Author's response to reviews

Title: Are the effects of a non-drug multimodal activation therapy of dementia sustainable? Follow-up study 10 months after completion of a randomised controlled trial

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Version: 3 Date: 12 November 2012

Author's response to reviews: see over
Dear Dr. Majithia,

We are delighted to send you today the revised version of our manuscript MS: 1057366737579850 - Are the effects of a non-drug multimodal activation therapy of dementia sustainable? Follow-up study 10 months after completion of a randomised controlled trial.

Please find below the comments of the reviewers and our answers (green). All changes in the manuscript are marked in yellow. Reviewer 1 provided his comments by using the comment function of word in the original document. In the interest of improving readability, we included his comments together with the applicable sections of the manuscript in one document that also includes the comments of Reviewer 2.

The revised manuscript was reviewed for language by Dr. Jane Zagorski, a professional English language editor.

Thank you for considering our paper for publication in your journal. We are looking forward to your answer.

With best wishes,
Dr. Katharina Luttenberger (first author)

Reviewer 1

Reviewer’s report

Title: Are the effects of a non-drug, multimodal activation therapy of dementia sustainable? Follow-up study 10 months after completion of a randomised controlled trial

Version: 2 Date: 18 September 2012

Reviewer: William R Shankle

Reviewer’s report: see comments in the attached file.

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: see the file I have attached.

Methods/sample: The authors need to comment on the accuracy of this diagnostic method, since they have excluded other dementias. It would have been more useful to not exclude other dementias because the diagnostic accuracy in the community is very poor, so that the authors’ results may not be easy to apply to the community given diagnostic inaccuracy in primary care settings.

Only 47 of 553 patients were excluded due to a “wrong” dementia diagnosis. Dementia diagnosis was obtained by a cognitive screening and the attending physician’s judgment. It therefore does not differ much from the clinical practice used in nursing homes. This is discussed in the sample paragraph.

Methods/sample

By excluding subjects, the authors have introduced selection bias, which will make it more difficult to compare these results to other published results. Exclusion is commonly done to "control" for variability. However, this can be done statistically and avoids the problem of introducing selection bias.
Variability can be controlled statistically if the sample is very large, but it would be impossible to find a sponsor who would be willing to fund a non-drug study that used the necessary number of patients because with non-drug therapy (unlike the situation with pharmacological therapy), there is no money to be gained. With only 56 to 98 persons, one is no longer able to control for all potential variables as subgroups become too small. Furthermore, controlling for all variables is never possible in practice as one is never aware of all potential confounders. Thus, inclusion or exclusion criteria and randomisation play a vital role in today’s clinical studies (see also the discussion below).

Besides these theoretical considerations, most patients in the MAKS trial were excluded due to very practical reasons:

- 220 were physically not able to attend the group therapy (9 blind; 5 deaf; 8 other reasons; 20 physical reasons (e.g., dialysis); 48 unable to communicate; 130 care level 3: bedridden);
- 128 achieved an MMSE score >24 and therefore had no dementia;
- 39 were unwilling to participate.

Inclusion criteria were much less rigorous than in most of the other therapy studies with dementia patients. Neither medication taken nor non-cognitive symptoms such as behaviour problems were used as exclusion criteria. The sample therefore reflects the clinical reality of nursing home dementia patients who would be able and willing to participate in a group therapy.

The CONSORT Statement (Moher et al. 2010, reference see below) states:

“Typical and widely accepted selection criteria relate to the nature and stage of the disease being studied, the exclusion of persons thought to be particularly vulnerable to harm from the study intervention, and to issues required to ensure that the study satisfies legal and ethical norms. Informed consent by study participants, for example, is typically required in intervention studies.”

The only requirement is the following:

“A comprehensive description of the eligibility criteria used to select the trial participants is needed to help readers interpret the study. In particular, a clear understanding of these criteria is one of several elements required to judge to whom the results of a trial apply (…)”

This we did in the CONSORT flowchart.

**Methods/ Instruments**

The ADAS-Cog carries significant measurement error in repeated measures settings. The test-retest effects for the non-memory components of the battery also makes it more difficult to determine if any observed stabilization is real or due to test-retest effects.

A paragraph addressing this limitation has been inserted into the discussion section.

**Discussion/ first paragraph**

Authors need to point out that the repeated measures analysis, adjusting for autocorrelation, did not show a significant treatment effect.

Done.

The authors also need to point out that randomization does not eliminate selection bias prior to study, nor does it protect one from the fact that randomization increases variability between treatment and control groups, thus potentially masking significant treatment effects. Randomization is not the holy grail that protects one from bias or confounding influences between groups. Randomization is a trade-off of injecting noise into the data that cannot be explained, in exchange for hopefully eliminating differences between treatment and control groups. See ET Jaynes The Logic of Science, for a good treatise on the potential problems of randomization.

Of course randomisation is “not the holy grail”; this is why we additionally controlled for the baseline value and further covariates. Yet, randomisation is – after all – the gold standard for
clinical trials and recommended by the CONSORT Statement (Schulz et al. 2010; Moher et al. 2010 and the references therein). (For references see below).

Discussion/ second paragraph
The potential problem here, as demonstrated and published by ITO et al. (Pfizer global research team), is that the treatment effects of cholinesterase inhibitor therapy alone last no more than 9 months compared to placebo. Furthermore, placebo effects due to study participation or intervention can last up to 9 months. So I am not sure whether one can distinguish the treatment effects of cholinesterase inhibitors, placebo or ROT when done within these time frames.

This problem is now mentioned in the discussion; the reference was inserted.

