Author's response to reviews

Title: The nature of relapse in schizophrenia

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Author's response to reviews: see over
Dear Editor

BMC Psychiatry

Revised manuscript for resubmission:  MS: 1284364549743182 “The nature of relapse in schizophrenia”

We would like to resubmit this revised manuscript for publication. We have carefully considered all of the comments of the reviewers and have revised the manuscript accordingly. A detailed description of how we responded to each comment is provided below.

We thank the reviewers for their helpful inputs and hope that the revised manuscript now meets requirements for publication.

Sincerely

Robin Emsley

Reviewer’s comments and our response:

In addition our Section Editor wanted the following points addressed:

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I strongly suggest there are some issues to be emphasized or added to make it current and suitable for publication. The authors write: “A key clinical question is how long antipsychotic treatment should be maintained after a single episode of psychosis, and whether the risk of relapse is reduced with a longer treatment period. Despite the fact that several studies have assessed the risk of relapse after discontinuation of antipsychotic medication, there is no consensus on the recommended duration of treatment.”

I think the question should be different. The field urges decisions about treatment be made collaboratively and thus the question is better what is the risk of discontinuation - info relevant for clinicians and patients. Advances in medicine I think have moved us past general recommendations for everyone to follow. In other words if I am the sufferer from sz and I want to stop my medication for any of a number of reasons what are the odds I will relapse and possibly not respond to medication again... re-framing the paper as such would make it publishable I think.

Our response: We have changed the sentence in question according to this recommendation. It now reads as follows: “A key clinical question is what the risk of relapse is after a single episode of psychosis, and whether the risk is reduced with a longer treatment period.” (p6, section 2, 1st sentence). Also, (on p4 last paragraph), we refer to the need for considering the risk of recurrence after discontinuation of treatment.

The available data does not lend itself to statistical calculations of the odds of relapse. We have rather presented the results in a Table, depicting the relapse rates at various time points for these studies. We conclude this section by stating: “Taken together, these results...
suggest that even after a single episode of psychosis the vast majority of patients will experience symptom recurrence if followed up for a sufficient period of time.” (p5, last sentence).

A smaller issue is that there are possible explanations for relapse which are psychological in nature and those must be noted. For instance it is possible that people relapse given an inability to manage interpersonal relationships and life stress and thus once medication is off board relapse may occur not only because aberrant biological processes will run rampant but also because life will present difficult solutions which lead to unbearable affects which trigger symptoms (work by Bentall or any of another of others support this possibility).

Our response: In order to note that factors other than treatment discontinuation may contribute to relapse we have introduced a new sentence referring to the results of a recent meta-analysis of factors contributing to relapse. Other factors found to be significant include persistent substance use, carers’ criticism and poorer premorbid adjustment (p2, last sentence). We considered the work of RP Bentall but did not find anything directly related to relapse that could add to this point.

Reviewer's report
Title: The nature of relapse in schizophrenia
Version: 1 Date: 17 October 2012
Reviewer: Brian Miller

Reviewer's report:
The authors critically reviewed selected literature regarding the nature and underlying neurobiology of relapse. Important findings include high relapse rates with treatment discontinuation; the absence of a relationship between length of treatment and relapse risk; abrupt transitions from remission to relapse with little-to-no “warning”, often very soon after treatment reduction or discontinuation; and a rapid improvement in symptoms following treatment for acute psychosis in most patients, although treatment resistance emerges in 1 in 6 patients. The research topic is important and timely. This research group has expertise and is well-known in this field. The manuscript is very well written and easy to follow. Many important considerations for future research are discussed. Addressing several Minor Essential Revisions would further enhance the quality of the manuscript:
1. In section 1, two additional references regarding the prevalence of antipsychotic discontinuation in first-episode psychosis could be included:

   Our response: We have included these two references (p3, line 5).

2. Page 5, line 6: the word “at” appears to be missing between 80% and 12.
   Our response: We have added “at” (p5, 2nd paragraph, line 7).

3. Regarding the section on the neurobiology of relapse in schizophrenia, the following material could be considered in the discussion:
   Growing evidence supports a role for immune system dysfunction in schizophrenia, including evidence from meta-analyses that blood levels of some
cytokine (a) and lymphocyte (b) parameters may be state-related markers for relapse in schizophrenia (levels in cross-sectional studies are significantly altered in relapsed patients versus controls; longitudinal studies show that these parameters begin to “normalize” following antipsychotic treatment for relapse). A study of patients who underwent weekly assessments for 1 year found that in vitro interleukin-2 production plus antihippocampal immunoglobulin G levels from the previous week significantly predicted relapse in some patients (c). Another study found increased cerebrospinal fluid interleukin-2 levels following haloperidol withdrawal were a significant predictor of acute psychotic relapse. The potential relationship between inflammation and relapse in schizophrenia is further supported by four trials that found adjunctive treatment with non-steroidal anti-inflammatory agents (versus placebo) in acutely relapsed patients showed significant improvement in total symptoms (e-h). Pro-inflammatory cytokine abnormalities may directly modulate dopaminergic neurotransmission, indirectly modulate glutamatergic neurotransmission through tryptophan catabolism, and/or contribute increased free radical production/oxidative stress, with resultant destabilization of neuronal cell membranes. Taken together, these findings suggest that immune/inflammatory dysfunction may play a role in the neurobiology of relapse in schizophrenia.


