Title: Stepped care treatment for depression and anxiety in primary care: A randomized controlled trial

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Author's response to reviews: see over
Cover letter

June, 2011

Dear Sir/Madam,

Hereby, I resubmit our paper named ‘Stepped care treatment for depression and anxiety in primary care: A randomized controlled trial’. Our paper describes the effectiveness of a stepped care model for patients with mood and / or anxiety disorders in primary care. The manuscript is 18 pages long and 3 tables plus 2 figures are included. We would be grateful if you would consider our revised manuscript for publication in Trials.

We inform you that this study is designed and carried out according to the APA ethical standards. This study received approval from an appropriate ethics committee. The trial is registered in the Current Controlled Trial’s register (ISRCTN17831610). This manuscript is not under consideration nor published by another journal. All authors do not have any interests that might be interpreted as influencing the research.

I added the letters to the reviewers and changed the format changes as suggested.

I will be serving as the corresponding author for this manuscript. All co-authors agreed to submission of the manuscript in this form. If you have any questions concerning the study, you can contact us by phone or email.

Sincerely,

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Stepped care treatment for depression and anxiety in primary care: A randomized controlled trial

Reviewer #1: Gerhard Andersson
We like to thank the reviewer for the positive response and the suggestions to improve the paper.

Title and abstract
Do the title and abstract accurately convey what has been found?
Could be clearer in title.

The title does not convey our results. We prefer to present our study question in the title instead of the results.

Discussion
One minor limitation that could be raised in the discussion is that the problem solving therapy might be too weak as part of a stepped care procedure and that a more intensive/advanced therapy may be needed.

We have no reasons to believe that problem solving therapy (PST) is too weak as part of a stepped care procedure. In general there is no evidence that PST is better (or worse) than other, longer, therapies for depression. (Cuijpers, 2008). Furthermore, PST has been studied extensively in primary care and these studies demonstrate promising results (Mynors-Wallis, 1995; Mynors-Wallis 1997; Mynors-Wallis, 2000) and as part of an effective collaborative care model (Ünutzer, 2001).

Major compulsory revisions
1. The treatment of missing data is not particularly clear. "Missing data were imputed using regression imputation..." – does this mean single imputation? Why not use multiple imputation? Or why impute at all, since there is no clear need for imputation given the analyses used?

We agree with the reviewer that imputation is not needed for GEE-analysis and therefore we did not impute in this main analysis. For the t-tests on the single assessments and the calculation of Cohen’s d, we wanted an intention-to-treat analysis and therefore used regression imputation. This is described on page 12 in the statistical analysis. We agree with the reviewer that multiple imputation might have been even more correct. We chose to use single imputation for these analysis because of pragmatic reasons and also because in our experience the results are usually very similar.

2. GEE is not robust to missingness (see Rotnitzky & Wypij, Biometrics 1994; Paik, J Am Stat Assoc, 1997), producing biased estimates when there are missing data. Please explain why mixed effects logit models (e.g., xlogit in Stata, glimmix in SAS) were not used instead.

The reviewer is right that in the literature mixed model analysis is preferred above GEE analysis when missing data is either MAR (missing at random) or MNAR (missing not at random). However, when
missing data is MCAR (missing completely at random), mixed model analysis is not ‘better’ compared to GEE analysis. Because in the present dataset, missing data was found to be not selective regarding important parameters such as symptoms of depression, symptoms of anxiety or gender, the results of the GEE analysis were not biased. So therefore we believe that the results of the GEE analysis can be trusted.

**Minor essential revisions**

3. *Please include page numbers.*

We added page numbers in the manuscript.

4. Abstract: "...there was no statistical significant..." should be "statistically significant"

We changed this into the correct formulation.

5. Intro: "...and not later or less intense..." should be "intensely"

We changed this into the correct formulation.

6. Intro: "In a stepped care model, all patients start with an evidence-based treatment..." – do all patients receive treatment or only those patients exhibiting symptoms of depression/anxiety?

We agree with the reviewer that this is somehow unclear. It should be all eligible patients, because stepped care programs are applicable to different kinds of health problems. We adjusted the sentence on page 4, line 1-2, into: "In a stepped care model, all eligible patients start with an evidence-based treatment of low intensity as a first step."

**Comment 7 to 17:** We thank the reviewer for reading our manuscript so carefully. We changed all the sentences as suggested by the reviewer.

