Author's response to reviews

Title: Impact of insufficient drug efficacy of antiparkinson agents on patient's quality of life. A cross-sectional study

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Version: 6
Date: 23 April 2015

Author's response to reviews: see over
Re: Impact of insufficient drug efficacy of antiparkinson agents on patient’s quality of life

Dear Editor,

We would like to resubmit our manuscript entitled “Impact of insufficient drug efficacy of antiparkinson agents on patient’s quality of life” for consideration for publication as an original article in your Journal.

Thank you very much for your letter dated on 2015-03-17, regarding our manuscript indicated above. We wish express our appreciation to the reviewers for their insightful comments, which have helpful us significantly to improve the paper.

We have made significant changes on this manuscript indicated by reviewer 2 and editor. Please find enclosed our updated manuscript with our responses point by point to reviewer’s comments.

We wish to thanks the reviewers again for his valuable comments. I believe that the revised manuscript is suitable for publication.

Again thank you for your assistance.

Sincerely yours,

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Response to referee 2

Comment 1: As I mentioned previously, the most important concern about this project is the validity of information since all data were gathered as self-reported by the patients without even checking with their medical records. Authors have accepted this problem but also replied that the large sample size of this study may have compensated this validity issue, however, I must note that large sample size could definitely lower the chance of random errors but not systematic errors or biases such as information bias. Therefore, I highly recommend extensively elaborating this problem in the limitation section of the manuscript and recommending more valid studies for future.

Response: Thank you for reviewer’s comment. We agree with this suggestion and added the following comments in the discussion. (p. 11, line 5-7)

“The large sample size could definitely lower the chance for random errors; however, due to the design of the study, one other limitation is the possibility of systematic errors or biases, such as information bias. Therefore, we recommend further studies to validate our findings.”

Comment 2: As previously mentioned, there are just few patients in the mild stage of disease due to the fact that these patients were not probably eager enough to participate in the survey. Thus, it is not possible to judge about the frequency of insufficient drug efficacy in a PD population based on the findings of this study. This important issue needs to be discussed in the “Discussion” section to clarify the generalizability issues in this study.

Response: Thank you for reviewer’s important comment. It is true that there are just a few patients in the mild stages of the disease in this study. We believe that this is because there is a deflection of the support group (Japan Parkinson’s Disease Association) configuration, which could show fewer patients in the mild stage of the disease. In general, patients in the mild stage hesitate joining a support group due to psychological and social issues. Therefore, we believe that there might be fewer tendencies to be such bias. At the same time, we did not find enough objective data to support our hypothesis. Therefore, we have inserted a discussion related to this possible bias in the revised manuscript (p. 10, line 22 – p.11, line 4).

“In this study, fewer patients were included that fell into the mild stage of the disease possibly due to the fact that there is a deflection of the support group (Japan Parkinson’s Disease Association) configuration, showing fewer patients in the mild stage of disease. On the other hand, we could not rule out the possibility that fewer patients in the mild stage participated in
our study due to a lack of motivation to respond to the survey. If this were the case, then it could account for the higher frequency of insufficient drug efficacy in the mild PD population included in this study.”

**Comment 3:** I previously recommended performing multivariate analysis to check if the insufficient drug efficacy could still have an independent effect on quality of life score after adjustment for Hoehn and Yahr score and/or disease duration adjusted for the baseline characteristics such as age and sex. Most of the data on these variables are already reported and seem to be available. Therefore, I think it is necessary to perform this additional analysis especially when the validity of information about the main variable (insufficiency of treatment) is doubtful based on the self-reported nature.

**Response:** Thank you for reviewer’s suggestion. We have performed a multivariate analysis to assess whether the insufficient drug efficacy could still have an independent effect on the quality of life score after adjustment for Hoehn and Yahr stage, disease duration, and baseline characteristics such as age and sex. Thus, the following sentence and Table has been added into the methods and results sections.

Table 5. Multivariate statistical analysis for PDQ-SI (General linear model)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B</th>
<th>SE</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient drug efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13.12</td>
<td>2.46</td>
<td>8.30 , 17.94</td>
<td>0.000</td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>8.69</td>
<td>2.26</td>
<td>4.25 , 13.12</td>
<td>0.000</td>
</tr>
<tr>
<td>Gendar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>-2.01</td>
<td>1.01</td>
<td>-3.98 , -0.03</td>
<td>0.046</td>
</tr>
<tr>
<td>Age</td>
<td>0.44</td>
<td>0.07</td>
<td>0.31 , 0.57</td>
<td>0.000</td>
</tr>
<tr>
<td>Disease duration</td>
<td>5.47</td>
<td>0.89</td>
<td>3.73 , 7.22</td>
<td>0.000</td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient drug efficacy(N), H&amp;Y&lt;3</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient drug efficacy(N), H&amp;Y≥3</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Insufficient drug efficacy(Y), H&Y<3  

<table>
<thead>
<tr>
<th>B: regression coefficient; 95%CI: 95% confidence interval; SI: standard error; GLM: General linear model; H&amp;Y: Hoehn and Yahr stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient drug efficacy(Y), H&amp;Y≧3</td>
</tr>
<tr>
<td>-5.71 2.81 -11.22 , -0.19 0.042</td>
</tr>
</tbody>
</table>

