Author's response to reviews

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

**Authors:**

Jun Tsugawa (tsujun1@msn.com)  
Rieko Onozawa (riefko@fukuoka-u.ac.jp)  
Jiro Fukae (jfukae@fukuoka-u.ac.jp)  
Takayasu Mishima (mishima1006@fukuoka-u.ac.jp)  
Shinsuke Fujioka (shinsuke@cis.fukuoka-u.ac.jp)  
Yoshio Tsuboi (tsuboi@cis.fukuoka-u.ac.jp)

**Version:** 5  
**Date:** 21 February 2015

**Author's response to reviews:** see over
February 12, 2015

Editor-in-Chief

*BMC Neurology*

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 a original article in your Journal.

Thank you very much for your letter dated on 2015-01-09, 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 1 and reviewer 2. 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,

Yoshio Tsuboi, M.D, Ph.D
Director of Department of Neurology, Fukuoka University School of Medicine
E-mail: tsuboi@cis.fukuoka-u.ac.jp
7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0133, Japan
Tel.: 092-801-1011 FAX: 092-865-7900
Response to referee 1

Comment 1: Table 2; How would you explain about the insignificant difference on PDQ-8 SI between patients with and without insufficient efficacy only in the Yahr 4 stage? You showed significant difference on PDQ-8SI between patients with and without insufficient efficacy even for patients with Yahr 1 stage. Additionally, in conclusion (abstract), you describe "greater awareness of insufficient drug efficacy "... then be taken" This is reasonable comment. Many patients feel insufficient drug efficacy even in the early stage of PD patients. However, most doctors do not increase the anti-PD drugs to maximal doses to remove all symptoms, because of the possible side effects in the future, although they understand insufficient drug efficacy in the early stage of PD patients. Would you explain about "appropriate action" in such occasion?

Response: Thank you for reviewer’s comment. In Yahr 4 stage, majority of PD patients would develop wearing-off phenomenon and aware of these symptom disturbing their quality of life (QOL). Thus, the physician may aware of them and needs for increasing dose of dopaminergic medication including L-DOPA and dopamine agonists. In addition, there is a possibility that non motor symptoms which are not resolved with dopaminergic drug strongly affect their QOL. These symptoms would decrease QOL in both patients with and without insufficient drug efficacy. We added these comments in the discussion. (p.9, line17-24)

“Our results revealed no statistical difference of PDQ-8 SI between patients with and without insufficient efficacy only in patients with Yahr 4 stage. It is speculated that majority of patients with Yahr 4 stage would develop wearing-off phenomenon and aware of these symptoms disturbing their quality of life (QOL). Thus, the physician may also aware of them and needs to increase the dose of dopaminergic medication including L-DOPA and dopamine agonists. In addition, there is a possibility that non motor symptoms which are not resolved with dopaminergic medication strongly affect their QOL. These symptoms could decrease their QOL in both patients with and without insufficient drug efficacy.”

Comment 2: Table 3; Could you show us which factor is more important on the QOL between only in the daytime zone and only in the time zone of sleeping and early morning without daytime inefficiency?
Response: Thank you for reviewer’s important comment. Because this study is based on objective evaluation of the patients, “insufficient drug efficacy” in this study includes various factors such as under medication of dopaminergic stimulation, which affects both in daytime and the early morning, and wearing off phenomenon only affected in the daytime. That’s the reason why there are patients with insufficient drug efficacy only in the daytime zone and those only in the time zone of sleeping and early morning without daytime inefficiency. There are more tendencies that physicians do not increase the dose of dopaminergic medication to maximal doses to remove PD symptoms, because of the fear of side effects in the future. In other words, PD patients may be administrated with dopaminergic medication with underdose rather than overdose. Thus, the following sentence has been added in the discussion (p.8, line 8-14),
“Because this study is based on objective evaluation of the patients, “insufficient drug efficacy” in this study includes various factors such as under medication of dopaminergic stimulation, which affects both in daytime and the early morning, and wearing off phenomenon only affected in the daytime. We recognize the necessity that comprehend it as an evidence our study suggested how to resolve this problem. It is however not easy to argue which factor is more important on the QOL between insufficient drug efficacy in the daytime zone and that in the time zone of sleeping and early morning.”

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

Response to referee 2

# ABSTRACT

Comment 1: A brief definition of the insufficient drug efficacy should be mentioned in the “Methods” section of the abstract.

