Author's response to reviews

Title: Does treatment of subsyndromal depression improve depression- and diabetes-related outcomes? A randomised controlled comparison of psychoeducation, physical exercise and diabetes re-education

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Response to the reviewers:

Reviewer: Hiran Thabrew

The authors present a well-defined question regarding the treatment of sub-syndromal depression in people with type 2 diabetes. The title of the paper is appropriate to the research question. Methods are clearly presented in adequate detail. Processes of randomization and controlling are also well described. We appreciate this opinion.

Improvements would be advisable in the following areas:

1. A clear statement about the prevalence of subsyndromal depression in the general and target populations would make it easier to understand the relevance of this issue to clinical practice.

   According to literature data, depression prevalence is roughly doubled in patients with diabetes compared with people without diabetes. A approximately 30% of diabetes patients report elevated depressive symptoms and one third of them suffer clinical depression (Anderson et al. 2001; Ali et al. 2006; Barnard et al. 2006). This implies that around 10% of diabetic patients would meet criteria of major or clinical depression, whereas around 20% of people with diabetes are affected by subsyndromal depression.

   The information about the prevalence of subsyndromal depression has been added to the introduction section.

2. The second paragraph of the introduction on page 3 states that subsyndromal depression rarely remits spontaneously, but this is potentially contradicted by the
study's findings where participants in all 3 arms showed improvement. Admittedly there was no absolute control group (receiving no treatment at all), but spontaneous improvement not related to any treatment would be one explanation that has not been discussed and should be.

This assumption might be a possible explanation of the obtained results. However, bearing in mind the previous findings on persistence of depressive symptoms in type 2 patients with diabetes (Nefs et al, 2012; Pibernik-Okanovic et al, 2008), and those on increased risk of developing major depression once diabetic patients are faced with elevated depressive symptoms (Bot et al, 2010), we do not assume that spontaneous recovery would occur in such a systematic way.

In accordance with the Reviewer’s recommendation, a hypothetical elaboration of this issue has been added to the discussion section.

3. My main concern about this paper is that, according to the methods section, data was collected at 8 weeks, 6 months and 12 months, but results are only presented in text and tables for the 12 month time point. Please could the authors provide the remainder of the results and comment on any discrepancies between short and long term findings?

Thank you for this comment.

As the study was powered to demonstrate the maintenance of intervention effects 12 months after the end of intervention, we decided to focus on long-term outcomes of our interventions. Reporting and discussing all the intermediate results would therefore exceed the space limits of the article. Nevertheless, Table 3 contains both P values referring to baseline to twelve months differences and overall P values referring to differences between baseline results compared to results obtained at six- and twelve months. The included F ratios and the corresponding P values indicate that all variables which demonstrate significant baseline to 12-month time effects demonstrated significant overall P’s as well. Post-hoc analyses of psychological outcomes (depressive symptoms, diabetes distress and quality of life) showed that there were significant improvements from baseline to six- and from baseline to twelve months. The same pattern could be seen in some behavioural variables (exercising, self-monitoring blood glucose, carrying about foot), while healthy eating and diabetes diet improved from baseline to 12 months but not from baseline to 6 months.

Total cholesterol, LDL cholesterol and triglycerides improved significantly from baseline to twelve months and from six to twelve months, indicating that the process of lipid reduction required a longer period.

Eight-week psychological and behavioural outcomes completely corresponded with 12-month follow-up indicators and were not presented in the manuscript.

4. Other confounders or population variables that might account for the obtained results have not been discussed. It would be good to see the discussion augmented to include this dialogue.

As shown in Table 1, the study groups were comparable with respect to demographic and diabetes-related characteristics. Therefore, controlling the
results for them did not reveal changes in their patterns.

5. Within the discussion it is mentioned that people with higher depressive symptoms and more serious emotional problems showed greater improvement. Were these analyses undertaken post-hoc or were they planned? I'm not sure they were mentioned in the methods section.

