Author's response to reviews

Title: A retrospective cohort study of psychosis in Parkinson disease: implications of patient-related risk factors and trigger medications

Authors:

Hideyuki Sawada (sawada@unh.hosp.go.jp)
Tomoko Oeda (MLB36641@nifty.com)
Kenji Yamamoto (kyama1024@yahoo.co.jp)
Atsushi Umemura (umemura@unh.hosp.go.jp)
Satoshi Tomita (tomitasatoshi@kpb.biglobe.ne.jp)
Ryutaro Hayashi (hayashi-r@unh.hosp.go.jp)
Masayuki Kousaka (co_saca@hotmail.co.jp)
Takashi Kawamura (kawax@kuhp.kyoto-u.ac.jp)

Version: 3 Date: 9 May 2013

Author's response to reviews: see over
Thank you for your letter concerning our manuscript entitled “Psychosis in Parkinson disease: implications of patient-side factors and medications.” The title has now been revised to “A retrospective cohort study of psychosis in Parkinson disease: implications of patient-related risk factors and trigger medications.”

We greatly appreciate the valuable and thoughtful comments from the reviewers. We have revised the manuscript according to the comments of the reviewers. Point-by-point responses to these comments are provided in the following pages. We revisited all the data of the study patients and found that one patient was diagnosed as having MSA-P (based on MRI findings) and one patient was double-counted, and therefore total patients who were eligible were changed to 331. The figure 1 was revised.

This work was supported by a Clinical Research Grant from the National Hospital Organization (Dr Sawada). Dr Sawada is funded by Grants-in-Aid from the National Hospital Organization and has received honoraria for lectures from GlaxoSmithKline and Boehringer Ingelheim. Dr Oeda is funded by Grants-in-Aid from the National Hospital Organization and has received honoraria for lectures from GlaxoSmithKline. Drs Umemura, Tomita, Yamamoto, Hayashi and Kawamura report no disclosures.

Yours sincerely,

Hideyuki Sawada, M.D., Ph.D.
Director, Clinical Research Center
Utano National Hospital
Response to the comments of Reviewer 1

1) Reviewer: The title of the manuscript is misleading. The authors did not look at psychosis in PD, but rather, at psychosis which was severe enough to justify antipsychotic treatment.

Response: In accordance with this comment, the title was revised to “A retrospective cohort study of psychosis in Parkinson disease: implications of patient-related risk factors and trigger medications” (Page 1, Title)

2) Reviewer: Were there clear criteria as to what type of psychosis is severe enough to justify antipsychotic treatment? In this matter there is substantial variability among clinicians.

Response: Prescription of antipsychotic medications was decided principally as follows: “Although antipsychotic drugs are contraindicated in PD patients, guidelines suggest that they could be used to treat psychosis when it is not improved by other treatments.” [Lines 232–234]

3) Reviewer: The definition of hazard period is not clear. What was the basis for decision that hazard period starts 1 day before initiation psychosis. Since the authors defined psychosis as psychotic symptoms severe enough to justify antipsychotic treatment, it may very well be that patients were psychotic for a substantial period of time before that time.

Response: Medications were prescribed every 14 days or 28 days in most cases, and therefore, drugs that were taken 1 day before had been taken for 14 or 28 days before the start of antipsychotic medications. In this context we defined the hazard period as 1 day before psychosis onset.

We added a description of this to the Methods section [Lines 150–153].

4) Reviewer: Looking at the MMSE and acknowledging the fact that some patients had a very low MMSE score and some were treated with cholinesterase inhibitors, it is clear that some subjects were frankly demented. Yet, the authors did not acknowledge this fact in description of patients included in the study or in the discussion.

Response: As described in the Methods section, patients who met the Consensus Criteria for probable or possible dementia with Lewy bodies were excluded. However, patients who developed dementia in the clinical course of Parkinson’s disease (Parkinson disease with dementia) were included. Cognitive dysfunction (those with MMSE <24) was revealed to be associated with serious psychosis in Analysis I. The proportion of patients with MMSE <24 is shown in Table 1. In the Discussion section we stated that “In the present study, the severity of PD and cognitive dysfunction were significant risk factors for psychosis.” [Lines 228-231]
5) Reviewer: The authors mentioned that subjects who underwent surgery were excluded from the study since in these subjects, psychosis may be part of delirium, yet, this patient population is prone for other medical conditions associated with delirium (UTI, pneumonia, etc). The authors did not refer to this issue in description of subjects, as a factor contributing to results or in the discussion. It is important to state if and how was delirium excluded.

Response: Patients who underwent surgery were not **excluded** but were **censored**. Censored data were analyzed in the survival time analysis.

