Author's response to reviews

**Title:** Bach Flower Remedies for psychological problems and pain: a systematic review

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**Author's response to reviews:** see over
To the editors,

Thank you for the opportunity to resubmit our manuscript to the BMC Complementary and Alternative Medicine. We greatly appreciated the insightful comments of the reviewers. We have attached a summary below of how the revised manuscript addresses the comments and suggestions of the reviewers. (Our comments in **bold & italic** script)

Please don’t hesitate to contact me if you have any further questions.

Sincerely,

Kylie Thaler
Reviewer’s report #1

Title: Bach Flower Remedies for psychological problems and pain: a systematic review

Version: 1 Date: 2 February 2009

Reviewer: Arndt Büssing

Reviewer’s report:

The systematic review of Thaler et al entitled “Bach Flower Remedies for psychological problems and pain: a systematic review” included prospective studies with a control group for efficacy analysis, and also retrospective, observational studies for safety analyses. The authors identified 5 RCTs and 2 other studies. They found no overall benefit for the Bach Flowers over placebo; moreover, as they cited “We conclude that BFRs are probably safe but not more efficacious than a placebo intervention for examination anxiety, anxiety, ADHD, stress, or pain.”

I am not really surprised that the Bach Flower Remedies are not more effective as compared to placebos, indicating unspecific effects in terms of high patients’ expectations – and thus may be ‘unspecifically (in-)effective’ particularly in cases of psychological problems and stress.

Taken together, the review provides useful information which are worth to be published.

Some details:

1. Beyond the description of “studies with a fatal flaw in one or more categories” described, are there hints of a publication bias (excluding negative rather than indifferent results)?

We have included references to possible publication and retrieval bias in the discussion:

“Because the evidence was insufficient to be pooled we did not conduct any formal statistical tests such as funnel plots or Kendall’s test to assess publication bias. We searched clinical trials registries and could not detect any studies that were registered but have not been published. Nevertheless, publication bias is always major threat to systematic reviews. Similarly, retrieval bias cannot be ruled out.”

2. Page 8: Please describe shortly the methodological limitations of the mentioned 3 studies.

The text has been changed to indicate the specific weaknesses of each study:

“The other two studies, one conducted in Germany [19], the other in the United Kingdom (UK) [20] enrolled fewer participants and both had a high risk of bias (inadequate randomization [19] or high loss to follow-up [20]).”
3. Page 9: The fact that BFRs reduced anxiety in the subgroup of students who demonstrated high levels of anxiety at the first measurement might not only be due to the suggested multiple testing, but could simply be a `regression to the mean´ effect.

This has been added to the text:

“However, this result should be interpreted with caution because subgroup analyses are prone to chance findings due to multiple testing, or alternatively “regression to the mean” may have occurred.[24] “

4. Page 11: Although I understand why you have excluded the study using the Yarrow Special Formula, which contains non-Bach flower essences, it would be interesting to sum up the results in contrast to the conventional BFR.

Reviewer 2 pointed out that neither of the studies for stress met our inclusion criteria, as they measured intermediate outcomes that did not meet our pre-defined inclusion criteria (patient-relevant outcomes). Nonetheless, we have briefly summarized the results of both of the studies in the text:

“Two randomized controlled trials from the same author examined the efficacy of BFRs in subjects under stress.[25, 26] We excluded both studies, as they did not meet our pre-specified inclusion criteria, however due to lack of evidence we summarize them briefly here. One study randomized the 24 participants to rescue remedy and Yarrow Special Formula, which contains non-Bach flower essences (Achillea millefolium, Achillea millefolium var. rubra, Achillea filipendulina, Arnica mollis, Echinacea purpurea).[26, 27] The subjects underwent “intense environmental stimulation by fluorescent lights and their accompanying electromagnetic fields”. The second study randomized 24 participants aged 18-67 to Five Flower Formula (Rescue Remedy) or placebo, and submitted the participants to a Paced Serial Arithmetic Task (PSAT).[25] Stress levels were determined by quantitative electroencephalography (qEEG), surface electromyography (sEMG), or hand temperature and skin conductance. None of these parameters meet our pre-specified outcome criteria (improvement of symptoms). Overall, there were no significant differences between the BFRs and placebo groups.”

5. It is less satisfying that the authors were unable to obtain some of the published studies, and thus did not “formally include” these studies. – This is a bias too.

This study by Cram was published in 2002 and included results on 12 moderately and 18 majorly depressed patients. The study would not have qualified for inclusion for efficacy, as it was a non-
controlled observational study of 30 participants. We have made further unsuccessful attempts to obtain the publication from the author of the 2002 systematic review (who included it) as well as from the journal and our journal-sourcing company in order to review the publication for potential safety information.

