

Format for ANSWERING REVIEWERS

September 18, 2013



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3800-review.doc).

Title: Meta-Analysis of Anti-Ribosomal P Antibodies in Lupus Psychosis

Author: Kim Linz, Brian J. Miller

Name of Journal: *World Journal of Meta-Analysis*

ESPS Manuscript NO: 3800

The manuscript has been improved according to the suggestions of reviewers:

1. In the introduction the authors refer to both "schizophrenia" and "psychosis". It would be important clearly introduce the terminology and to specify what do we mean, when we say "schizophrenia" and what we mean when we say "psychosis". In principle the paper refers to psychosis in patients with lupus and as such more emphasis should be put in the introduction on psychosis rather than on schizophrenia.

We agree with the Reviewer's feedback. We have included definitions and refocused the Introduction on lupus psychosis.

2. In the introduction several studies are referenced that show an association between schizophrenia and immune system abnormalities. Are those findings specific for schizophrenia, for psychosis or are there similar results in patients with e.g. depression?

We appreciate the Reviewer's feedback. There is evidence for immune-inflammatory abnormalities in other psychiatric disorders (e.g., mood disorders), although it is not clear which findings may be specific to schizophrenia. Given the greater overlap in symptoms between schizophrenia and lupus psychosis, we felt that to discuss immune abnormalities in other disorders was beyond the scope of the present study.

3. "Psychosis is rare, but a very well-documented neuropsychiatric sequelae of SLE". Please add a reference. How rare (please quantify)? What are psychotic features present in SLE and are they similar/different to the psychotic features present in schizophrenia? - "A number of previous studies have reported an association between aRP antibodies and lupus psychosis". Please add references. Please add one sentence summarizing whether those findings differ or not.

We appreciate the Reviewer's feedback, and have incorporated these changes.

4. Is reference 12 really a meta-analysis as mentioned in the text?

We appreciate the Reviewer's attention to detail. This reference is for Briani et al. (2009). The correct reference for the previous meta-analysis is Karassa et al. (2006), which is now included.

5. Why not add "schizophrenia" in the search term? Would that identify further studies?

We appreciate the Reviewer's feedback. We have previously published a quantitative review of autoantibodies in schizophrenia (Ezeoke et al. (2013) *Schizophrenia Research*), and there were not enough studies to perform a meta-analysis of anti-ribosomal P antibodies in schizophrenia.

6. The authors exclude studies in which there were no cases of lupus psychosis (n=4). Why? That might have created a bias in the results. Please change or discuss as a limitation.

We reviewed these 4 studies and for all 4, have revised the exclusion to “Psychosis not stratified from other neuropsychiatric sequelae.”

7. What is a "significant overlap"? Please quantify.

Since this did not apply to any studies, we have removed it as an exclusion criterion.

8. Page 5: what are "ES estimates"? Effect size estimates? Please introduce abbreviation.

Correct. We have introduced the abbreviation for Effect Size (ES) estimates.

9. In the methods section the authors state that heterogeneity was considered significant when $p < 0.1$. In the results $p = 0.09$ is reported but the authors state that there was no significant heterogeneity.

We thank the Reviewer for catching this typo. We now state that that the heterogeneity was significant.

10. Please add Egger's test to check for funnel plot asymmetry.

We have added this test.

11. The moderating effect of covariates on effect size measures should be investigated. Is there an effect of year of publication, assay type, gender and age of patients.

We now present data on the effect of these covariates.

12. In the discussion it is stated that the effect of covariates was not tested. Why?

See #11 above.

13. The studies included in the meta-analysis should be specified in greater detail. What were the characteristics of the patient samples (age, gender, symptom scores, medication). What were the psychotic symptoms reported. What were the rheumatic symptoms they reported. In which stage of SLE were the patients. Did they receive immune-suppressive medication?

We now provide the requested information on subject age, gender, and illness duration. This information was available for only about half of studies. Data regarding symptom scores/specific psychotic or rheumatologic symptoms, stage of illness, and medications were even less frequently recorded, and therefore are not included.

14. In the funnel plot and in the forest plot only 15 studies are shown. It seems Caponi et al., 2002 is missing. Please add and update results.

We have added this study and updated the results.

15. Page 6 typo: "that more that..."

This typo has been corrected.

16. Page 7 typo: "as well at the PAR%...."

This typo has been corrected.

17. Are there other antibodies that could be investigated? - Is there any pathophysiological hypothesis how the aRP antibodies lead to psychosis?

Based on our literature review, no other antibodies have been extensively investigated in lupus psychosis. The mechanism(s) underlying this association is unclear, and we now briefly comment on pathophysiology.

Thank you again for publishing our manuscript in the *World Journal of Meta-Analysis*.

Sincerely yours,

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