“Patients who underwent surgery were also censored because delirium could be caused by surgical interventions but not be associated with PD medications, or antipsychotic medications might be prescribed to avoid surgery-associated delirium.” (Lines 102–105)

Furthermore we added the following sentences; "Patients whose medical records demonstrated that antipsychotic drugs were prescribed for delirium were censored, although patients with medical conditions such as infection were included because these conditions did not always cause delirium.” (Lines 105–108)

Additionally we added the sentence, “No patients were prescribed antipsychotic drugs for delirium.” (Lines 190–191)

6) Reviewer: The authors state that hospitalized patients were included. Elderly subjects suffering from a neurodegenerative disease that are hospitalized are prone for delirium—either due to the medical condition due to which they were hospitalized, the hospitalization itself or the treatments received. This issue did not receive attention in the manuscript.

Response: As suggested, hospitalization itself might be a risk factor for psychosis in elderly patients and this was not analyzed. In this study we focused on obvious factors such as age, cognitive function, disease severity and anti-Parkinson medications. In response to this comment, we added the following sentence to the Discussion section: “Although psychosis might also be associated with sleep disorders, concomitant diseases, drugs other than those used in PD, hospitalization, or ocular disorders, these factors were not investigated in the present study.” (Lines 263–265)

7) Reviewer: The primary outcome of the study was serious psychosis, i.e. psychosis requiring prescription of antipsychotic drugs in the presence of psychotic symptoms (illusions, false sense of presence, hallucinations, delusions). What about antipsychotics prescribed for agitation, aggression?

Response: Although illusions, false sense of presence, hallucinations, and delusions are commonly reported by Parkinson’s disease patients, as suggested, antipsychotic drugs might also be used for agitation or aggression. However, in this study nobody was agitated or aggressive without delusions or hallucinations.

8) Reviewer: The description of record review process is not clear. What does it mean "...records were retrospectively reviewed in two years"?
Response: The procedure of reviewing medical records is as follows:

All prescriptions were collected to investigate the prescription of antipsychotic drugs throughout the observation period (up to 2 years). Patients who had never been prescribed antipsychotic drugs within the observation period (from enrollment to the end of the study (730 days or censored) were regarded as controls or censored. In cases where antipsychotic drugs were prescribed, the reason why the antipsychotic drugs were prescribed was confirmed based on medical recordings. All patients who were prescribed antipsychotic drugs suffered from psychosis, and therefore, they were regarded as cases.

9) Reviewer: The authors state that "Modified Hoehn–Yahr (mH–Y) stage and the score of Mini-Mental State Examination (MMSE) of the patients were thought to be stable in the study period and were collected at the enrollment. In contrast prescription was collected consecutively because it was changeable weekly or monthly". Why did the authors assume that mH-Y and MMSE would remain stable? In PD both motor and cognitive progression of disease are seen over time.

Response: We agree with this comment, and, in response to it, the following sentence was added to the manuscript: "Although age and duration of PD increased during the study period, and mH–Y stage and Mini-Mental State Examination (MMSE) scores might deteriorate, these variables were collected at the time of enrollment on the assumption that changes in them would not have much influence on the results of the survival time analysis." (Lines 122–125)

10) Reviewer: Discussion: in general, in the discussion section of this manuscript, significant effort is devoted to discuss mechanisms (which were not assessed in the current study) rather than to discuss the results, their importance and potential implications.

Response: We agree with this comment, although the purpose of this study was to investigate the incidence of psychosis and identify risk factors. We added the following sentence to the Discussion: “Although the mechanisms by which impairment of cholinergic neurons leads to psychosis are still unclear, the possibility that impairment of the inhibitory cholinergic circuit in the cerebral motor cortex is associated with visual hallucinations has been proposed.” (Lines 260–262)

11) Reviewer: The first sentence of the discussion refers the reader to another study that deals with different patient population the current (population based study vs clinic based). The first sentences of a discussion should summarize the main findings and stress their importance.

In accordance with this comment, the first two sentences were revised to “In this study, psychosis developed in 52 patients and was associated with disease severity, cognitive dysfunction, and longer disease duration. Furthermore, the occurrence of psychosis was associated with the use of anticholinergic drugs, suggesting that cholinergic neuronal degeneration could be associated with the occurrence of psychosis.” (Lines 228–231)
12) The authors claim that incidence of psychosis in the current study is high relative to other reports due to recurrence of psychosis- this statement is not clear.

As described in the Introduction, “psychosis often reoccurs in some patients and seldom occurs in others.” (Line 69) In the current study patients with history of psychosis were involved.

