Title: How healthy are chronically ill patients after eight years of homeopathic treatment? - Results from a long term observational study

Authors:

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Version: 2 Date: 24 October 2008

Author's response to reviews: see over
Response to Reviewer

Reviewer: Jennifer Jacobs
Reviewer's report:
Major Revisions
None

Minor Essential revisions
1) Use of term "adolescent" is used incorrectly in this paper. Adolescents are ages 12-18. The authors refer to "adolescents below the age of 8." These should be called "children."

    Authors: this has been changed to ‘children’ throughout the paper.

2) Section 3.3, paragraph 1 the authors refer incorrectly to "effect sizes" that were estimated from the linear model. I believe the correct term here should be "odds ratios."

    Authors: We agree with the reviewer that “effect size” might be somewhat confusing in this context. Essentially, the linear model estimated standardised changes, i.e. mean changes divided by the standard deviation at baseline. We added a respective sentence to the statistics section (page 6, 2.4, 3rd paragraph) and rephrased the term “effect size” by “standardised mean change” in section 3.3 (page 8)

3) Again on page 9 the term "effect size" is used incorrectly in reference to severity ratings after 8 years. It should say the "change" in severity ratings after 8 years.

    Authors: this has been changed as suggested.

4) Several English grammar mistakes- suggest authors have paper reviewed by native English speaker.

    Authors: the paper has now been checked and revised by a native English speaker.
Reviewer: Charlotte Paterson
Reviewer's report:
This is a large-scale and unique observational study of homeopathic patient outcomes now reporting on its 8 year follow up data. The paper is well set out and all sections are appropriate in content, detail and presentation. It is clearly written, although the editor will be able to improve the English grammar in some places. I have highlighted some of the more important grammatical/typo errors below.
Apart from this I have very few suggestions for improvement and consider that the paper could be published with no, or very few minor, corrections.

Discretionary revisions:
1. Page 4. ‘In this paper we present only the long-term results (2 and 8 years), for more details on earlier time points refer to [10].’
This paper is almost entirely concerned with the 8 year data, only presenting some 2 year data for comparison. So I think this sentence is a bit confusing for the reader and should just say 8 years.

Authors: this has been changed as suggested.

2. Table 1 indicates that the presenting symptoms were of long duration. More could be made of this within the results and discussion, because it strengthens the likelihood that the improvement is not purely due to the natural history of the condition.

Authors: we have now included this information in the results (see page 7, section 3.1 second sentence) and addressed this as a strength in the discussion (see page 10 para 3).

3. Table 2. This is entitled ‘Number of patients who reported improvements or worsening of complaints at the 8-years follow-up, grouped whether or not they still were under homeopathic Treatment’
I think it would be clearer to say ‘Number of patients whose change in symptom scores indicated improvements or worsening .....

Authors: this has been changed as suggested.

4. Discussion. 1st paragraph: ‘Improvements were more pronounced in younger patients, females, and those with greater disease severity at baseline’
Would it be correct to add ‘those with multiple infections’ to this list, as this is useful clinical information?

Authors: The reviewer is right, multiple infections turned out to be a positive predictor in our analyses. There are, however, two reasons why we did not add it to the list. First, this list was meant to be a comprehensive summary of the most important results in this study. If we included “multiple infections” in this summary, we should add the other (negative) predictors, too, which would make the list rather long. Second, although “multiple infections” was a predictor in the statistical models we are not sure whether this essentially is a valid result from a clinical perspective: multiple infections most often occur in children, their
frequency decreases with age. Thus, our result might be completely unrelated to the homeopathic treatment and simply reflect the natural course of the disease.

English language errors (minor essential revisions)
The younger patients are children, not adolescents.

Authors: this has been changed as suggested.

P5 ‘groud these therapies’ should be ‘grouped these therapies’

Authors: this has been changed as suggested.

P6. ‘If patients reported of cured complaints we replaced missing values with a severity=0 in subsequent records’ would better be ‘If patients reported that their complaints were cured, we replaced …..’

Authors: this has been changed as suggested.

P8. ‘we found slidely higher effects’ should be ‘slightly’.

Authors: this has been changed as suggested.

P9. ‘Moreover, the already observed QoL improvements are impossibly caused by regression to the mean alone’, should be ‘it is most unlikely that regression to the mean accounts for all the QoL improvements that we have described’.

