Author’s response to reviews

Title: Trigger medications and patient-related risk factors for Parkinson disease psychosis requiring anti-psychotic drugs: a retrospective cohort study

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 Kohsaka (co_saca@hotmail.co.jp)
Takashi Kawamura (kawax@kuhp.kyoto-u.ac.jp)

Version: 4 Date: 4 September 2013

Author’s response to reviews: see over
Dear Dr. Shipley,

Thank you for your letter concerning our manuscript entitled “A retrospective cohort study of psychosis in Parkinson disease: implications of patient-related risk factors and trigger medications.” The title has now been revised to “Trigger medications and patient-related risk factors for Parkinson disease psychosis requiring anti-psychotic drugs: a retrospective cohort study.”

We greatly appreciate the valuable and thoughtful comments of the reviewers. We have revised the manuscript in accordance with their suggestions. Our point-by-point responses to these comments are provided in the following pages.

Yours sincerely,

Hideyuki Sawada, M.D., Ph.D.
Director, Clinical Research Center
Utano National Hospital
Clinical Professor, School of Medicine, Kyoto University
Reviewer 1

1) **Reviewer:** the authors have not addressed my concern which related to the severity of the psychosis and not to its etiology.

Response: In accordance with this suggestion, the title was revised to “Trigger medications and patient-related risk factors for Parkinson disease psychosis requiring anti-psychotic drugs: a retrospective cohort study.”

2) **Reviewer:** the authors should address the issue of definition of psychosis severe enough to justify antipsychotic treatment in the method section. Also, psychosis per se in PD patients does not necessarily justify antipsychotic treatment, even if prolonged. The factors that are usually considered are patient suffering and behavioral changes severe enough to endanger the patient or others.

Response: In accordance with this comment, we added the following sentences to the Methods and Results section: “According to the guidelines of PD psychosis, we assumed that prescription of anti-psychotic drugs was justified principally when psychosis was not improved by other treatments[23, 24] and patient suffering and behavioral changes were severe enough to endanger the patients or others.” (Lines 106–109) “The assumption that anti-psychotic drugs were prescribed when psychotic symptoms were not improved by other treatments and the patients suffered was confirmed.” (Lines 207–209)

3) **Reviewer:** This response is not yet clear. The authors themselves claim that medications that had been administered 1 day before were the same as those administered 14-28 days before, so they should explain why the “1 day” period was chosen. This is also important in the context of duration of trigger medication treatment prior the psychosis initiation.

Response: We regarded the medications prescribed before the endpoint (prescription of anti-psychotic drugs) as trigger medications. The hazard and control periods are shown in Supplemental Figure 2. The red period is the hazard period, in other words, the period with trigger medications. Medications were prescribed every 14 or 28 days; therefore, the duration of the hazard period was 14 to 28 days. Drugs taken in the hazard period were not changed in the period. Therefore, drugs that were taken 1 day before the endpoint (red arrow) represent drugs prescribed in the hazard period. Similarly drugs that were taken 30 days or 90 days before the endpoint (blue periods) represent drugs prescribed in the 2 control periods (blue arrows). We added the following descriptions in the methods section and added Supplemental Figure 2. “For the case-crossover analysis, the prescriptions in the hazard period and those in the control periods were compared. Medications were prescribed every 14 days or 28 days in most cases, and drugs that were taken 1 day before the endpoint (the start of anti-psychotic medications) had been taken for 14 or 28 days before the endpoint; therefore, medications taken 1 day before the endpoint represent those taken for 14 days before the endpoint. In this context, the prescription 1 day before the endpoint was regarded as that in the hazard period.
Medications in the hazard period were compared with those in the control periods (30 and 90 days before psychosis) (Supplemental Figure 2).” (lines 136─143)

4) Reviewer: What is the rationale for differentiating between surgery-induced delirium to delirium caused by any other medical condition? Also, based on the following sentence: 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.”, it is not clear which patients were censored and which were included in the analysis?

