Author's response to reviews

Title: Sustained favorable long-term outcome in the treatment of schizophrenia: a 3-year prospective observational study

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Author's response to reviews: see over
Reviewer #1
Major Compulsory Revisions
1. The conclusion of the study that the findings “suggest there is room for improvement in the treatment of schizophrenia” is understated, and in any case widely known. A more thought-through conclusion is warranted.

Reply: Thank you for your feedback. We have revised the discussion of the manuscript to address this comment. The conclusion in the abstract and in the discussion now states “Only a small percentage of patients achieved sustained favorable long-term outcome in this study, suggesting there continues to be a great unmet need for improvement in the treatment of schizophrenia. Findings suggest that clinicians could make early projections of health states and identify those patients more likely to achieve favorable long-term outcomes enabling early therapeutic interventions to enhance benefits for patients.” (Page 3, 17)

The following text was added to further discuss some of the findings from Figure 2: “Of particular interest, the results indicate that more daily activities and receiving less help with shopping or leisure activities were associated with sustained favorable long-term outcome. These factors are potentially modifiable and easy to assess, thus enabling clinicians to better understand and help optimize the treatment plan for the patient.” (Page 15)

2. More details of the treatment should be provided. Also, was adherence assessed? If so, its role in outcome should be considered.

Reply: We have added details about the treatment (page 5), indicating that at enrollment, almost all patients (94.7%) were treated with at least one antipsychotic medication, including oral typical (36.7%), oral atypical (58.1%), and depot typical antipsychotics (19.6%). Treatment throughout the study was based on physicians’ decisions, which could include medication augmentation, switching or discontinuation, reflecting the dynamic antipsychotic treatment observed in naturalistic care settings.

Adherence with antipsychotic medication regimen was assessed in two ways: The Medication possession ratio (MPR), and patient-reported non-adherence.

The Medication possession ratio (MPR) was defined as the cumulative number of days the patient had been prescribed any antipsychotic drug divided by the number of days in the assessment period multiplied by 100. The MPR ranges from 0% to 100%, with higher values indicating greater time with any prescribed antipsychotic medication. This measure was calculated using medication information in the MRAF form, which was abstracted from patients’ medical records by trained examiners every 6 months. Nonadherent patients were defined as those with a MPR < .80. Patient-reported non-adherence was
assessed via the SCAP-HQ adherence item which assesses how regularly the patients reported taking their medications in the past 4 weeks: “(1) I never missed taking my medicine; (2) I missed only a couple of times, but basically took all the medicine; (3) I missed the medicine several times, but took at least half of it; (4) I took less than half of what was prescribed; and (5) I stopped taking the medicine altogether.” Patients who also chose alternative 1 or 2 on the SCAP-HQ adherence item were considered “adherent”, while all other patients were classified as “nonadherent”. Information about the adherence variables are presented in Table 1 and Table 3 under “Medication Adherence.”

3. Patients were assessed only at 3 time points (annually). This is a significant limitation of the study. While listed as such, it should be pointed out that, as schizophrenia is an illness characterized by relapses and remissions, the present study will not reflect the true course of illness.

Reply: We agree that this is an important point to highlight. This limitation has been reinforced in the discussion section, page 16, stating: “This study has a number of limitations, including infrequent assessments. Clinician-reported outcomes were obtained only annually, and patient-reported outcomes were assessed every 6 months. Due to the infrequent assessments and the fact that schizophrenia is an illness characterized by relapses and remissions, this study was unable to capture episodic exacerbations or relapses that may have occurred between assessments. Because of these infrequent assessments, other changes within those time periods and the potentially important variable of patients’ early response to therapy were not captured.”

4. The outcome measure utilized in this study incorporates symptom severity, functionality and use of acute care resources. It is known that symptomatic and functional remission do not necessarily occur simultaneously. It would be important to know how the different components of outcome correlated with one another.

Reply: The correlations between the PANSS factor subscale scores and clinician-rated occupational functioning ranged between -0.25 and -0.19 while the correlations between the PANSS factor subscale scores and clinician-rated level of accomplishment ranged from -0.38 to -0.26. Although the correlations between symptoms and functioning were not strong, the effect of this does not impact the cluster analysis. The cluster analysis performed in this study grouped patients in clusters based on the similarities between each other as opposed to the correlation between the measures, such that the variability within clusters was lower than the variability between clusters.

And while symptomatic and functional improvements – at least in some functional domains - do not necessarily occur simultaneously, the assumption that improvement in functional outcomes is delayed relative to improvement in symptoms in the treatment of schizophrenia has been recently empirically challenged (Kinon BJ, Chen L, Ascher-Svanum H, Stauffer VL, Kollack-Walker

Minor Essential Revisions
1. p 3 “..non-adherence can lead to early treatment discontinuation… ” Non-adherence and treatment discontinuation are the same thing.
   
   Reply: Revised as requested.

2. Outcome measures p6: Several scales are listed that are not mentioned in the study – these should be omitted.
   
   Reply: There are many scales/variables used in this retrospective study, therefore we went back to double check that all of the potential predictors mentioned on page 6 were also included in the analyses (i.e. included in tables 1 and 3). We did not identify any scales on page 6 that were not included in the analyses. Please let us know if we have overlooked something.

Discretionary Revisions
1. p 14: why is only lack of early response listed as a predictor that was omitted? What about others, e.g. DUP, premorbid functioning etc?
   
