Author's response to reviews

Title: Pharmacotherapy of elderly patients in everyday anthroposophic medical practice: a prospective, multicenter observational study

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Author's response to reviews: see over
Dear Editor,

Please find enclosed our revised manuscript “Pharmacotherapy of elderly patients in everyday anthroposophic medical practice - a prospective, multicenter observational study”.

We are grateful for the thorough review process; the comments were very helpful and increased the quality of our paper. Below you will find a point-by-point list of replies to the reviewers’ concerns. All changes in the manuscript are in red.

We hope that the revised version of the manuscript will be suitable for publication.

Thank you again for your time and consideration!

Yours sincerely,

Elke Jeschke

Response to the comments

Referee 1
Major Compulsory Revisions
Statistical Analysis

1. Referee 1: A multivariate logistic regression model (LR) is a useful statistical model to determine predictors for medical use. Did the authors conduct a univariate analysis? I presume a univariate analysis MUST have been conducted. I would like to know if a bonferroni correction was done.

   Author: Yes, a univariate analysis with a bonferroni correction was done. We described the procedures and their results in the respective chapters (page 8, para 4; page 13, para 2)

2. Referee 1: How were the variables selected to be incorporated into the LR model? The description of conducting a multivariate LR is not an adequate explanation of the statistical analysis employed. More detail is required (Goodness-of-fit and collinearity diagnostics). Further did the authors conduct interaction effects with age*diagnosis, i.e. for each of the diagnosis?

   Author: We have described and applied multivariate LR in more detail, i.e. selection of variables with backward stepwise inclusion, dependent and undependent variables, goodness-of-fit with Hosmer-Lemeshow-Test and collinearity diagnosis. As suggested, we also looked
for interaction effects of independent variables in our analysis and included 2 terms of interaction in the final model. Estimators for the other predictors however only changed marginally and were corrected. To detect interactions we calculated ORs for the prescription of AM before the logistic regression for different indications and age strata. Changes and results were described in detail: (page 9, para 2; page 13, para 3, page 14 para 1, Figure 2)

Minor Essential Revisions

3. **Referee 1:** The authors make the case for the public health importance of the topic and I concur. I agree the evidence for using conventional pharmacotherapy is lacking in older people. Is there any strong evidence for using CAM in this vulnerable population?

   **Author:** We already had a link on this topic in the first version of our manuscript (page 4, para 4 References 4-7); we however added the example “mistletoe” for illustration: “In the field of oncology for example, anthroposophical remedies based on mistletoe extracts are the most important drugs in Germany. According to a survey of Münstedt et al. every third GP (35%) has a special preference for mistletoe extracts for the treatment of cancer.” (page 5, para 3)

4. **Referee 1:** Page 6, Line 13, 29 – “physicians had practiced for at least five years in primary care in addition to completing training in anthroposophic medicine.” A control group of physicians without training in anthroposophic medicine would have made this study more robust. I think this is a limitation.

   **Author:** Thank you. It is a limitation and we have put it in the respective section (page 20, para 1)

5. **Referee 1:** It is interesting to note CAM medications were prescribed in patients with cancer and dementia, whilst conventional medications accounted for the majority in patients with cardiovascular and metabolic disorders. Could the authors offer an explanation for this trend?

   **Author:** Unfortunately not really. But we think this is important to mention and have added the following sequence: “….It is quite interesting to note that CAM medications were mainly prescribed in patients with cancer and dementia, whilst conventional medications accounted for the majority in patients with cardiovascular and metabolic disorders. This is in accordance with a previous analysis [13]; however there is no direct explanation for this trend.” (page 16, para 2)
6. **Referee 1:** Table2: AOR for Mood and affective disorders was not significant. This is not consistent with statement made Page 15, Line 4 – “This also applies to depression as visiting an anthroposophic GP has shown specific benefits in terms of quality of life for patients suffering from depression”. Is this a general statement or relates to findings from this study. Please provide more clarity.

**Author:** The reviewer is right and we rephrased accordingly: “… This however does not directly yield to higher prescription rate in drugs of AM. Particularly in the field of depression our physicians of course also follow the trend to prescribe proven herbal remedies like St. Johns Wort which are not directly linked to AM.” (page 15, para 2)

7. **Referee 1:** The authors rightly point put coding inaccuracies cannot be ruled out entirely. However, it would be useful to know who carried out the coding and is inter-rater reliability was conducted. How reliable is the data?

**Author:** participating physicians carried out the coding (page 7, para 3); We now have limited our results as follows: “…Firstly, although physician prescribing data were subjected to an internal review, as described above, coding inaccuracies cannot be ruled out entirely. However, according to Himmel (2006), we can assume that relevant data like patient age, gender, and prescriptions are sufficiently documented by the physicians and that it is possible to use routine data for identification and classification of therapeutic actions as well as for quality assurance in ambulatory patient care.” (page 20, para 1)

8. **Referee 1:** I’m pleased to see the authors have listed non recording of patient self-medication with CAM remedies or over-the-counter (OTC) drugs as a limitation. I think this is an important limitation? This may explain why only 36% of patients in this study took more than 5 medications whilst that reported in the literature differ significantly.

**Author:** Yes, and we have integrated this thought: (page 20, para 1)

9. **Referee 1:** Page 18, Para 3: I’m surprised to note antidepressants amitriptyline (19.3% of all antidepressants) and doxepin (7.5%) are still being employed in primary care to treat depression in older people. I’m particularly concerned with the peripheral and CNS anticholinergic adverse effects. It would be interesting to see how many were co-prescribed hypericum? I know it’s hard but this data would be valuable insight to this study?

**Author:** Indeed, and we conducted the requested analysis: (page 12, para 2; page 19 para 2)
10. **Referee 1**: I agree the evidence was acetyl cholinesterase inhibitors in demenia are not stronger either. However, the readers would benefit to know how many patients were co-prescribed ginkgo biloba with AcHEI.