Response: In this study the definition of serious psychosis was psychosis that required antipsychotic drugs for treatment. The diagnosis of psychosis was according to the diagnostic criteria for PD associated psychosis (Ravina et al. 2007), as described in the methods section. Therefore, conditions with delirium were not included in the analysis; in other words, patients who became delirious were censored in the survival-time analysis (censoring due to alternate outcome), but the data from the enrollment to the time of censoring were incorporated in the analysis (because of survival-time analysis).

Patients who underwent surgery were often prescribed anti-psychotic drugs prophylactically to avoid surgery-induced delirium; therefore, such patients must be censored at that point (censoring due to alternate outcome). In contrast to surgery, patients with medical conditions such as infection were not censored because they were usually not prescribed antipsychotic drugs for the reason of their condition, but they were censored at the time when they were diagnosed as showing delirium.

We added the following description to the methods section.

“In a survival time analysis, the observation period, censoring, and endpoint were defined as follows. The observation period was from the time of study enrollment to the endpoint, which was defined as the occurrence of any psychosis that required anti-psychotic drugs or the end of the 730-day study period. Observation was censored if patients were lost to follow-up or experienced an alternative outcome. Patients were censored when they were transferred to other hospitals because data could not be obtained (lost to follow-up). Because anti-psychotic medications were often prescribed prophylactically by surgeons to avoid surgery-associated delirium, patients who underwent surgery were also censored just before surgery (alternative outcome).” (Lines 120─128)

5) Reviewer: a relevant remark should be added in the discussion.

Response: In accordance with this comment, the following sentences were added to the discussion section; “Although anti-psychotic drugs are contraindicated in PD patients, guidelines suggest that they could be used to treat psychosis when it is not improved by other treatments[23, 24]. In this study, prescription of anti-psychotic drugs in such patients was justified by the reason described above. Antipsychotic drugs might also be used against agitation or aggression. However, in this study, no patients were agitated or aggressive without having delusions or hallucinations.” (Lines 251-256)

6) Reviewer: this should be further clarified in the methods section.

Response: In accordance with this suggestion, the following sentences were added to the methods section. “All prescriptions were collected to investigate the prescription of
antipsychotic drugs throughout the observation period (of up to 2 years). Patients who had never been prescribed antipsychotic drugs within the observation period 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 records." (Lines 146–150)

7) **Reviewer: the findings regarding mild psychosis cannot appear for the first time in the discussion.**

Response: In accordance with this comment, the following sentence was moved to the introduction.

“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.” (Lines 60-62)

8) **Reviewer: could the authors discuss their differentiation between psychosis secondary to PD medications versus psychosis as part of delirium? This is especially relevant since hospitalized patients were included in the analysis.**

Response: We think psychosis is caused by multiple factors including patient-related factors and trigger medications. There is no way to clearly differentiate psychosis due to drugs from that due to other conditions. We added the following sentences to the Discussion. “Psychosis is caused by multiple factors including patient-related factors and trigger medications, and there is no way to clearly differentiate psychosis due to drugs from that due to other conditions.” (Lines 268–270)

9) **Reviewer: I was referring to the implication of treatment of cholinesterase inhibitors on psychosis and not on cognition.**

Response: We discussed the effect of another cholinesterase inhibitor, rivastigmine, on psychosis in PD patients; “This result is consistent with a previous report showing that rivastigmine, another acetylcholine esterase inhibitor, improves psychosis in PD[32] and these data suggest that psychosis is caused mainly by degeneration of cholinergic neurons in the brain arousal system.” (Lines 280–283) However, we feel that the issue of indication is beyond the purpose of the study.
**Reviewer 2**

1) **Reviewer:** Considering H&Y and MMSE to be stable over an observation period of 2 years and if not, assuming that their deterioration would not affect the results is in my view difficult. It seems that the co-reviewer feels the same on this issue. I consider this a limitation which deserves to be discussed in a limitations section.