7. Intro: "...and where necessary changes are made" – delete "where"

We deleted the word “where”.

8. Method: April and May should be capitalized

We capitalized the words as suggested.

9. Method: "...all participants gave, written,..." – delete the comma after "gave"

We deleted the coma after “gave”.

10. Method: "...few studies who report..." – change to "that report"

We changed this into the correct formulation.

11. Method: "...detect clinical relevant..." – should be "clinically"

We changed this into the correct formulation.

12. Method, results and throughout: please ensure that past tense is used when describing the study and the results of the study. For example, "The first is a generic intervention...", "It is primarily aimed at helping people to understand the techniques which are offered in the course.", "If the patient experiences extreme
dysfunctioning", "But there is no significant difference..." – these and many other examples should all be in past tense.

We agree with the reviewer that this was inconsistent. We changed this into past tense.


We added a dot in this sentence.

14. Method: Consider using gender neutral language, "...he/she was directed immediately to the fourth step..."

Where necessary we now use gender neutral language.

15. Method: "GEE is taking into account..." should be "GEE takes into account..."

We changed this into the correct formulation.

16. Method: "...the percentages of patients who have recovered..." – consider deleting "have"

We deleted the word “have” in this sentence.

17. Results: "...were referred to specialized mental health care after they run through..." – add "had" before "run"

We added the word “had” to the sentence.

18. Results: It is not clear what the estimates listed in the treatment effect paragraphs refer to: "(B=31.17..." and "(B=10.30..." – are these the effects of time or the interaction effects or something else? They seem to be significant as the CIs do not include zero.

We are very glad that the reviewer noticed this. The previous reported results were the intercept instead of the interaction effect. We changed this to the correct results of the interaction (group*time) on page 16, lines 4 and 8.

19. Discussion: consider replacing "is outperforming" with "outperformed" in the first sentence.

We replaced “is outperforming” with “outperformed”.

20. Discussion: consider replacing "suffered" with "received" in the second sentence.

We replaced “suffered” with “received.”

21. Discussion: "...care as usual have a, on average, mild to moderate symptom level, but because of the small change over time and the high number of still existing diagnosis at the end of the study suggests that we included..." – suggest changing to "...care as usual have, on average, mild to moderate symptom levels, but the small change in symptoms over time and the high number of existing diagnoses at the end of the study suggest that we included..."

We changed this sentence as suggested.
22. Discussion: The second paragraph is very long. Considering starting new paragraphs at "Patients with relatively mild symptoms..." and "Our suggestion to improve the model..."

We changed this as suggested by the reviewer.

23. Discussion: "...the freedom of choice for feedback has probably lead..." – consider changing to "...may have led..."

We changed this as suggested by the reviewer.

24. Discussion: "...adherence to the self-help course guidance by..." – add a comma after "course"

We added a comma after “course”.

25. Discussion: What effect did the reminders have on adherence or treatment effects? For example, did the authors examine differences to those who received all of their reminders to those who did not?

Unfortunately it is unclear which reminders the reviewer means. We send reminders to all patients if they did not return their questionnaires. They received two reminders via email and an additional one via telephone. Every participant, in both stepped care and care as usual received the same amount of reminders. During the treatment, no reminders were send to the participants. Therefore we could not examine the differences the reviewer probably means.

26. Discussion: "...and it is easy accessible for patients." – change to easily.

We changed this into the correct adjective.

27. Table 1: decimal places should be consistent, i.e., p = 1.00 instead of 1.0.

We agree with the reviewer that this should be consistent, we changed it as suggested in Table 1.

Discretionary revisions

28. Discussion: The study examined stepped care for treating depression/anxiety. The authors could comment on whether such an approach might work better for the prevention (rather than treatment) of depression/anxiety, particularly since many of the participants in the study had chronic conditions.

We agree with the reviewer that this is a useful recommendation. Especially because this already has been proven effective for elderly (van ’t Veer-Tazelaar, 2009). We added our thought about this in the discussion on page 18, lines 1-4.

29. Discussion: Further evidence for the chronicity of depression in the study sample can be seen in that the mean age of the sample is 50 years but the mean age of onset is 28, apparently suggesting an average 22 year chronicity.

This is certainly further evidence for the chronicity. We added this on page 17, lines 19-20.

Finally, we made some additional language-corrections (in track-changes).