Response: Thank you for reviewer’s comment. A definition of the insufficient drug efficacy is subjectively representing dissatisfaction to the treatment in individual. We have mentioned in detail in the method section as the following, “Does it take time for the drugs to take effect? (yes, no),” “When dose this occur during the day? (early morning, during the day, night; multiple answers possible)”.
Comment 2: The “Results” section of the abstract needs to be improved by using the effect sizes for the mentioned correlations/associations.

Response: Thank you for the comment. We added the statistical data on the Results of the abstract (p.2, line14-15).

(PDQ-8 summary index; 42.0 ± 20.1 vs. 30.0 ± 19.5; p < 0.0001)

Comment 3: The final “Conclusion” presented in the abstract is not in line with the main aim of this study to answer the question how insufficient drug efficacy might affect quality of life. It needs to be revised.

Response: Thank you for reviewer’s suggestion. We changed the sentences in Conclusion of the abstract as following, “These results suggested that insufficient drug efficacy might affect their quality of life for PD patients in most stages, even in early stages. Greater awareness of insufficient drug efficacy must be achieved by questioning patients so that appropriate action can then be taken.” (p2, line15-18).

# INTRODUCTION

Comment 4: The first sentence of the “Introduction” section should be revised since Parkinson’s disease is the second commonest neurodegenerative disease among the elderly and not the entire population. This needs to be clarified.

Response: Thank you for reviewer’s important comment. We have changed the following text (p3, lines 4-6) from

“Parkinson’s disease (PD), a progressive neurodegenerative disease, has the second highest prevalence after Alzheimer’s dementia and affects approximately 141,000 people in Japan (1),”

to

“Parkinson’s disease (PD), a progressive neurodegenerative disease, has the second highest prevalence after Alzheimer’s dementia among elderly population and affects approximately 141,000 people in Japan (1),”
Comment 5: The following statements need to be cited to their relevant references: “… as the Japanese population continues to rapidly age” “Inappropriate pharmacotherapy or insufficient management of wearing-off can lead to insufficient drug efficacy”

Response: Thank you for reviewer’s suggestion. We have added the following references.

Comment 6: I recommend providing more explanations about the concept of “insufficient drug efficacy” and what exactly do the authors mean by this term.

Response: As we responded in the question 1, a definition of the insufficient drug efficacy is subjectively representing dissatisfaction to the treatment in individual PD patient. Because this study is based on objective evaluation of the patients, “insufficient drug efficacy” in this study includes various factors such as under medication of dopaminergic stimulation, which affects both in daytime and the early morning, and wearing off phenomenon only affected in the daytime. Because of these reasons, there are patients with insufficient drug efficacy only in the daytime zone, and others with it only in night and early morning without daytime inefficiency.

# METHODS

Comment 7: Page 4, line 1: the first age category should be probably written as <3 years. Please check it again.

Response: Thank you for reviewer’s kind indication. We have changed as following (p. 4, line 3) from “>3 years” to “<3 years”
**Comment 8:** 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. How could authors deal with this issue? How valid are patients’ answers on their Hoehn and Yahr staging? How valid are the answers given by patients on their complete list of medication?

**Response:** Thank you for reviewer’s comment. These concerns always exist in such studies using self-reported questionnaire. All of the participants in this study are members of Japan Parkinson Disease association. The expert doctors of PD are providing educational lectures for patients to belong the Parkinson Disease association on regular basis in each location, and they provide information repeatedly regarding Hoehn and Yahr stage and antiparkinson agents. We are recognizing that participants in this study have high awareness to the PD information such as staging and medications. The large numbers of subjects is another advantage in this study. This may offset the variation in the data, and secure the accuracy of these data.

**Comment 9:** As the questionnaire was mailed to participants, I wonder how the authors managed the problem of cognitive deficit in study population. Nowadays, there are growing evidence to show that at least some degrees of mild cognitive impairment is present even in the early stages of Parkinson’s disease in many of them.

**Response:** We excluded from this study if returned questionnaires would include inappropriate response or multiple missing values. In this way, we have considered that can prevent the variation in the data from the cognitive decline.

