Author's response to reviews

Title: Psychosis in Parkinson disease: implications of patient-side factors and medications

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Editor-in-Chief, BMC Neurology

Dear Editor,

In medical treatments it is important to maximize benefits and to minimize risk of adverse effects. Therefore, in addition to intervention studies including randomized clinical trials (RCTs) that give us the data of treatment efficacy, studies to investigate adverse effects are required. The former studies usually precede the latter studies that are often delayed for decades.

In Parkinson disease, the second most prevalent disease of the brain, a series of RCTs of anti-Parkinson drugs give us the data of the efficacy; however clinical evidence of adverse effects is limited and based on frequency comparison of adverse events detected in the RCTs, or on small-size retrospective studies including case reports.

RCTs focused on harmful events cannot be conducted for ethic reasons, and therefore, evidences have been obtained mainly from retrospective or non-randomized prospective studies. Rare events are usually analyzed by retrospective case-control study, comparing case patients presenting adverse events and control patients. However, there are two concerns in case-control studies. 1) There may be confounding factors required to be adjusted between cases and controls. However, it is impossible to match factors that have not been detected. 2) Another concern is how to detect “endpoint.” In retrospective analyses judgment of the occurrence of endpoint may be arbitrary due to prejudgments.

To resolve the former issue we adopted a case-crossover design study, which is used in analysis of the association of “trigger factors” and “endpoint.” Case-crossover design minimize the effects of confounding factors, even they
are undetected, because the data in the “hazard period” are contrasted to those in “control period” of the same subject. To avoid the latter issue we set “hard endpoint”; we defined the prescription of anti-psychotic drugs as the occurrence of psychosis. Though anti-psychotic drugs are contraindicated to patients with PD, it should be used for psychosis that could not be improved by any other treatments, and therefore, the use is not arbitrary. When only the use of anti-psychotics is defined as the occurrence of psychosis, mild psychosis could be overlooked; however, it is suitable method because the scope of the study is to demonstrate the way how to avoid the hard endpoints.

Though there have not been systemic analyses about risk of psychosis by medications, we identified high-risk group, and then, we tried to identify trigger medications using case-crossover analysis. The results of the study demonstrate that cholinergic medications were associated with psychosis in PD. In addition dopamine agonists were risk of psychosis in elderly patients. We accomplished evaluation of risk size by using this statistical method and we believe that this study gives great impact not only on neurologists but also on a lot of research physicians.

We hope the manuscript will be considered to be published in BMC Neurology.

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