Response: We agree with this comment and revised the text as follows: “In the present survival analysis, the maximal length of the observation period was two years. Therefore, several factors such as cognitive function and PD severity could deteriorate during the observation period. In the survival analysis, patient-related factors were assumed to be stable because of limitations of the statistical methods.” (Lines 265–268)

2) **Reviewer:** The aim of the study was to assess patient related risk factors for psychosis. Patients having undergone surgery were censored, and the reason the authors give is that delirium (or psychosis?) could have been a sequel to surgical interventions. On the other hand, patients suffering from other medical conditions such as infections were included, since infections not always cause delirium. The same is true for surgery: not all patients become delirious after an operation. This reasoning does not seem plausible to me.

Response: As suggested by the reviewer, delirium is not always elicited by surgery or infections. However, anti-psychotic drugs were often prescribed prophylactically to avoid delirium. These prescriptions of antipsychotic drugs were regarded as an “alternative outcome” in a survival analysis. In contrast, infections did not lead to antipsychotic medication, and the use of anti-psychotic drugs was due to psychosis (true outcome). Therefore, patients with “alternative outcome” were handled as censored (in a survival-time analysis patients with alternative outcome must be censored). Those with infections were regarded as cases if they were prescribed anti-psychotic drugs, and were regarded as controls if they had never been prescribed anti-psychotic drugs. This is the standard method for a survival analysis. To clarify these points, we revised the text as follows; “In a survival time analysis, the observation period, censoring, and endpoint were defined as follows. The observation period was from the time of study enrollment to the endpoint, which was defined as the occurrence of any psychosis that required anti-psychotic drugs or the end of the 730-day study period. Observation was censored if patients were lost to follow-up or experienced an alternative outcome. Patients were censored when they were transferred to other hospitals because data could not be obtained (lost to follow-up). Because anti-psychotic medications were often prescribed prophylactically by surgeons to avoid surgery-associated delirium, patients who underwent surgery were also censored just before surgery (alternative outcome)” (Lines 120–128)

3) **Reviewer:** So, not differentiating between patients with or without concomitant medical conditions still is a limitation which deserves to be mentioned and discussed in a limitations section. I do understand, however, that this differentiation in many cases of in-patients is difficult, especially when doing a retrospective analysis, since the presenting symptom in an emergency room may be psychosis or delirium and the reason for that finally turns out to be a new drug or a UTI.

Response: Surely it is impossible to differentiate psychosis in patients with medical conditions from psychosis in those without medical conditions clearly. Psychosis is elicited by multiple
factors including medical conditions in addition to patient-related factors and trigger medications. In this study we focused on patient-related factors and trigger medications, and risk owing to medically conditions was not assessed. If medical conditions including pneumonia or urinary tract infections are a strong confounder of other predictable factors (age, duration, MMSE, and medications, for example), this would be a major limitation of the current study. However, we feel that medical conditions are not a strong confounder. Therefore, we added the following sentence to the discussion section. “Psychosis is caused by multiple factors including patient-related factors and trigger medications, and there is no way to clearly differentiate psychosis due to drugs from that due to other conditions. Although these issues are limitations of the study, the results demonstrated that the severity of PD, cognitive dysfunction, and use of anti-cholinergic drugs were significant risk factors for psychosis.” (Lines 268–273)

4) Reviewer: Furthermore, a point that I feel could be discussed differently is the frequently is the high frequency of anticholinergics in this cohort. It seems that a remarkable amount of elderly patients that turned psychotic were prescribed anticholinergics, and as I understand from the text this was so because these patients were taking them for a long time and their treating physicians probably forgot to discontinue them as the disease progressed. May there are a few more reasons for this otherwise unusual medication. Anyhow, as the authors demonstrate a high risk for psychosis associated with these drugs, the frequent use of anticholinergics may be a bias towards a higher prevalence of psychosis in this study.

Response: At the time of study enrollment, 7 of 52 cases (with psychosis) and 12 of 136 controls (without psychosis) were prescribed anti-cholinergic drugs (excluding patients who were censored). Therefore, we feel that the prevalence of anti-cholinergic prescriptions was not markedly high in this cohort.