, 1-year pragmatic trial of patients with schizophrenia spectrum disorder. Data from 399 patients who were treated with first- and second generation antipsychotics in the usual clinical settings. The PANSS was used at week 0, 1, 3, 9, 21, 33, and 49. Individual-based growth mixture modeling combined with interplay matrix was used to identify the latent trajectory patterns for both the negative and positive symptoms. Pearson correlation coefficients were used to examine the relationship between the changes of these two symptom domains. They identified 4 negative symptom trajectories and 3 positive symptom trajectories. Among 11 combined trajectory patterns formed from these positive and negative symptom trajectories, it is shown that negative and positive symptom trajectories moved generally in parallel. Further, correlation
coefficients for changes in negative and positive symptom subscale scores were positive and statistically significant. Their results suggest that negative and positive symptoms were dependently related with each other. The study is well designed. The scientific content of this manuscript is clear and the methods are clear. The results are interesting. The findings in the present study could provide additional information in the field. The manuscript is worthy of being published. If possible, I would suggest that the authors pay attention to the following comments:

1. Detailed information about the antipsychotic drugs used in the present study should be provided.

Response: In the Method section, we described the antipsychotic drugs used in the study: “Patients were randomized to olanzapine, risperidone, or first-generation antipsychotics (FGAs).” Since the original trial was designed as a pragmatic clinical trial in which dosing and switching of medication were allowed per physician discretion, we did not extend this study to explore the treatment effect of certain drugs.

2. The results of PANSS at different time points should be present in a Table.

Response: We reviewed other schizophrenia papers reporting trajectories (eg. Case 2010, Levin 2010, Marques 2011) and found that PANSS at different times are presented in figures, but not tables. We feel such figures well represent the longitudinal feature of the trajectory, while adding tables may offer redundancies with PANSS scores already shown in Figures 1-3.

3. Whether there was a gender difference in the trajectory patterns for both the negative and positive symptoms or the relationship between the changes of negative and positive symptom domains?

Response: We have conducted an additional analysis and found no gender differences in the trajectory pattern.