We appreciate this useful reminder. Comparison of the effects of the interventions in patients with more serious emotional symptoms vs those with milder symptoms was undertaken post-hoc. A rationale for doing so relied on a recent systematic review and meta-analysis (Krishna et al, 2013) suggesting that treating sub-clinical depression is effective but that the overall effect sizes are modest. The latter can be attributed to relatively low baseline level of depressive symptoms in this population causing a ceiling effect as a consequence. Therefore, we decided to introduce this additional analysis aimed to determine who of the treated patients benefited more.

A part referring to the usage of this analysis has been added to the methods section, and to the Consort check list.

6. Were any of the participants receiving medication or other treatments for depression during the study?

Patients who initiated receiving pharmacological or any other treatment for depression during the follow-up period were excluded from the analysis.

7. Do you know what the cause of death was in the 3 patients who died during the study?

In all three cases it was cancer.

Reviewer: Sarah Hetrick

This is an excellent study and a very well written manuscript that was a pleasure to read.

We appreciate this comment.

There are a few issues that need to be addressed to ensure that this manuscript is of the high standard required by Trials for publication.

Major compulsory revisions:

1. There is very limited description of what this “control group” received in terms of how many sessions (only in the discussion is it clear that it was only one session), the length of session(s), and I wasn’t clear exactly was being discussed in terms of ‘current laboratory findings” (was this research findings or findings of the investigations done on each individual?). Further description of this arm is required so that it is clear what the nature of this arm is.

We appreciate this remark. Further description of this study arm has been added
to the Methods section, clarifying that it consisted of one group session lasting for 90 minutes which addressed: a) patients’ understanding of their current HbA1C and lipid values; b) patients’ goals in self-managing diabetes; c) patients’ concerns caused by diabetes in general, and the current laboratory findings. A method of delivery is additionally described, specifying that patient centred counselling in a group was used.

2. Related, there is considerable inconsistency in describing this “control group”; at times the authors describe “three behavioural interventions” (pg 4), “three treatment arms” (pg 8 and in the discussion), but they also state that they use a “control group” (abstract), and a “minimal intervention” (pg 6). This needs to be addressed by the use of an accurate and consistent term throughout.

Thank you for this comment. Realizing that enhanced treatment as usual (TAU) suggested in the next comment would be the most appropriate term, we have made changes in the text using it consistently throughout.

3. There are significant implication with regard to points 1 and 2 above in terms of how the results of the trial are understood i.e. if there is no difference between three intervention groups, one can implement any of the interventions tested that might best suit the population you are working with. However, if as I read it, there are no differences between the two intervention arms and a control group or minimal intervention, then one would question whether an intervention was justified and the conclusions of the study should not be as stated “that patients were responsive to treatment”. The second two paragraphs on page 13, therefore, go beyond the results of the study in that they suggest physical activity and psychoeducational treatment are effective. However, in fact compared with a ‘minimal intervention’ (a one off diabetes education session), they are no different. The discussion up to these last two paragraphs on page 13 is useful in suggesting that attention, concern and support with a focus on addressing diabetes-related problems (given they may underlie the depression symptoms) might be all that is required and this I think constitutes the main finding of the study. Therefore, the conclusion should be that this type of minimal intervention (which may also be described as enhanced TAU) might be sufficient. Authors need to address this key issue of needing to ensure that the discussion and conclusions are adequately supported by the data.

We appreciate this suggestion very much. The two paragraphs on page 13 elaborating the efficacy of psychoeducation and physical exercise in treating subsyndromal depression have now been omitted and the interpretation of the obtained data relies on the main finding (no between-group effects) and hypothetical mechanisms to explain comparable improvements in all three study arms. The same refers to the study conclusion.