We were able to locate the full text of the preliminary findings of the study (in the 12 moderately depressed patients) and this publication revealed no information on adverse events.

We have adjusted our comments in the text to reflect this:

“We located one publication, titled “preliminary findings”, of an open time-series that compared one month of usual care followed by three months of usual care plus individualized flower essence therapy in 12 moderately depressed patients. This study was not controlled and included non-BFR essences and therefore we excluded it. Another study by the same author with the same design was included in a previous systematic review and reported as including 12 patients with moderate depression and 18 patients with major depression. Based on available information the study would not have met our inclusion criteria for efficacy (not controlled, non-BFR essences). Despite multiple attempts we were unable to locate the full text to confirm the exclusion. There was no safety information reported in the preliminary findings publication.”

6. o Regarding the discussion of methodological problems: There are at least some hints that patients (not healthy individuals) willing to be randomised are less active in the ‘process of recovery’ (I have tried to avoid the term ‘interested’).

Indeed there are many difficulties raised in the literature regarding CAM and EBM, and we have discussed some of the more relevant arguments in the discussion. We think that discussing this issue would be beyond the scope of this review.

7. o Maybe you should add some sentences on the unspecific (placebo) effects which could contribute to the discussion, particularly to explain the citation (page 15): “Bach flower practitioner argues that ‘qualities such as compassion, trust, empathy, and positive motivation can directly help to improve outcomes’”.

This has been added to the discussion:

“For example, one Bach flower practitioner argues that “qualities such as compassion, trust, empathy, and positive motivation can directly help to improve outcomes”. [8] Indeed, a recent survey of physicians demonstrated that many prescribe inert or minimally active pharmacological substances, presumably in order to “promote positive therapeutic expectations”. [33]”

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.
Reviewer's report #2

Title: Bach Flower Remedies for psychological problems and pain: a systematic review

Version: 1 Date: 5 February 2009

Reviewer: Harald Johan Hamre

Reviewer's report:

This is a systematic review comprising six studies (four placebo-controlled RCTs and two case series) of Bach Flower Remedies (BFR) for two clinical domains. Compared to a previous review from 2002 it adds at least four studies, published 2004-2007.

Major Compulsory Revisions

1. Background: Has a lengthy section on BFR, but the following is missing and could be relevant:
   Therapy setting (Who prescribes BFR? Self-treatment? Non-medical practitioners? Physicians?)
   Extent of use? Cost? Any relevant pre-clinical or observational data? Results of previous systematic reviews? Why was this review undertaken?

   We have added information regarding training and over-the-counter availability. Cost is also included.

   “Training as a Bach Flower Remedy practitioner is offered through the Bach Foundation in the UK and at other centres in Europe.[10, 11] The courses are designed for therapists in similar fields who would like to incorporate BFRs into their practice. BFRs are also available “over-the-counter” in some countries, and on-line through several websites.[12] One bottle of BFRs cost approximately £6 (€7 or US$10).”

2. Efficacy of BFRs for stress: Cram 2004 is included, but the only outcomes of this study cited in the present review are EMG, skin temperature and skin conductance. So apparently none of the outcomes specified in the eligibility criteria in Table 2 (pain reduction, improvement of symptoms, adverse events) were used in the study. If this is correct, the study should not be included in the review, although it might be mentioned in the Backgrounds section.

   We have formally excluded this study, however we briefly summarize the results in the text due to lack of evidence:

   “Two randomized controlled trials from the same author examined the efficacy of BFRs in subjects under stress.[25, 26] We excluded both studies, as they did not meet our pre-specified inclusion criteria, however due to lack of evidence we summarize them briefly here. One study randomized the 24 participants to rescue remedy and Yarrow Special Formula, which contains non-Bach flower essences (Achillea millefolium, Achillea millefolium var. rubra, Achillea filipendulina, Arnica mollis,
Echinacea purpurea).[26, 27] The subjects underwent “intense environmental stimulation by fluorescent lights and their accompanying electromagnetic fields”. The second study randomized 24 participants aged 18-67 to Five Flower Formula (Rescue Remedy) or placebo, and submitted the participants to a Paced Serial Arithmetic Task (PSAT).[25] Stress levels were determined by quantitative electroencephalography (qEEG), surface electromyography (sEMG), or hand temperature and skin conductance. None of these parameters meet our pre-specified outcome criteria (improvement of symptoms). Overall, there were no significant differences between the BFRs and placebo groups.”