   **Author**: We also think that the readers will benefit and added the data: (page 12, para 2; page 19, para 2)

**Discretionary Revisions**

11. **Referee 1**: Page 5, Para 2, replace general practitioners with physicians.

   **Author**: Done as requested.

12. **Referee 1**: Page 7, Para 3, Line 8, lease abbreviate adjusted odds ratio as AOR

   **Author**: Done as requested (Page 9, para 2), and throughout the manuscript.

13. **Referee 1**: Page 14, Line 3, replace ‘GPs’ with physicians to be consistent with the rest of the manuscript.

   **Author**: Done as requested

14. **Referee 1**: Page 18, Para 2, Another interesting observation- Ginkgo biloba was the most frequently prescribed anti-dementia drug over all (68.9% of all anti-dementia drugs). I refer to the Cochrane review Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia. 2009. There is no convincing evidence that Ginkgo biloba is efficacious for dementia and cognitive impairment.

   **Author**: We already quoted the Cochrane review in Ref. [52] (page 18, para 4)

**Referee 2**

**Major Compulsory Revisions**

15. **Referee 2**: Background, p4 (and elsewhere): As someone who is admittedly not well versed in CAM or anthroposophic medicine, the most difficult thing for me to follow was how different drugs were placed in the different categories. The terminology does not seem to be used consistently. For example, on this page the authors mention “complimentary drugs”. Does this
mean the same thing as CAM? What exactly does that include? It may be obvious to others, but I would consider including a Venn diagram that includes all different categories of drugs evaluated (complementary, CAM, anthroposophic therapies, homeopathic, phytotherapeutic, etc.).

**Author:** We explained the background in the introductory part of the article (page 5, page 6) but decided against a Venn-Diagramm as this would go far beyond the scope and dimension of this paper.

Minor Essential Revisions

16. **Referee 2:** Background, p4: In the data cited from reference 2, are these prescription drugs only, prescription + over-the-counter, or something else. Please clarify.

   **Author:** Thank you very much for pointing out, it’s insurance data of prescription drugs only; We corrected the respective sentence (page 4, para 2)

17. **Referee 2:** Results, p9: The authors discuss, here and elsewhere, “treatment diagnoses per year”. Does this mean new diagnoses, all diagnoses, etc.?

   **Author:** It’s about “all treatment relevant diagnoses“, which we have put more concrete in the methods section (page 7, para 3)

18. **Referee 2:** Results, p10 and Table 2: What criteria were used to classify drugs as conventional or CAM? Also, based on the statement regarding hypericum being “phytopharmaceutical, homeopathic, or anthroposophic remedy”, it appears that a drug could fall into > 1 category. How was that done?

   **Author:** We now have explained the background (page 6, para 2) and added a sequence in the methods section: „...the first three of these groups according to the regulations of the German Drug Law were defined and are referred to below as CAM remedies.” (page 8, para 1)

19. **Referee 2:** Discussion, p17: The statement that HTN management in elderly patients is more important at reducing morbidity than any other intervention should ideally be referenced.

   **Author:** Done as requested (page 18, para 3)

Discretionary Revisions
20. **Referee 2**: Background, p4: The authors state that knowing prescribing pattern in the elderly is “hardly understandable”. I read this to mean “difficult to understand”. Was this the intent? If so, would consider revising to state exactly that.

   **Author**: We changed it in: “…Even in cases where there is clinical data on the effects of pharmacology on elderly patients, prescribing patterns in primary care are likely to be unknown, which is difficult to understand, as the elderly are the main users of pharmacotherapy.” (page 4, para 3)

21. **Referee 2**: Background, p5: During what time period did the findings reported from reference 9 occur? A specific year, decade, forever, etc.?

   **Author**: It’s one year: (page 5, para 1)

22. **Referee 2**: Background, p5: Again, it might be just me, but as someone who was never heard of anthroposophic medicine, it would be nice to have a little more description about what it is, how it differs from other forms of CAM, etc. Here. Later, the authors discuss anthroposophic remedies. I have no idea what these might entail.

   **Author**: Done as requested (page 5, page 6)

**Editor**

23. **Editor**: Clearly define CAM including anthroposophic, homeopathic, and phytherapeutic using examples as pointed out by the reviewer.

   **Author**: Done as requested (page 5, page 6)

24. **Editor**: Clearly define the dependent and independent variables in the logistic analysis as pointed out by the reviewer

   **Author**: Done as requested (page 9, para 2)

25. **Editor**: Subgroup analysis of overall medication use is changing the focus from CAM use; just describe the overall use and do not analyze across the subgroups, Remove unnecessary bivariate analysis:
   Comparison of median age across specialties,
   Comparison of median prescriptions across specialties
Comparison of median diagnosis across age

**Author:** Done as requested (page 10, page 11)

26. **Editor:** Discussion the first para seems like conclusion; move it to appropriate section; Move limitations the last part of the discussion

   **Author:** Done as requested (page 20, page 19).

27. **Editor:** Discus the variables found significant in the multivariate analysis in relation to previous studies

   **Author:** There is data on the use of CAM in the elderly; however in the case of prescription data we did not find any data nor on CAM, neither AM. We therefore stated: “….In addition, the associations between AM prescribing and factors like age, sex, consultation typ and, diagnoses to our knowledge do not have a correlate in other prescription studies in primary care and should also be investigated more closely.” (page 19 para 3)

28. **Editor:** Briefly discus the implications for practice and policy for the key findings

   **Author:** Done as requested: we rearranged and extended the discussion with a section on “implications for practice and policy” (page 19, para 3). However, we are not sure whether it would be more appropriate in the conclusion section.