Author's response to reviews

Title: Relationships Among Neurocognition, Symptoms and Functioning in Patients with Schizophrenia: A Path-Analytic Approach for Associations at Baseline and Following 24 Weeks of Antipsychotic Drug Therapy

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Version: 2  Date: 30 June 2009

Author's response to reviews: see over
June 23, 2009

Dear Editor:

We have completed revisions to our manuscript (MS: 1466203774226218) focusing on neurocognition, symptoms and functioning following antipsychotic drug therapy. The manuscript is titled “Relationships Among Neurocognition, Symptoms and Functioning in Patients with Schizophrenia: A path-Analytic Approach for Associations at Baseline and Following 24 Weeks of Antipsychotic Drug Therapy.” We would like to have our revised manuscript considered for publication in BMC Psychiatry. We have also attached a detailed response to the reviewer’s comments.

As noted previously, the data presented in this manuscript have not been published previously and are not under consideration for publication elsewhere. All authors have made a substantive contribution to the work, and each has read and approved the manuscript.

Please address all correspondence to either: Dr. Ilya Lipkovich, Ph.D., Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, DC 6054, Indianapolis, IN 46285; Telephone: (317) 651-6095; Facsimile: (317) 433-1304; E-mail: lipkovichia@lilly.com, or Dr. Sara Kollack-Walker, Ph.D., Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285; Telephone: (317) 433-4654; Facsimile: (317) 276-7100; Kollack-Walker_Sara@lilly.com.

Sincerely,

Ilya Lipkovich, Ph.D.                 Sara Kollack-Walker, Ph.D.
Dear Dr Kollack-Walker,

I hope you are well. First of all, we would like to apologise for the long delay you have experienced in receiving an initial editorial decision from us. This was due to the fact that, despite several chases, a promised second referee had been unable to return their report. However, in order to prevent any further delay, the Associate Editor has looked over the manuscript and the report we do have.

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the link below. Do let us know if you have any problems opening the file.

Referee 1:  
http://www.biomedcentral.com/imedia/5251070472365050_comment.pdf

Also please make the following changes to the abstract:

*Please remove the information regarding the trial registration number from the abstract. **REPLY: This information has been removed.**  
* Please include a background section and some context information in addition to the aims **REPLY: Change made as requested.**

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals ). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 12 May 2009. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.biomedcentral.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=1466203774226218. You will find more detailed instructions at the base of this email.

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,
Reviewer's report

Title: Relationships Among Neurocognition, Symptoms and Functioning in Patients with Schizophrenia: A Path-Analytic Approach for Associations at Baseline and Following 24 Weeks of Antipsychotic Drug Therapy

Version: 1 Date: 16 November 2008
Reviewer: Michael Minzenberg

Reviewer's report:

The paper by Lipkovich et al describes an analysis of the relationships between cognition, symptoms, and functioning in a large sample of stable chronic schizophrenia patients during the course of a randomized, one-year antipsychotic medication trial. They found that at baseline, "processing speed" predicted function via negative symptoms, and that at 24 weeks, changes in processing speed were related to changes in function both directly and indirectly through changes in negative symptoms. Working and verbal memory did not contribute significantly to these path models, and positive symptoms contributed to function only at baseline.

This is a well-designed study that adds to an important literature addressing the relationships of cognition and symptoms to functional outcome. I have only a few concerns and queries about the study. All are discretionary in nature.

1. Because this is a medication treatment study, can the 3 treatment groups be added to the models, or somehow otherwise considered as a factor in these relationships? It would be quite interesting to know if these relationships varied by treatment. REPLY: While the relationship by treatment could vary, dividing the data by treatment would result in small subgroups with limited power to detect significant differences. In the original study (Keefe et al. 2006), at the 52-week endpoint, neurocognition (neurocognitive composite score) had significantly improved in each group, with no significant differences between groups. Olanzapine- and risperidone-treated patients had shown significant improvement on domains of executive function, learning/memory, processing speed, attention/vigilance, verbal working memory, and motor functions. Additionally, risperidone-treated patients improved on domains of visuospatial memory. Haloperidol-treated patients improved only on domains of learning/memory. Patients able to remain in treatment for the entire 52 weeks (observed case analysis) benefited more from olanzapine or risperidone treatment than haloperidol treatment. However, per protocol, the haloperidol arm had been discontinued. Therefore, it is not likely that the current study would reveal meaningful comparisons across the 3 treatment groups.

