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Research Article

# HOMEOPATHIC TREATMENT OF HEADACHES & MIGRAINE: A META-ANALYSIS OF THE RANDOMIZED CONTROLLED TRIALS

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**ABSTRACT**

Background: Homeopathy seems scientifically implausible and is the most controversial forms of CAM therapies. This review aims to summarize treatment effects of individualized homeopathy in headaches and migraine.

Methods: Relevant studies were identified by a comprehensive literature search in electronic databases, reference list of relevant papers, and contacts with experts. Randomized controlled trials comparing individualized homeopathic treatment strategy with placebo were eligible. Information on patients, methods, interventions, outcomes, and results was extracted in a standardized manner and quality was assessed using a checklist and scoring system. Trials providing sufficient data were pooled in a quantitative meta-analysis. Risk ratio above 1 indicated benefit. Bias effects were examined in funnel plot model.

Results: A total of four randomized placebo-controlled trials involving 390 patients were considered for the analysis. Methodological quality of the trials was variable. The combined risk ratio for the four studies entered into the meta-analysis was 1.58 (95% CI 0.8 to 3.1) [when corrected for publication bias it becomes 0.98 (0.5, 1.9), i.e. negative], showing positive trend, but no statistically significant difference in favor of homeopathy.

Conclusion: The results of our meta-analysis are not compatible with the notion that homeopathy has significant effect beyond placebo. However, the evidences are not convincing because of methodological inconsistencies and are too insufficient to arrive at a definite conclusion. Further replications are warranted provided the trials are rigorous and systematic.

Systematic review registration number: CRD42013004714; date May 29, 2013 [PROSPERO]

**Keywords:** Homeopathy, headache, meta-analysis, migraine, randomized controlled trials, systematic review

## INTRODUCTION

**Rationale:** Homeopathy seems scientifically implausible [1], but has widespread use [2]. It is popular, but highly controversial [3]. Popularity does not, of course, prove efficacy [4]. No conclusive evidence exists that highly diluted homeopathic remedies are different from placebos, and the benefits the patients experience, are claimed to be due to non-specific treatment effects [4]. The Lancet meta-analysis of 1997 concluded that "the clinical effects of homeopathy are not completely due to placebo" [2], while another meta-analysis published in the same journal in 2005, concluded that "the clinical effects of homeopathy are placebo effects" [3]. After a meta-analysis of randomized trials of individualized homeopathy versus placebo, Linde et al arrived at a conclusion that homeopathy had an effect over placebo; however, they also admitted that the evidence was not convincing because of methodological shortcomings and inconsistencies [5]. Other meta-analyses performed by the European Commission and Cucherat M et al yielded similar results [6,7]. A systemic review of the 17 reviews conducted by Ernst E in 2002 concluded that "the best clinical evidence for homeopathy available till date does not warrant positive recommendations of its use in clinical practice" [8]. A systematic review of Cochrane studies in homeopathy by the same author in 2010 arrived again at a negative conclusion that "homeopathic medicines are unlikely to have any clinical effect beyond placebo" [9]. Re-analyzing their own data, Linde et al concluded that 'there was clear evidence that studies with better methodological quality tended to yield less positive results' [10]. Proponents of homeopathy argued that systematic reviews that fail to generate positive conclusions about homeopathy are biased [11]. They point to observational studies to suggest that homeopathy is effective [12]. A positive tilt in favor of homeopathy could not be eliminated even with the strictest criteria devised [13]. Many patients swear by homeopathy and homeopaths insist they witness therapeutic success everyday of their professional lives [14]. However, again these positive outcomes of observational studies have been ascribed to non-specific effects (e.g. the empathic and lengthy consultation typical of homeopathic services) [9,15]. Even, 'homeopathic aggravations', one of the main axioms of homeopathy, have been scrutinized in RCTs to occur infrequently in the verum than in the control group [16].

World Health Organization (WHO) report on homeopathy concluded that "a growing scientific evidence profile…suggests the effectiveness of homeopathy"; however, in the light of existing clinical evidences, this statement seemed to be perplexing and required correction [4]. The notion of a yet-to-be-discovered scientific law to 'explain' homeopathy amounts only to ad hoc speculation and thereby makes its use ethically unacceptable [17]. Both the scientific and non-scientific worlds are in almost perfect equipoise, with the high-quality meta-analyses evenly divided between showing that homeopathy is and is not placebo [13,18].

Migraine comprises a complex constellation of symptoms, affecting the nervous system, the gastro-intestinal tract and the vascular system. Though has much to offer and well-tolerated, it seems pointless to suggest prolonged conventional prophylactic approaches that require daily adherence in intermittent migraine attacks. A number of complementary and alternative medicine (CAM) approaches including homeopathy have been suggested in the management of this condition. However, as evidences from RCTs remain inconclusive, the use of homeopathy in migraine is largely the product of descriptive uncontrolled observations over the previous 200 years; some of recent remarkable ones are identified in this article [19]. A review by Ernst E in 1999 concluded that the methodological quality of the RCTs conducted on migraine was variable, but on average, satisfactory. Surprisingly, methodologically stronger trials do not support the notion that homeopathic remedies were effective and homeopathy has any effect beyond placebo effect [20].

So it would be 'very tempting' to lump all the contrasting results of several reasonably well-performed studies all together and take away the message that, on the whole, homeopathy is not effective in headaches and migraine [21].

**Objectives:** The objective of this systematic review and meta-analysis is to evaluate whether there is any evidence that homeopathy produced different effect beyond placebo in treatment of headaches and migraine in randomized controlled trials (RCTs).