B: regression coefficient; 95%CI: 95% confidence interval; SI: standard error; GLM: General linear model; H&Y: Hoehn and Yahr stage

In the Subjects and Methods section (p.4, line 23 - p.5, line 5):

“We also performed multivariate statistics using the general linear model (GLM) to evaluate whether insufficient drug efficacy influenced PDQ-SI after adjustment for several confounding factors (e.g., age, gender, Hoehn and Yahr stage, and disease duration). If we found a factor that had a significant interaction with insufficient drug efficacy, we performed a model design that included that interaction term. Gender and Hoehn and Yahr stage were set as categorical scale, age as metric scale, and disease duration as ordinal scale variables of < 3 year = 0, ≧ 3 - < 7 year = 1, ≧ 7 = 2.”

In the Results section (p.6, line 17 – p.7, line 4);

“The result of a GLM analysis is shown in Table 5. We performed this analysis to evaluate the impact of insufficient drug efficacy on the PDQ-SI. Because we found a significant difference of interaction term of insufficient drug efficacy + Hoehn and Yahr stage to PDQ-SI according to GLM analysis including all interaction term (P = 0.0218, data not shown). We have provided Table 5 to include these interaction terms (insufficient drug efficacy + H & Y stage). These analyses confirmed that insufficient drug efficacy has a significant effect on PDQ-SI, independent of confounding factors such as age, gender, Hoehn and Yahr stage, and disease duration; PDQ-SI of insufficient drug efficacy (Yes) found 13.12 (95% CI:8.30,17.94) higher compared to those of insufficient drug efficacy (No) (P<0.001). However, we also found a significant interaction between insufficient drug efficacy and Hoehn and Yahr stage; Hoehn and Yahr stage group of ≧ 3 found PDQ-SI increasing score reduced 5.71(95%CI: 2.81, -11.22) compared to Hoehn and Yahr stage group of < 3.”

Comment 4: Page 8, line 5: If “no previous reports investigated Japanese subjects” using the PDQ-8, then it becomes necessary to provide statistical data on the reliability and validity of the Japanese version of the questionnaire prior to interpreting any findings from that. If this is still the case, please perform reliability and validity analysis to check the Japanese version of the PDQ-8.
Response: Thank you reviewer’s important comment. We have previously added the following reference, which provides statistical data on the reliability and validity of the Japanese version of the questionnaire.


Response to Editor:

Comment 1: Because the main focus of the study is to investigate the association of “insufficient drug efficacy” on QOL, the strength of the association should be expressed statistically as pointed by Reviewer 2. The primary outcome measure is the score of PDQ-8 summary index, which can be handled as scale variable. Possible main confounding factors are PD duration (Years) and the severity of PD (mH-Y) at least. I feel that the impact of “insufficient drug efficacy” should be evaluated after adjustment for these factors. Could it be adapted to ANCOVA (or univariate GLM)? For example, incorporating insufficient drug efficacy (Y/N), mH-Y (1-2.5 vs 3-5) as fixed factors, PD duration (years) as a covariate, and the score of PDQ-8 as dependent variable. In case of no statistically significant interactions of predictable variables, the strength of the impact (or effect size) would be estimated as parameter B with range. Though "the authors did not decide to perform analysis because the database had insufficient data", the size of missing data seems small.

Response: Thank you for the reviewer’s comment. As we responded to reviewer 2, we performed a multivariate analysis to assess whether the insufficient drug efficacy could have an independent effect on the quality of life score after adjustment for Hoehn and Yahr stage, disease duration, and baseline characteristics such as age and sex. We add comments in the methods and results section, as well as summarized our results in Table 5. Please see our response to reviewer 2.

Comment 2: As mentioned by Reviewer, I also feel that selection bias should be considered (More patients who feel insufficient efficacy may response more frequently and in contrast, patients without insufficient drug efficacy may not provide responses to questionnaire). Please state the possibility of selection bias.

Response: Thank you for your important suggestion. It is true that this study included just a few patients in the mild stage of the disease; we believe that this could be due to a deflection of
the support group (Japan Parkinson’s Disease Association) configuration, showing fewer patients in the mild stage of disease. In general, patients in the mild stage of the disease might hesitate joining a support group, probably due to psychological and social issues. Therefore, we believe that there might be fewer tendencies to be such bias. At the same time, we did not find enough objective data to support our hypothesis. Therefore, we have inserted a discussion related to this possible bias in the revised manuscript (p. 10, line 22 – p.11, line 4).

“In this study, fewer patients were included that fell into the mild stage of the disease possibly due to the fact that there is a deflection of the support group (Japan Parkinson’s Disease Association) configuration, showing fewer patients in the mild stage of disease. On the other hand, we could not rule out the possibility that fewer patients in the mild stage participated in our study due to a lack of motivation to respond to the survey. If this were the case, then it could account for the higher frequency of insufficient drug efficacy in the mild PD population included in this study.”