   Reply: Early response in particular was singled out because of the recent literature showing the potential predictive relationship between early response and subsequence response/non-response in the treatment of schizophrenia. While DUP and premorbid functioning are important predictors, they were not assessed in this study, whereas symptom improvement was assessed. However, the ability to investigate it after 2 weeks of therapy was not feasible due to the infrequent symptom assessment schedule in SCAP. We agree that there are other key variables not collected, thus not explored, and have added a sentence to that effect in the manuscript (page 17).

Reviewer #2

Major revisions
1. the methods are hard to follow and could use some more editing to clearly state the objectives. For example, Table 2 is the baseline cluster and Figure 2 is the predictive cluster results but this took me several readings and I am still not sure I understand the step-wise approach taken.
   
   Reply: We appreciate the feedback and have revised the methods section to more clearly articulate the steps that were taken in this rather complex analysis. The results shown in Table 2 are for those variables used in the broad definition of health states; these are the results from the cluster analysis which was the first step in the analysis. The second step in the analysis was identifying those with sustained favorable long-term outcome. Figure 2 shows the results from the last step in the
analysis which was to determine potential predictors of sustained favorable long-term outcome.

2. Table 2: while I am sure it was explained in the manuscript, I’m not sure how these variables came to be the ones used for baseline, and that they differ from the outcome predictive variables shown in Figure 2.
   
   Reply: To clarify this point, the title of Table 2 has been changed to better reflect the content and avoid confusion. The variables in Table 2 were “cluster variables” and were those that were used in the definition of the health states. The table is presenting the baseline patient characteristics by cluster to show the reader how the clusters differed (best, second best, etc). Figure 2 shows the results from the last step in the analyses, where stepwise logistic regression was used to determine the best baseline predictors of sustained favorable long-term outcome from 62 variables.

3. Figure 2 is the main point of the paper. It is very interesting. It should be better organized to communicate the main findings; for example the patient reported “clearer thoughts” item should be reverse coded to make the directionality of favorable predictors consistent
   
   Reply: Thanks for your suggestion. The patient reported “clearer thoughts” variable was reverse coded in the revised manuscript and reflected in Figure 2.

4. Figure 2 also has some very interesting findings that would be worth further discussion. Some have direct relevance in terms of how to assess patients; for example, not receiving help with shopping or leisure activities is assessable and as I understand it more important than the extent to which the patient engages in these activities.
   
   Reply: The following text was added to further discuss some of the findings from Figure 2: “Of particular interest, the results indicate that more daily activities and receiving less help with shopping or leisure activities were associated with sustained favorable long-term outcome. These factors are potentially modifiable and easy to assess, thus enabling clinicians to better understand and help optimize the treatment plan for the patient.” (Page 15)

5. Figure 2 Also the finding that individual therapy is a negative predictor of outcome. If I understand this correctly, patients who received individual therapy are about half as likely to do well than those who do not. Is this variable lifetime or current individual therapy? What %age of patients does this variable cover?
   
   Reply: Your interpretation of the results is correct. The timeframe associated with the individual therapy question was within 6 months. Ninety-three percent (1517/1635) of the patients responded to this question. For the 118 patients with missing data, values were imputed using five multiple imputations for inclusion in the stepwise regression analysis. The mean age for patients represented in figure 2 was 42.3 years (SD=11.0) with a range of 18.0 to 76.0 years.

Minor revisions
1. Table 2: I think the text states that these variables were tested for interdependency and highly correlated variables removed. However, the ER and hospitalization results are concerning about non-independence of the variables driving the clusters. For example, does a psychiatric hospitalization automatically mean that that person cannot be in the top 2 clusters? If so, then would it not be circular to report that as an outcome of cluster?

Reply: The variables in Table 2 were those that were used in the cluster analysis to define the health states. The cluster analysis performed in this study grouped patients in clusters based on the similarities between each other as opposed to the correlation between the measures, such that the variability within clusters was lower than the variability between clusters. Therefore, those patients with ER and psychiatric hospitalizations had similar symptom severity and functioning compared with those patients without ER and psychiatric hospitalizations. The testing of interdependency of variables was performed for the logistic regression analysis as opposed to the cluster analysis. So, those independent variables included in the logistic model were tested for collinearity using a variance inflation factor (VIF) cutoff value of 10. Since the ER and psychiatric hospitalizations VIF values were less than 10, they were kept in the model.

2. Table 2: Also there should be a column for the entire cohort values.

Reply: We have added the requested additional column to Table 2.

Discretionary
The authors do not discuss the implications of their findings in the discussion section, which then leaves this reviewer wondering why the authors went through all the trouble to do this analysis in the first place. Some discussion of the specific findings – with appropriate caveats about the need to replicate the work – would be helpful in getting a sense of the context and meaning of their findings.

Reply: Thank you for your helpful suggestions. We have revised the discussion of the manuscript to address this comment. The conclusion in the abstract and in the discussion now states “Only a small percentage of patients achieved sustained favorable long-term outcome in this study, suggesting there continues to be a great unmet need for improvement in the treatment of schizophrenia. Findings suggest that clinicians could make early projections of health states and identify those patients more likely to achieve favorable long-term outcomes enabling early therapeutic interventions to enhance benefits for patients.” (Page 3, 17)

Also, in the limitations section, we have pointed out that this analysis is hypothesis-generating work and thus the results would need to be replicated.