13) Then, the authors refer to mild psychosis, which was even more prevalent in previous studies, yet was not at all assessed in the current study.

As pointed out, the prevalence of mild psychosis was not investigated in the current study. However, it was commented on in the Discussion, as follows: “The prevalence, including mild psychosis with preserved insight, is ~40–60%[2], so psychosis is one of the most prevalent and important non-motor complications.” (Line 241–243)

14) In page 10, 2nd paragraph, the authors cite previous studies which address sleep disorders as risk factors for psychosis in PD, yet sleep disorders were not assessed in the current study and mechanisms associating psychosis to sleep disorders are not relevant.

As pointed out, sleep disorders were not included in the analysis. This is one of the limitations of the current study. We added the following sentence to the Discussion: “Although psychosis might also be associated with sleep disorders, concomitant diseases, drugs other than those used in PD, hospitalization, or ocular disorders, these factors were not investigated in the present study.” (Lines 263–265)

15) The role of anticholinergic medications and their association with cognitive decline and delirium is not discussed.

We agree about the importance of the association of anticholinergic drugs with delirium. However, in the current study, no patients were prescribed antipsychotic drugs for delirium. Therefore, their association with delirium was not discussed.

16) When discussing results regarding cholinesterase inhibitors, the authors should discuss the indication, which is Parkinson’s disease dementia and the implication of this on the results.

As suggested, the indication for use of cholinesterase inhibitors in PD patients with dementia is a very important clinical issue. However, the efficacy of these for treating cognitive dysfunction was not investigated in this study; therefore, we feel that it could not be discussed here, but rather is a future issue to be resolved.

17) In the middle paragraph on page 10, the authors write that there was a significant interaction between PD duration and use of anticholinergics because anticholinergics are old drugs and prescribed for patients with longer duration. The rationale behind this claim is not at all clear. If anything, clinicians should and do avoid these medications in the elderly.
As shown in Line 223, the interaction between use of anticholinergic drugs and PD duration was statistically significant. As suggested, the reason for this interaction is not fully clarified; it might be because anticholinergic drugs are “old drugs” and patients who were diagnosed recently would more likely be prescribed anti-PD drugs other than anticholinergic drugs.
Reviewer 2

Reviewer: The paper in its current form demonstrates basically "clinical everyday knowledge", and the strength of this work, namely the calculation of the actual risk of medication, is discussed only marginally. I had wished to have a more concise discussion of the HRs the group found and its clinical implications.

Response: In response to this comment, we revised the Discussion section as follows:

"Although no association between dopamine agonists and psychosis was identified in Analysis II, the risk posed by dopamine agonists was identified as being significant in the subgroup analysis of elderly patients. Relative risk of psychosis owing to dopamine agonists was 1.65 (1.02–2.66) per 100 mg (LDED)/day in patients aged ≥70 years, but was not significant in patients aged <70 years." [Lines 268–270]

"These data show that dose escalation of dopaminergic drugs is a significant trigger in elderly patients but not in the entire cohort of patients, suggesting that dopamine agonists elevate the risk in psychosis-prone elderly patients but not in low-risk younger patients. In this context, psychosis could be avoided by careful application of dopamine replacement therapy in elderly or high-risk patients." [Lines 276–279]

Reviewer: BMC demands a title revealing a study design. The title does not reveal the study design.

Response: In accordance with this comment, the title was revised to the following: “A retrospective cohort study of psychosis in Parkinson disease: implications of patient-related risk factors and trigger medications”

Reviewer: Citations are put consequently behind the punctuation marks (i.e. "...even those without dementia. [1]"). According to journal requirements it should be "...even those without dementia [1]."

Response: In accordance with this comment, the citation format was corrected.

Reviewer: "de passage hallucination" is probably "passage hallucinations"

Response: This sentence was revised as suggested (Line 60).

Reviewer: I do not understand the following sentence: "Then, with adjustment of these factors, a case-crossover design study or self-matched comparison [...] was performed [...]." Were there two tests?

Response: A case–crossover design study involves a self-matched comparison that compares the hazard and control periods in each patient. We revised the sentence to: “Then, with adjustment for these factors, a case–crossover design study (self-matched comparison that
compared hazard and control periods in each patient with psychosis) was performed to evaluate the risk associated with medications” (Lines 83–85).

Reviewer: What does "(16-18)" in "Bioethics Committee of Utano National Hospital (16-18) refer to?