Since Ito et al. showed that the maximum duration of any cholinesterase inhibitor effect is less than 12 months, it may be more accurate to state that the cholinesterase inhibitor monotherapy probably had no treatment effect, and that any attributable differences between treatment and control group was more likely related to either the behavioral therapy or the study's design or sample biases.

As both groups were treated with the cholinesterase inhibitor, differences must be due to one of the mentioned factors. This is made evident by the study design. Nevertheless, a sentence has been included in the discussion section.

Discussion/ sentence “How can… be explained”? (now end of page 13)
This appears to me to be an overstatement, given the non-significant treatment effects results of the repeated measures analysis with a random effect in the model.

Our formulation is now more cautious.

We are all hopeful that these non-medication interventions are useful, but the design of the present study can only hypothesize that the observed differences (that did not remain significant in the sensitivity analysis) are due to the behavioral intervention.

The most important result of this study is that it poses a hypothesis, and identifies problems that need to be addressed in designing a more definitive trial. These problems are:
1. The issue of randomization vs. a better analytical model that does not depend upon randomization.
2. The issue of exclusion criteria, which inject sample bias, and reduce generalizability of the results.
3. The issue of measurement instruments with low signal-to-noise ratios (ie MMSE, ADAS-Cog).
4. The issue of ensuring a long enough followup to get beyond the placebo and cholinesterase treatment effects that persist for 6 months to 1 year.

I think this study should be published, but it is very important not to assume that the results can be so simply interpreted as a positive treatment effect. This would deter researchers from pursuing a better design to more definitively evaluate the proposed therapy.

For points 1 and 2, see the above comments.
We included points 3 and 4 in the discussion and in the conclusion. We also stated that future research should try to overcome the mentioned limitations.

Discussion/ now page 14
No it cannot for all the reasons previously mentioned. The areas highlighted in yellow in my opinion are an overinterpretation of the results.

These areas are now clearly marked as a hypothesis that should be addressed by future research as the reviewer recommended above.

Discussion/ limitations
Much of the discussion I previously provided as caveats to overinterpretation of the data could be provided here.

Done.

Discussion/ strength RCT
This is the blind faith reliance on randomization that permeates medical research. Randomization is a double edged sword that can cut in both directions.

See above.

Conclusion/ first sentence
References need to be provided to support these statements.

Done.

Conclusion/ last sentence
The problem with this writing is that we would all like to believe it is true. However, I think the focus should be to encourage a better designed study to further define whether the "hoped" results are verifiable, and not due to the many problems I have previously mentioned.

See above. The need for further research is included in the last sentence.

Literature:


Reviewer 2

Reviewer’s report

Title: Are the effects of a non-drug, multimodal activation therapy of dementia sustainable? Follow-up study 10 months after completion of a randomised controlled trial

Version: 2 Date: 1 October 2012

Reviewer: Michael Rafii

Reviewer’s report:

Major Compulsory Revisions

This is a well written paper summarizing results from a study looking at the effects of a one year multimodal therapy 10 months after completion of therapy.

1. There is significant overlap between the error bars of MAKS and control group in figure 2 and 3. It is not clear that there is a statistically significant difference
between the two groups at 12 months or 2 months. The authors should clarify this difference.

Figures 2 and 3 do not show error bars but represent median effects (solid lines) together with the corresponding boxplots. Boxplots show the distribution of the raw data and do not represent the error of estimation (such as the standard error) and thus are not suitable for deriving "significance tests" from. In addition to the boxplots, we now include the “notched boxplots” in which the notches can be interpreted as a sort of confidence interval. Non-overlapping notches give a rough indicator of medians that differ significantly and thus offer further information to the reader. The primary aim of these figures is to get an idea of the variability of the outcome and see marginal trends (confounding not taken into consideration).

In the paper, statistical significance is judged in a multivariate setting with a confound adjustment. This cannot be reflected by this display of the raw data (and not with the notched boxplots either).

2. Need to include error bars for figures 4 and 5.

Thank you for this comment. We added the standard errors to the model summary tables in the additional material. Because of the complex calculations (i.e., the multivariate mixed effects model) that are visualised in Figures 4 and 5, the addition of the correct error bars as related to the performed analyses is complicated and – more importantly – would be confusing rather than illustrative. For example, we can derive standard errors only for the MAKs group at 12 months but not for the control group. This is due to the applied (dummy) coding of effects. We hope you agree with this solution.

3. The authors should describe the other potential forms of dementia that may be diagnostic considerations in their study population, and impact on treatment effect.

In the sample section and in the discussion, the potential forms of dementia included in the study are mentioned. The resulting limitation is now given in the discussion section.

4. The authors comment "Hence, intensive multimodal therapy should be started as early as possible and especially applied continuously to retain as long as possible not only the ADLs abilities but also the cognitive functions, and thus to retain the independence of people with dementia." The authors show no data that earlier intervention has any greater effect; i.e. patients with higher baseline performing better on subsequent testing.

Therapy in dementia should always begin as early as possible as it is only possible to maintain the abilities the patient still has and not to recover lost ones. MAKs therapy had better effect sizes for mild and moderate than for severe dementia; this information together with the reference is provided in the conclusion. But we now make clear in the conclusion of the abstract that the most important point is the continuation of therapy.

5. Did the authors do a subgroup analysis of those on ChEI vs not on ChEI to see if there was synergy with non-drug and drug +MAKS therapy?

We would love to do this, but unfortunately, only 6 persons had Antidementiva medication, as indicated in the methods section (chapter patients). Of them, only 3 were in the therapy group; therefore, a subgroup analysis would rather be a case report.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a
statistician.

**Declaration of competing interests:**
'I declare that I have no competing interests