Author’s response to reviews

Title: Antiviral Treatment Perspective against Borna disease virus 1 infection in Major Depression: A Double-Blind Placebo-Controlled Randomized Clinical Trial

Authors:
Detlef Dietrich (DEDietrich@web.de; detlef.dietrich@burghof-klinik.de)
Liv Bode (liv.bode@web.de)
Carsten Spannhuth (cspann@gmx.net)
Hartmut Hecker (hecker.hartmut@gmx.de)
Hanns Ludwig (hanns.ludwig@web.de)
Hinderk Emrich (drdedietrich@gmail.com)

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Author’s response to reviews:

PHAT-D-19-00096R1

Authors’ response to reviewer 2:

First, we like to thank reviewer 2 for acknowledging the first revision of our manuscript.

The additional point he raised concerning the cross-over period II is comprehensible. We agree that the study would benefit from further details.

The cross-over therapy switch after period I (7 weeks) was designed for legitimate ethical reasons. It was conducted to ensure that all patients benefit from the putative efficacy of amantadine. Thus, cross-over treatment was in the first place provided in our trial protocol but at the same time requested by the Ethical Committee due to previous results in open trials.
The cross-over design had, however, a clear disadvantage in that carryover-effects of the first treatment period could not be excluded despite the one week wash out. Therefore, we decided to focus on period I for the primary clinical outcome which was defined as change of depressive symptoms measured by total HAMD (21 items) after 6 weeks of treatment plus one week wash out, comparing amantadine and placebo groups. Additionally and in parallel, the change of BDV-1 activity was studied. Consequently, period I but not period II was subjected to statistical in-depth analysis of HAMD single-item scores, as well as the correlation of clinical and infection variables.

However, both treatment periods were considered in that the entire study was mapped at weeks 2, 4, 7, 9, 11, and 14 for differences between amantadine and placebo. The respective clinical course analysed for different items was illustrated in Fig. 3 to Fig. 6 of the manuscript. The overall clinical response after cross-over as well confirmed a clear treatment benefit of amantadine. After 14 weeks, 22 of 31 patients (71.0%) responded by >25% reduction, and 17 of 31 patients (54.8%) by >50% reduction of the HAMD-score.

Revised manuscript, methods: we added a paragraph under “Clinical assessments” in Methods which explains the reason for the cross-over design and why the evaluation of period II was limited (new lines 184-188).

Revised manuscript, results: we refined terms and short text passages under “Clinical Outcomes” in Results to describe more precisely which evaluation measures were applied for different study parts (changes in lines 306, 325 – 327, and 334 - 336).

Revised manuscript, discussion: we inserted a sentence at the end of the discussion which points to the limitations through cross-over design (new lines 699 - 701).

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Authors’ remarks to the Editor
Dear Prof. Gümüstekin,

The additional point raised by reviewer 2 concerning the cross-over period II of the study has led us to explain the reasoning behind the study design as well as outcome criteria in more detail. In the revised manuscript, this has been done through changed or inserted short text passages in Methods, Results, and at the end of the Discussion.

In our response to Reviewer 2, please find our explanations and changes in the manuscript (lines indicated).

We believe the additionally revised manuscript could again benefit from the helpful comments of reviewer 2.

Again, we like to thank you very much for your assistance and hope to receive a favourable answer soon.

Yours sincerely,

Prof. Detlef E. Dietrich, corresponding author,

Dr. Liv Bode, co-corresponding author