Response: It is the study number given by the Bioethics Committee. The sentence was revised as follows: “This study was approved by the Bioethics Committee of Utano National Hospital (No.18-16).” (Line 87)

Reviewer: In PD patients, not only surgery, but any other concurrent disease such as infections or use of centrally active agents such as analgesics or antidepressants may trigger delirium. Was this data collected and how did the authors deal with these patients?

Response: Although patients who had concurrent disease such as infections or use of centrally active agents were not excluded, those who were prescribed antipsychotic drugs for delirium were censored by investigating medical records. We added the following sentence as follows: “Patients whose medical records demonstrated that antipsychotic drugs were prescribed against delirium were censored, although patients with medical conditions such as infection were included because these conditions did not always cause delirium.” (Lines 105–108)

“No patients were prescribed antipsychotic drugs for delirium.” (Lines 190–191)

Reviewer: The first sentences in which the authors justify the definition "serious psychosis" might be more suitable in the discussion section, and the authors might wish to adapt the passage on this issue in the discussion. I would start with the "The primary study outcome was serious psychosis defined as psychosis requiring antipsychotic medication ... ".

Response: In accordance with this suggestion, the sentence was revised and moved to the Discussion section.

Reviewer: How is modified Hoehn-Yahr defined?

Response: In patients with motor fluctuations, modified Hoehn-Yahr was evaluated in the “ON period.” A sentence explaining this was added. (Lines 121–122)

Reviewer: The mH-Y and MMSE were considered stable in the observation period of 2 years. In clinical experience, especially patients over 65 and with a H-Y stage over 3 tend to deteriorate within such a period. Does this influence the result?

Response: We agree with this comment, and the following sentence was added: “Although age and duration of PD increased during the study period, and mH–Y stage and Mini-Mental State Examination (MMSE) scores might deteriorate, these variables were collected
at the time of enrollment on the assumption that changes in them would not have much influence on the results of the survival time analysis.” (Lines 122–125)

_Reviewer:_ The equivalent doses of dopamine agonists seem somewhat low for pramipexole, cabergoline and especially for pergolide and do differ from those indicated in references 26 and 28.

Response: The cited reference number was mistyped and the correct references are as follows:


Except for ropinirole, the formula was according to the manuscript by Forsaa et al. LDED of ropinirole was according to the report by Fenelon et al.

_Reviewer:_ Did the authors look at rivastigmine?

Response: Rivastigmine was not available in Japan at the time of the study. Therefore, we did not look at rivastigmine. The following sentence was added. “Records of prescription of rivastigmine were not collected because this drug was unavailable in Japan during the study period.” (Lines 138–140)

_Reviewer:_ Doses of dopaminergic drugs were recorded. Why was the use of (anti-) cholinergics regarded as dichotomous? Did they choose this approach because it was problematic to calculate equivalent doses for drugs with anticholinergic properties?

Response: As suggested, trihexyphenidyl blocks the M1 muscarinic receptor; therefore, we assumed that it does not act in a dose-dependent manner, but in a dichotomous manner. Similarly we regarded the other anticholinergic drugs as dichotomous.
Reviewer: Doses of dopaminergic medication was collected, but data for the groups (e.g. patients >70 without and with psychosis, patients < 70 without and with psychosis) is not shown in the results. I would consider this important information.

Response: We agree with this comment. In the revised manuscript the following supplemental table was added in response to this comment.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Patients with psychosis</th>
<th></th>
<th></th>
<th>Patients without psychosis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean</td>
<td>SEM</td>
<td>n</td>
<td>mean</td>
<td>SEM</td>
</tr>
<tr>
<td>Age&lt;70 years</td>
<td>25</td>
<td>81.2</td>
<td>18.4</td>
<td>69</td>
<td>84.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Age&gt;=70 years</td>
<td>27</td>
<td>87.0</td>
<td>22.4</td>
<td>71</td>
<td>70.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>84.2</td>
<td>14.5</td>
<td>140</td>
<td>76.9</td>
<td>7.0</td>
</tr>
</tbody>
</table>

We added the following sentence, “To clarify the risk owing to dopamine agonists in elderly patients, dose at the time of study enrollment (Supplemental table) in patients stratified by age (<70 vs ≥70) was examined. There was no significant difference in these doses between patients with psychosis and those without psychosis (Supplemental Table).” (Lines 270–273)

Reviewer: I am somewhat puzzled by the figures. In how many patients the patient-related risk factors were analysed? Was it in 333 (as figure 1 states, and of which 140 did not fulfill the inclusion criteria) or was it in 193 (of which I gather all data was available)? And did this affect the power of the statistical analysis? Please clarify.

