Reviewer’s report

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

Version: 3 Date: 10 June 2013

Reviewer: Ramit Ravona-Springer

Reviewer’s report:

Review: MS: 8602909218705317
Psychosis in Parkinson disease: implications of patient-side factors and medications

Previous comment: 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)

Current comment: the authors have not addressed my concern which related to the severity of the psychosis and not to its etiology.

Previous comment: 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]

Current comment: the authors should address the issue of definition of psychosis severe enough to justify antipsychotic treatment in the methods 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.

Previous comment: 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].

Current comment: 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.

Previous comment: 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
casted 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)
Current comment: 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?

Previous comment: 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.
Current remark: a relevant remark should be added in the discussion.

Previous remarks: 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.

Current remark: this should be further clarified in the methods section.

Previous comment: ……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.

Response: 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)

Current remark: the findings regarding mild psychosis cannot appear for the first time in the discussion.

Previous comment: The role of anticholinergic medications and their association with cognitive decline and delirium is not discussed.

Response: 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.

Current remark: 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.

Previous remark: 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.
Response: 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.

Current remark: I was referring to the implication of treatment of cholinesterase inhibitors on psychosis and not on cognition.