Reviewer's report

Title: Homeopathy for Depression: a randomized, partially double-blind, placebo controlled, four armed study DEP-HOM

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Reviewer: George Lewith

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Thank you for asking me to read this fascinating paper which I think addresses a vitally important issue in homeopathy: is it the consultation or the remedy that appears to produce the outcome or a combination of both?

I think in general this trial design is excellent but there are two major issues which leave me with some quite substantial concerns.

1. The type of homeopathy used. The majority of individuals who prescribe classical homeopathy in Western Europe would not tend to start by using LM or Q potencies. In the majority of instances, in my experience, the treatment of depression by homeopathy is based on the appropriate use of 30C, 200C and sometimes 1M potencies. This study appears to be based on one preliminary study carried out in Brazil and, as a consequence, does not reflect the reality of the day to day practice of homeopathy in Europe. Many of the clinical trials published within the field of homeopathy have adopted non-standardised methodology for conditions which are rarely treated by homeopaths in clinical practice. Depression and anxiety are commonly treated, but the authors would need to provide a much more convincing argument that the particular potencies they've chosen would be part of the standard management of anxiety and depression within a homeopathic context.

The second issue relating to this is the very limited information given about the type of homeopathic encounter that will be used in this study. The introduction suggests that the Brazilian study assessed homeopathy as "a whole system". Without knowing very much about the consultation approaches that will be used (the authors state they don't want to compromise blinding), it is difficult to know whether real homeopathy will be delivered in a way that is generalisable to the practice of homeopathy in Europe.

2. The Homeopathic Consultation. The homeopathic consultation in itself is likely to be a vital component of the effectiveness of homeopathy in this condition. It is independently a very powerful therapeutic interaction.

3. The nature and effect of the consultation. Because so little information is provided about the consultation itself, it is very difficult to know whether this will be a convincing generalisable and appropriate intervention. It appears that the homeopathic "diagnosis" will be made by one skilled physician based on answers to relatively standardised questionnaires. Have these questionnaires been piloted? How valid are they? Have other homeopaths looked at the
questionnaires and are they generalisable to the very detailed nature of homeopathic practice within Europe?

Given that the homeopathic questionnaires and case histories will be vital, how convincing are the two different types of homeopathic consultation to the patient? Does belief influence outcome? Is there equipoise among both the patients and the practitioners with respect to this method of delivering homeopathy and if there is not, won't this give subtle messages to the patients which may serve to confound and bias the trial? This whole study revolves around the validity and generalisability of the consultation techniques used and yet we are given very little information about this absolutely vital component. Furthermore, the effect of the component and its credibility is poorly evaluated. There are no outcomes relating to empathy or credibility, simply to depression and general well-being.

The statistics, sample size calculation, blinding and randomisation appear to me to be described well and represent a thorough, competent and rigorous understanding of high quality clinical trial methodology as one would expect from these authors. There are, however, fundamental flaws with the design as it has been presented (it may well be much more thoughtful but critical information is not available to the reviewer).

At the moment I think this study has fundamental problems in relation to its generalisability, the very nature of the homeopathic consultations and the mechanisms for evaluating outcome that may be related to prior conditions, equipoise and the subtle interactions that may occur within the consultation and which may help to explain the outcome. It's an interesting trial protocol but one that I think is going to be far more complex to interpret than the authors might suggest.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.