Reviewer's report

Title: The nature of relapse in schizophrenia

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Reviewer: Martijn Kikkert

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The paper describes an interesting and clinically important problem. Many patients with schizophrenia suffer from relapses which are associated with major consequences for patients, their relatives, mental health carers, and finally high costs. The objectives in this paper are to critically review selected literature regarding the nature and underlying neurobiology of relapse. It is to be appreciated that the authors try to improve our understanding of relapse in patients with schizophrenia.

The underlying remarks may be considered as ‘major compulsory revisions'.

1. During recent studies the authors made several observations which are used in this paper as starting point. Most of them are interesting and relevant but one could argue that they do not necessarily reflect all important aspects of relapse in schizophrenia. For instance, considering the objective of this paper, an elaborate discussion of risk factors for relapse should to my opinion be included.

2. In the paper, the above mentioned observations are described and underpinned by selected literature. One of the concerns with this approach is that it remains unclear if the described literature objectively reflects all relevant studies in this field.

3. “1. Relapse rates after treatment [...]” The authors describe three important considerations regarding medication discontinuation. For me the purpose of this paragraph is not clear to me. In addition, when looking at the extensive literature on non-adherence or discontinuation, there are more reasons which I think should be mentioned here. For instance, treatment resistance is not described in this paragraph.

4. In the description of relapse rates after discontinuation the authors correctly conclude that relapse risk is high after discontinuation. This is not new and has been demonstrated in many studies. However two important, and for this paper relevant conclusions are overlooked. Firstly, also patients who do adhere to medication have a significant risk of relapse, and secondly, there is a subsample of patients who remain stable without medication for a longer period of time (studies indicate that in approximately half of patients symptoms swiftly return after discontinuation, but approximately a quarter of patients are able to remain stable for at least a year). In a discussion of the nature of relapse this should not be ignored.
5. In the description of the study of Wunderink et al, it is suggested that 89% (43% and 46%) unsuccessfully discontinued medication. This is not correct.

6. “2. Duration of antipsychotic [..]” The authors do not represent any study results and conclude that there is no consensus. A solid foundation for this conclusion is not provided.

7. “3. Time to relapse after [..]” Despite the availability of several studies in the literature, the authors present no study results of others or their own work regarding time to relapse after discontinuation. This seems to me an important omission.

8. “5. Once illness recurrence [..]” The authors only briefly describe their own observation and fail to report on existing literature.

9. “6. Is relapse associated [..]” As above, a concern is that the literature presented here is not an elaborate overview. The authors refrain from drawing any conclusions.

10. “Dopamine and the neurobiology [..]” I would like to suggest that the authors indicate which part of the described hypothesis is new.

11. I greatly appreciate the authors’ endeavor to review literature concerning relapse in schizophrenia. The objectives, describing the nature of relapse and a neurobiological model, seem rather ambitious. Perhaps as a consequence, the paper is short in detail on most topics it describes and therefore does not convince as an objective and scientific overview of existing knowledge. This may not be correct, but I believe that the paper would greatly benefit from a more objective approach including a systematic literature search and more detailed description of findings. I do encourage the authors to continue with their work on this important topic.

**Level of interest:** An article of limited interest

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.