**Comment 10:** Another major issue is the sampling method that has been used in this study. While authors mentioned that finding “the frequency of insufficient drug efficacy” is one part of their aims, the mailing questionnaire method without any random sampling method could not be able to provide frequency information. Patients who have experienced insufficient drug efficacy were more likely to participate in this survey and sent back their filled questionnaires. As a result, the study population is not representative of the general Parkinson’s disease individuals. How have the authors dealt with this problem?
Response: We appreciate the reviewer’s comment on this point. We conducted this study to aim to survey the QOL problem in PD patients. Although questionnaires include several questions regarding insufficient drug efficacy, which is only a part of their aims but not entirely, we do not believe there is bias of sent back their questionnaires as you are worried about.

Comment 11: Please clarify if the Japanese-translated and validated version of the PDQ-8 has been used in this study. Also please provide a reference for that.

Response: Thank you reviewer’s important comment. We have added the following reference.

Comment 12: It seems helpful to give more information about the PDQ-8 questionnaire including its scale and direction of the scores. How was the PDQ-8-SI calculated?

Response: Thank you for reviewer’s comment. We added short comment and reference in the text for better understanding PDQ-SI as following:

“The PDQ-8-SI is derived by the sum of PDQ-8 scale scores divided by eight (the number of scales), which yields a score between 0 and 100, which means higher number indicates more health problems. (p.4. line 19-21)

Comment 13: Have the authors used a standard definition for “insufficient drug efficacy”? What is the reference for that? If not, how could the authors be sure that these four questions could lead to valid answers to assess the “insufficient drug efficacy”?

Response: Thank you for the comment. As mentioned above, we investigated purely objective evaluation of the patients representing dissatisfaction to the treatment in individual PD patient. We
used this method to avoid bias due to excessive description. We have documented in detail in the method section.

# RESULTS

Comment 14: Unlike general PD populations, there is a female preponderance in this study population that has made it non-representative sample.

Response: We always encounter this question whenever we perform the clinical research of PD in Japan. Multiple epidemiological studies have shown a female preponderance or no difference in male-female prevalence in Japanese PD patients. This is very interesting for epidemiological point of view; however, it is not clear whether these epidemiological data would be related to any genetic factor or environmental factor as a background. We did not add the comment or reference regarding this issue on the manuscript. Just for the reviewer, please refer this manuscript; Taylor KSM, Cook JA, Counsell CE. Heterogeneity in male to female risk for Parkinson's disease J Neurol Neurosurg Psychiatry. 2007; 78: 905–906.

Comment 15: Moreover and 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.

Response: Thank you for reviewer’s comment. There may be a deflection of the support group (Japan Parkinson’s Disease Association) configuration, showing fewer patients in the mild stage of disease. In general, patients with mild stage tend to not participate in Japan Parkinson’s Disease Association. Therefore, there is a deflection in the number of cases in each stage.

Comment 16: Please provide statistical details such as the test’s name and the appropriate effect size while assessing the relationship between self-reported severity of PD and frequency of insufficient drug efficacy.

Response: We use t-test in the comparison of the two groups. We added the statistical name on the
Methods section (p 4, line 21-22).

**Comment 17:** It could be of interest to perform 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. I recommend using multivariate linear regression model for this purpose.

**Response:** Thank you for your kind comment. As the suggestion, we should think about multivariate linear regression. In mean time, we did not decide to do this because our database had insufficient data to assess the multivariate linear regression model. However, we will think about it in the future. We appreciate the suggestion.

# DISCUSSION

**Comment 18:** 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.

**Response:** Thank you for the comment. Our statement is true that no previous studies investigated Japanese subjects by using the PDQ-8 Japanese edition. Because PDQ-8 Japanese edition was validated on the effectiveness, we think about using it in this study for the first time with a more important thing.

**Comment 19:** As previously mentioned, it is really difficult to extrapolate the findings of this study since the sampling method was inappropriate and the validity of the answers and variables has not been assessed. Therefore, many parts of the discussions should be mentioned cautiously.

**Response:** Than you for the comment. We avoided the predicable expression in the discussion.

**Comment 20:** This study has totally ignored the non-motor features of Parkinson’s disease, which are in fact very important determinants of quality of life in these patients. Non-motor symptoms could also accompany insufficient efficacy of the medication and also worsen quality of life as a
confounder factor or even a mediating variable. How could the authors discuss the issues? It seems that this manuscript does not have good quality and I recommend rejection.

**Response:** As you indicated, the impact of non-motor symptoms for the QOL probably might be greater than the problem of drug efficacy. Although it should be considered in the future, in this study, we have not discussed the non-motor symptom or non-motor fluctuation in this study because these were not the aim of this study. However, thank you again for the reviewer’s important point for evaluating quality of life in PD patients.

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