We have added the following statements to the current manuscript (Limitations, page: 13): "While the relationships among variables could vary by treatment, analyzing the data separately by treatment groups would result in small subgroups with limited power to detect significant differences. In the original study [16], at the 52-week endpoint, neurocognition had significantly improved in each group, with no significant differences observed between groups. Although differences were observed on what specific domains improved in the three treatment arms, the lack of differences observed across the treatment groups overall and discontinuation..."
of the haloperidol arm per protocol limit further analysis of this important issue in the current study."

2. Digit-symbol and verbal fluency are both complex tasks that draw on a variety of discrete cognitive processes, and this is obscured by grouping them together simply as measures of "processing speed." How do these 2 measures perform when considered separately in the models? REPLY: The reviewer is indeed correct that digit-symbol and verbal fluency are complex tasks that draw on a variety of cognitive processes. However, in order to reduce the number of statistical analyses with potential redundancy and issues with testing multiple hypotheses, we followed the conceptualization of the MATRICS group, who placed verbal fluency and digit-symbol together in the same domain of "processing speed" based upon their review of several factor analyses available at the time (Nuechterlein et al., 2004). We have added the following sentence to the manuscript (page 7): “Although digit-symbol and verbal fluency are complex tasks that draw on a variety of cognitive processes, we followed the conceptualization of the MATRICS group, who placed verbal fluency and digit-symbol together in the same domain of "processing speed" based upon their review of several factor analyses available at the time [14].”

3. Can some measurement properties (e.g. internal and test-retest reliability) be provided for the function measure, since the hypotheses are so dependent on them? REPLY: The original publication for the Quality of Life Scale (Heinrich et al., 1984) contains the factor structure and other psychometric properties assessed.

   To determine the interrater agreement on the QLS, pairs of authors independently rated 24 of the 111 schizophrenic outpatients at a research clinic on an initial version of the scale. Intraclass correlations (ICCs) for the categories and for the total score (the average for all the items) were as follows: Intrapsychic Foundations = .91; Interpersonal Relations = .94; Instrumental Role = .97; Common Objects and Activities = .94; and Total Score = .94.

   The authors also assessed training requirements and rater reliability of clinicians who had not been involved in developing the QLS. Approximately 3 hours after discussing the instrument and its use, a reliability study consisting of simultaneous ratings of 10 live interviews with 5 raters alternating the role of principal interviewer resulted in the following ICCs for category and total scores: Intrapsychic Foundations = .84; Interpersonal Relations = .87; Instrumental Role = .94; Common Objects and Activities = .94; and Total Score = .88. For both the authors and the trained clinicians, good reliability was obtained on both the total score and the category scores.

   No inter-rater reliability assessments had been collected during the conduct of the HGGN clinical trial.

4. It would be helpful and interesting to know what those change scores were, for symptoms, cognition and function, both to get a feel for the treatment response, and to consider if there were some restricted change scores that may limit the power of the models. REPLY: Changes in cognitive measures and functioning from baseline were provided in Figure 2. For cognition, significant improvement from baseline was observed in working memory and verbal memory, although not in processing speed. For functioning, significant improvement from baseline was observed for the QLS Instrumental and Intrapsychic subdomains, but not for QLS Interpersonal subdomain. While a similar summary diagram was not provided for scores from the PANSS total, positive and negative subscales, the improvement observed was reported in the primary manuscript (Keefe et al. 2006). At Week 52, the following changes from baseline to endpoint were observed for the PANSS total score (OLZ, -12.4 +/- 16.0; RIS, -9.5 +/- 15.5; HAL, -7.6 +/- 16.3), PANSS positive score (OLZ, -4.3 +/- 4.9;
RIS, -3.6 +/- 5.5; HAL, -3.1 +/- 5.8) and PANSS negative score (OLZ, -2.5 +/- 5.3; RIS, -1.6 +/- 4.9; HAL, -1.5 +/- 4.8).

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:**  
I declare that I have no competing interests.