3. Four times (Conclusions in Abstract, Summary of findings in Discussion, Comparison with existing literature in Discussion, Conclusions) the authors state "BFR are not efficacious," "evidence for lack of efficacy" and similar. Isn't rather a statement such as "no evidence of efficacy" or "no evidence of benefit compared to placebo" justified? Absence of evidence is not necessarily evidence of absence, and especially so in this review:

*We have changed the wording to reflect this*

*In the abstract:* “Our analysis of the four controlled trials of BFRs for examination anxiety and ADHD indicates that there is no evidence of benefit compared to a placebo intervention.”

*In the discussion:* “failed to demonstrate a benefit beyond the placebo effect”

*In the conclusion:* “Our review demonstrates that the currently available evidence indicates that BFRs are not more efficacious than a placebo intervention for psychological problems but are probably safe. Due to a lack of methodologically sound trials, there is a high level of uncertainty associated with this statement.”

4. The authors comment on the high risk of bias in the studies (dropout rates of 42.5% and 55%, n=10 in a study they excluded for other reasons but nevertheless described) which would seemingly not allow for any firm conclusion about lack of efficacy.

*We agree with this comment and have changed our text accordingly (see above).*

5. Moreover, although the authors refer to the discussion of suitability of CAM therapies for RCTs, they do not assess whether the RCTs were adequately designed to enable any effects of BFR, if present, to be demonstrated (risk of false-negative results): Were the indications appropriate for ordinary BFR practice? (E.g. experimentally induced anxiety in one study). Was the selection of individual BFR among the 38 herbs adequate regarding the symptoms treated? (Background section: "The ... patient is prescribed remedies... which should be individually tailored and adjusted during the course of therapy." Was this implemented in the studies?)
We have commented on the difficulties of using RCTs to evaluate BFRs and also on the specific weaknesses of the RCTs (lack of applicability) in the discussion, we have also added comments about the applicability of the trials to the section strengths and limitations of this review:

“All of the studies in this review used a pre-determined mixture of BFRs which does not correspond with their use in real practice. Furthermore, the anxiety states in several of the trials were experimentally induced, and may differ from typical anxiety as experienced by patients. The short period of BFR administration in several of the trials (ten minutes, three hours, one week) does not comply with the recommendations of BFR practitioners, though it may be typical of “over-the-counter” use.[4]"

6. Were the psychological symptoms and states allegedly affected by BFR (Table 1) reflected in the outcome measures used in the studies? Was the follow-up period adequate to assess clinically relevant effects? (Background section: "therapy ... typically over weeks to months". Table 3: Duration of treatment: 10 minutes, 3 hours, 7 days...)

We have commented on this in the discussion (see above).

Minor Essential Revisions

7. Methods/Study selection: 1st paragraph should probably read: "we included randomised controlled trials..."

We have adjusted the text to make this clear:

“we included randomized controlled trials as well as prospective, controlled observational studies”

8. Efficacy of BFRs for stress: One study was excluded because the intervention was not just a BFR but also a non-Bach flower remedy. However, this combination is not specified as an exclusion criterion in Table 2.

We have changed table 2 accordingly:

“Bach Flower Remedies only”
9. Discussion and Conclusion: Any clinical implications of these findings? Any concrete suggestions for future research? (Suggestions for clinical domains and outcomes? Individualised or fixed BFR therapy? Suggestions for designs, e.g. placebo control or pragmatic studies?)

This is an interesting point. We have added such a discussion to the conclusions section of the text:

“We recommend that future trials employ methods that minimize bias and confounding such as randomization and blinding; that trials are conducted with an adequate sample size to be able to detect effects with statistical significance; that attempts are made to minimize loss-to-follow-up; and that patient-relevant end-point parameters are analyzed. Furthermore, we think it appropriate and important for the applicability of the evidence that adequate flexibility in personalising BFR therapy and a suitable length of follow-up is allowed.”

Discretionary Revisions

10. Background, last paragraph: The present review is limited to two clinical domains. The authors mention a corresponding review from 2002 which, according to the title, was apparently not restricted to specific indications, and which comprised only four studies. Accordingly, a small number of studies would be expected also for the present review. It is therefore unclear why this review was limited to only two clinical domains.

It is methodologically necessary to define a narrow key question for a systematic review following the PICO-system. We restricted the population for our systematic review to “persons with psychological problems or pain” because these are the most common indications for Bach Flower Remedies.

Level of interest: An article whose findings are important to those with closely related research interests

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