4. The authors state that there are more detailed descriptions of the study methods in other publications, however, this paper should also be able to be read as a complete and whole description of the study and therefore include all of the basic details one would expect to see as per the CONSORT statement. The aspects most noticeably missing were descriptions of how allocation according to
the randomisation sequence was concealed from the researchers (to avoid any manipulation of the randomization sequence according to knowledge of patient characteristics) and whether the outcome assessors were blinded. The (participant) Flow Chart should include a description of those who did not complete the intervention (drop outs and/or withdrawals) as well as (separately) the numbers who completed the assessment at each time point.

Randomizing patients into the groups (carried out by using the WINPEPI - a computer-generated algorithm stratified by gender; Abramson 2011) was done after a telephone interview in which patients’ eligibility was determined, basic information about the interventions was given to them, and they were invited to the clinic for baseline assessments. No deviations from computer-generated assignments occurred with the exception of one patient who did not accept the proposed group assignment when coming to the baseline assessment. This patient was not included in the study but suggested to choose between other sources of professional help.

The outcome assessors were not blinded for the patients’ group assignment, since the included measures (laboratory tests, standardized psychological questionnaires) were not considered likely to cause bias.

Additional information about how allocating patients to the groups was carried out was added to the Methods section.

Details about patients who dropped out/withdraw have been added to Patients’ Flow Chart and numbers of patients who completed assessments at each study level are given separately.

5. Authors should discuss the assumptions and limitations with regard to how they have dealt with missing assessment/outcome data and with reference to the now commonly accepted gold standard approaches such as multiple imputation e.g. Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., Wood, A.M., Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. The British Medical Journal, 338, b2393.

As mentioned in the Statistical analyses and the Results sections, we have used a conservative estimator of treatment effects related to missing assessment/outcome data (ITT relying on baseline-observation-carried-forward approach). Although being aware that estimation derived from multiple predictors (multiple imputation) is now a commonly accepted gold standard, we did not carry out this analysis, partially because of assuming that the absence of between-group effects would not necessarily request a more complex approach.

6. A section about the limitations of the study is required (which should address the risk of bias that may have been introduced by e.g. not having adequately concealed allocation and/or not have blinded outcome assessment, as well as the issue regarding missing outcome assessment data).

These hypothetical courses of bias have been added to the section referring to study strengths and limitations.
7. Authors should include a discussion of the clinical as well as research implications e.g. some interesting mechanisms are discussed but this requires further study (which are mentioned in the abstract but do not appear in the main text). A useful format for writing a discussion is provided in Docherty, M., & Smith, R. (1999). The case for structuring the discussion of scientific papers. BMJ, 318, 1224-1225. We hope that our re-structured discussion would meet the requested criteria.

8. Authors should also conform to the reporting standards of TIDieR (Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., ... & Michie, S. (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ: British Medical Journal, 348.). Again, the most noticeable aspects that weren’t described included the rationale/theory for the interventions/essential elements of the intervention were chosen; where the materials used (e.g. manuals) could be sourced from; details about the procedures e.g. how long did participants spend watching presentations vs engaging in activities or exercise, where were these done, what equipment was used; whether there was any tailoring e.g. for the exercise intervention was this gentle to start with and then increased in intensity; there is no description of how fidelity to the intervention was assessed or strategies to maintain fidelity and whether it was delivered as planned. Ensuring an adequate description of the intervention helps with implementing successful interventions in every day clinical practice. In the case where interventions do not prove to be beneficial, understanding aspects of the intervention in this detail can provide some insight to why they may not have been effective.

We appreciate this suggestion. Some additional information about how the interventions were delivered has been introduced into the Interventions section. Templates for Intervention Description and Replication (TIDieR) have been filled for the three interventions and sent as additional file.

9. Given the above points, the conclusions in the abstract require careful attention to ensure that the results are accurately reflected.

The abstract has been re-writing as follows: The employed interventions had comparable positive effects on 12-month psychological and diabetes-related outcomes suggesting that even minimal intervention addressing patients’ diabetes-related problems and concerns had favourable clinical implications and might be sufficient to treat subsyndromal depression. Further investigation is warranted to clarify possible mechanisms of improvement.