Our response: We have revised this section extensively, taking into account the reviewer’s suggestions, to better elucidate the possible role of immune/inflammatory dysfunction in the neurobiology of relapse. We have included several of the suggested references, as well as additional references (from p12, last paragraph).
4. Table 1: consider spelling out the word (Months) in the header rows for both “Treatment duration” and “Symptom recurrence rates”, instead of using the abbreviation “m” throughout. Consider also adding a separate column for the 9 month recurrence rate for the study by Boonstra et al.

Our response: we have revised Table 1 accordingly.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** No, the manuscript does not need to be seen by a statistician.  
**Declaration of competing interests:**  
The reviewers do not have any financial or non-financial competing interests to disclose.

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**Reviewer's report**  
**Title:** The nature of relapse in schizophrenia  
**Version:** 1  
**Date:** 1 November 2012  
**Reviewer:** Martijn Kikkert  

**Reviewer's report:**  
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.

Our response: We have introduced a sentence referring to the results of a recent comprehensive review and meta-analysis of factors contributing to relapse (p2, last sentence). A detailed discussion of risk factors would duplicate this work, and is beyond the scope of our article. We acknowledge that we have not attempted to cover all of the important aspects of relapse, as this would be a mammoth task. Rather, we elected to focus on selected issues that became apparent to us in our own recent work on the topic. To make this explicit we have added the following sentence: “We have not attempted to cover all of the important aspects such as risk-factors and predictors of relapse, ...” (bottom of p3).
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.

Our response: We have now conducted a systematic literature review of studies reporting treatment discontinuation in first-episode schizophrenia. This is described in the text (p5, 2nd paragraph). This search confirmed the eight studies reported in our original submission. The findings of all of these studies are summarised in Table 1. All of these studies form the basis of our discussions in sections 1, 2 and 3. For section 3 we have now included all of the reported mean times to relapse from these studies (top of p7). For section 4 we attempted to summarize the vast literature investigating early warning signs in relapse, and have presented a balanced selection of the findings – i.e. studies reporting both presence and absence of early warning signs (p 8).

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.

Our response: In re-reading this paragraph we see that the wording was confusing. We have revised this sentence to clarify that we are referring to the reasons for clinicians to consider antipsychotic discontinuation, and specifically after successful treatment of a first-episode of schizophrenia (p4, section 1).

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.

Our response:
1. The significant risk of relapse with ongoing antipsychotic treatment is considered in the Conclusion as follows: “… it needs to be kept in mind that ongoing maintenance treatment carries its own burden, including substantial risk of relapse, significant side-effects and even the possibility of brain morphological changes” (p15, line 4).
2. Regarding the subsample of patients who remain relapse-free for a considerable period of time: In Section 3 we refer to the interval between treatment discontinuation and symptom recurrence being highly variable (p7, 1st line). Also, we now provide mean times to relapse in the 3 studies reporting this information (p7, 2nd sentence). Finally, we have added a sentence referring to those subjects who have a longer survival time to relapse, and the possibility of treatment discontinuation in these subjects (top of p6).

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.
Our response: We have revised this accordingly (p5, 7th line from bottom).

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.

Our response: We have included sentence describing the results of a recent systematic review of guidelines for maintenance treatment of schizophrenia to support this statement (p6, section 2).

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.

Our response: We have reviewed the relevant studies and include details of time to relapse in the 3 studies reporting this information (p7, 2nd sentence).

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

Our response: We have referred to another study failing to find a correlation between time to treatment and symptom severity. This is the only other study that we found that reported on the severity of symptoms after a first relapse (section 5, p 9).

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.

Our response: We have specified that this section is based on a comprehensive search of the literature on the evidence for disease progression after relapse (which is the subject of a separate manuscript, in submission) (p10, line 8). All of the relevant studies that we identified have been included in this section. We have attempted to provide a balanced view by presenting the evidence for disease progression, followed by the evidence against disease progression. We have included here reference to a very recent publication in this regard (p11, last paragraph).

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

Our response: We have re-worded this sentence to better explain this hypothesis (p12, 4th line).

11. I greatly appreciate the authors endeavour to review literature concerning relapse in schizophrenia. The objectives, describing the nature or relapse and a neurological 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.

Our response: We have expanded on the relevant sections to provide more detailed information. Also, we have included a systematic literature review of studies describing relapse after treatment discontinuation in first-episode schizophrenia. Finally, we have attempted to provide an objective approach throughout by highlighting inconsistencies in the literature and reporting findings that contrasted with our own.

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.