Authors: this has been changed as suggested.

Conclusion: ‘These effects maintain for as long as 8 years’ should be ‘These effects were maintained for eight years.’

Authors: this has been changed as suggested.

Table 5 ‘agee’ should be ‘agree’

Authors: this has been changed as suggested.
Reviewer: Wayne B Jonas  
Reviewer's report:  
This is a clearly written, straight forward, long-term observational trial of homeopathic treatment for a mixed group of chronically ill patients.  
Major Compulsory Revisions:  
1. The findings are interesting, but the article definitely needs some statistical evaluation. The primary reason for this is that there are no diagnostic restrictions and there are significant follow-up differences. Of the 3981 individuals or 3677 who were initially contacted, approximately 2722 were followed-up. Interestingly, 1/3 dropped out for reasons of improvement, 1/3 dropped out for reasons of no improvement, and the other 1/3 continued. Therefore, an accurate assessment of what homeopathic treatment was on the middle third that actually continued is needed.  

Authors: this follow-up after 8 years was based on patient data only and did not include physician's data. Due to the fact that in ‘classical’ homeopathy physicians sometimes don’t inform the patients about the name of the homeopathic remedy the necessary information would have been incomplete when using only patients data. In addition, this information would have been on very individual level, because patients in our study suffered from a broad range of diagnoses and received individual homeopathic treatment.  

Statistical evaluation of confounders is appropriately approached but this requires statistical evaluation by an expert, which I am not. Several questions that may be confounders here are the wide and unrestricted diagnostic categories, the clinical and personal relevance of the improvements over the long period of time, whether a 2-point clinically relevant evaluation is valid and why children were left out unless the term “adolescence” refers also to children.  

Authors:  
1.) The reviewer is right: the wide and unrestricted range of diagnoses might be a problem with interpreting the results. But, this only applies if one takes a conventional point of view. From a homeopathic point of view these disease categories are (more or less) meaningless. Thus, our evaluation is appropriate from the homeopathic point of view. Moreover, we tried to incorporate the conventional point of view when searching for predictive factors. Interestingly, only few diagnoses turned out to be predictive for treatment success. This might be taken as an indicator that diagnoses is not that much a confounder as has been hypothesised by the reviewer.  
We added a respective sentence to the discussion section (page 10).  
2.) A 2-point improvement in the NRS can be expected to be clinically relevant, because it approximately represents the improvement of one standard deviation at baseline. We added a respective sentence to the statistics section 2.4 (page 6, 4th paragraph).  
Moreover, to provide information about the overall size of the effect on the NRS we calculated standardised changes (sometimes also called effect sizes according to Cohen.) All effect sizes for changes on the NRS were large (page section 3.3.).  
3.) we used the term ‘adolescents’ for all patients < 16 years of age at baseline (who were 10 years or older at the follow-up). This has now been changed to ‘children’.
Of importance is that 41% of the population apparently used other CAM approaches and so it is difficult to say that this was due to homeopathic treatment.

    Authors: we have now added the use of other CAM approaches as a limitation in the discussion section: ‘As patients were allowed to use conventional therapies and other complementary therapies during the study period, the observed improvements cannot be attributed to homeopathic treatment alone.’ (see page 10 para 2).

Minor Essential Revisions:
1. There are minor English corrections that need to be made. Second paragraph, line 7: “In” should be used instead of “Of”

    Authors: this was changed as suggested.

2. Page 1, paragraph 3: “Little data” is the best term

    Authors: this was changed as suggested.

3. Page 2, paragraph 1, line 2: “recruitment” should be used here

    Authors: this was changed as suggested.

4. Page 2: does “adolescence” also include children and to what age does this occur?

    Authors: this point was addressed by all reviewers and we have changed ‘adolescents’ to ‘children’ according to the suggestion of both the other reviewers.

5. Page 5: it is unclear what is grouped in the regression analysis in the evaluation of potential confounders

    Authors: We added a respective paragraph to the statistics sections 2.4 (page 6, 4th paragraph)

Discretionary Revisions:
1. It would be good to read through the manuscript to correct the English grammar.

    Authors: the paper has now been checked and revised by a native English speaker.