Response: Excluding patients without MMSE scores (due to missing data), the survival curves are for a total 276 patients (as shown in Table 1). Figure 1A shows survival curves by MMSE >24 (n=160) vs MMSE ≤ 24 (n=116). Similarly, excluding patients with an undetermined mH-Y stage, a total of 318 patients were assessed for an association with MMSE score. The survival curves are divided by mH-Y 1–3 (n=199) vs MH-Y 4–5 (n=119).

Reviewer: As a clinician I do not understand the supplemental figure and the legend in their current form.

Response: In accordance with this suggestion, we revised the legend for the supplemental figure as follows:

“To confirm the assumption that the correlation of medication dose with psychosis depends on the intervals between data collecting time points, doses of L-Dopa (A), dopamine agonists (B), selegiline (C), and amantadine (D) were plotted between 1, 30, and
90 days before the occurrence of psychosis. There were correlations between time points, and the correlation depended on the intervals between data collection time points. Therefore, data were analyzed using an autoregressive working correlation matrix as described in the Methods.” (Lines 448–453)

Reviewer: Table 2: is the p-value for the use of anticholinergics in patients over 70 is really 0.00 or rather < 0.0001?
Response: As suggested, the p value was <0.0001. Table 2 was corrected.

Reviewer: anti-psychiatrics = anti-psychotics?
Response: As suggested, the word was corrected.

Reviewer: A dose dependency of psychotic episodes in dopaminergic drugs obviously could not be demonstrated in this study as the authors state in the last paragraph. Why is that so? This is in my view important information since the authors spent some efforts on collecting information on drug doses and equivalent doses.
Response: As described in the Discussion (Lines 284–285), it has not been elucidated whether there is a dose threshold for dopamine agonists to cause psychosis. However, because there was no significant difference in the dose of agonists at baseline (as shown in the Supplemental Table), dose escalation might play an important role in the occurrence of psychosis. We revised the sentence as follows: “Although no association between dopamine agonists and psychosis was identified in Analysis II, the risk posed by dopamine agonists was identified as being significant in the subgroup analysis of elderly patients. Relative risk of psychosis owing to dopamine agonists was 1.65 (1.02–2.66) per 100 mg (LDED)/day in patients aged ≥ 70 years, but was not significant in patients aged <70 years. To clarify the risk owing to dopamine agonists in elderly patients, dose at the time of study enrollment (Supplemental table) in patients stratified by age (<70 vs ≥70) was examined. There was no significant difference in these doses between patients with psychosis and those without psychosis (Supplemental Table). These data show that dose escalation of dopaminergic drugs is a significant trigger in elderly patients but not in the entire cohort of patients, suggesting that dopamine agonists elevate the risk in psychosis-prone elderly patients but not in low-risk younger patients.” (Lines 266–278)

Reviewer: Reference 24 seems to be incomplete
Response: As pointed out, the reference was revised.

Reviewer: Table title: Is this baseline characteristics or is this the clinical characteristics at the onset of psychosis? Maybe “Clinical characteristics” is a more appropriate title.
Response: These data were obtained at the time of study enrollment because this was a retrospective cohort study. We added the following sentence to the footnote. “Data were obtained at the time of study enrollment.”

Reviewer: see Analysis I - why is there information on censored (i.e. excluded?) patients that did not meet the inclusion criteria?

Response: In Analysis I, the “censored” patients are patients who had been eligible and observed, but were unable to be followed to the endpoint. They had never presented psychosis, but the observation period was less than 2 years. In the following schema, patients A, B, C are observed for 2 years and have never presented psychosis. They are control patients. Patients D and E are enrolled in the study and observed; however the observation is abandoned without development of psychosis. They are “censored.” Patients F and G develop psychosis during the study period, and are case patients.

Reviewer: Did the inclusion of missing data affect the statistical analysis?

Response: Table 1 shows the highly significant difference in sex, mH-Y stage, MMSE score, and duration of PD between groups. Therefore, missing data did not affect the statistical analysis.

Reviewer: A discussion of the limitations of this study deserves an own paragraph. This could include all topics that may arise from the comments above, and furthermore other variables that were not assessed and that might influence the incidence of psychosis (such as concomitant disease, drugs other than used in PD, sleep disorders, ocular disorders).

Response: In accordance with this comment, we revised the text as follows:
“Although psychosis might also be associated with sleep disorders, concomitant diseases, drugs other than those used in PD, hospitalization, or ocular disorders, these factors were not investigated in the present study.” (Lines 263–265)

Reviewer: In several passages articles are omitted, British and American English spellings are mixed up, and singular and plural of several terms are oftentimes confused. I recommend having the paper edited by a native speaker prior to publication.

Response: The manuscript was edited by a native speaker.