**METHODS**

**Protocol & Registration:** A specific protocol (02/2013-14/CRU(H)/Slg/MTA/SS; verson 1.0, date May 25, 2013) was developed for conducting this systematic review and meta-analysis. The review was registered vide CRD42013004714, date May 29, 2013 with the PROSPERO International prospective register of systematic reviews, Center for Reviews and Dissemination, the University of York, National Institute of Health Research, York, UK. PRISMA guidelines [22] were followed in structuring of this review.

**Eligibility criteria:** Trials were eligible for this review if (1) they compared individualized (classic) homeopathy applied for preventive or treatment of headache with placebo; (2) allocation to homeopathy and control was randomized; (3) if there was a clear statement that the trial was double-blind making an unbiased method of allocation likely; (4) a complete, accessible, peer-reviewed, research journal paper was available in English language and published between 1950 and 2013. Eligibility was assessed by the reviewers.

**Search strategy:** Different electronic bibliographic databases like MEDLINE (via PubMed), Cochrane, Google Scholar, EMBASE (Elsevier), AMED (British Library), CCRH (India), CINAHL (EBSCO Publishing, Ovid Technologies, ProQuest), CISCOM (RCCM, London), CAM (University of Maryland, School of Medicine), HomInform (Glasgow Homeopathic Hospital), LILACS (Virtual Health Library, Brasil), MANTIS (ChiroAccess), and SIGLE (Europe) were searched for relevant literature.

**Study selection:** Only prospective, randomized, double-blind controlled studies with clearly defined pre-determined outcomes and peer-reviewed published research journal literature in English language were included.

**Data collection process:** A data extraction form was designed and tested by the readers. For each trial, main characteristics and results were extracted independently by the two reviewers. Inter-rater reliability of methodological scoring by the two independent reviewers was tested using Spearman's rank-order correlation coefficient test.

**Data items:** Data were extracted on the following grounds: methods (allocation to group, blinding, concealment of allocation, selection bias after allocation, and duration of observation), patients (number included/analyzed, condition treated, demographics, setting), intervention (homeopathic intervention, comparator/control), results (overall assessment, and number of patients assessed globally as improved), and three scoring indices – Jadad scoring index [23] (maximum score 5; 3 items; Yes: 1/No: 0), an internal validity scoring index as used by Linde et al [2,5] (maximum score 6; 6 items; Yes: 1/No: 0), and a methodological quality index (MQI; 20 items; Likert scale – Yes: 1/No: 0/Not applicable) scoring percentage, as used by Owen JM et al [24].

**Summary measures:** Apart from the descriptive summary deduced from each study using the standardized data extraction form, risk ratio and the respective 95% confidence interval for each study was calculated. Then a pooled random effects estimate was calculated for all studies. Other effect size measures were also calculated. The statistical calculations were performed using the Comprehensive Meta Analysis (CMA) software by BioStat (UK), version 2.0. Risk ratios were computed such that a result greater than one indicates greater effectiveness of homeopathic therapy compared with placebo. It was used as the measure of effect in the overall comparison test of this meta-analysis as a satisfactory metric to combine across trials with discrete outcomes using random effect models. The random effect method is more appropriate because the treatments and conditions in these studies are expected to be statistically heterogenous even though all trials met the specific criteria necessary for answering the study hypothesis.

**Additional analyses:** No sensitivity or sub-group analyses were planned to perform due to limited number of conducted trials.

**RESULTS**

**Study selection**: We identified different papers on homeopathy in headaches and migraine. Seven observational studies were identified; four considered only homeopathy [25-28], and three others included homeopathy as one CAM therapies [29-31]. Four RCTs were conducted [32-35] and a protocol was found suggesting appropriate methods to use individualized homeopathy in treatment of headaches [36]. Besides, seven systematic reviews were found [19-21,24,37-39]. A total of different five meta-analyses were identified which incorporated some (not all) of the RCTs mentioned [2,3,5-7]. Only the RCTs were considered for this meta-analysis.

**Study characteristics:** An overview of the patients, methods, interventions and results of the four included trials is given in table 1. A total of 390 patients participated in the studies (median number n = 84.5, range 79 to 142). Three trials studied migraine and one included headaches of all types (tension, migraine etc.). All tested efficacy of individualized homeopathic therapy against placebo. However, in two studies, the choice of remedy and dosage seemed to be unrestricted; other two used pre-defined or available medicines, i.e. patients were included only if they matched the remedy picture of one of a preset range of remedies. No cross-over design was adopted in any of the studies as well as none mentioned to consider the trial as pilot. The trials were conducted in four different countries. The methodological quality and quality of reporting of the trials was variable. There were no obvious fundamental flaws that would automatically invalidate the findings. The study by Walach et al [33] in 1997, though yielding negative results for homeopathy, was found to be of the highest quality using any of the scoring indices (Table 1).

**Results of individual studies:** The study by Brigo B [32] in 1991 yielded the most positive result (RR=3.778) in favor of homeopathy; but suffered from improper reporting of randomization procedure, primary study objective, interventions adopted, and valid conclusion related directly to primary objective. The study also suffered from absence of unbiased (blinded) outcome assessor, confidence intervals, description of drop-outs, ITT analysis, and adjustment for multiple testing. Baseline data indicated that patients had probably also other headaches than migraine. The study by Walach et al [33] in 1997 was of the highest methodological quality; however lacked appropriate description of drop-outs. Striking difference in number of patients randomized to treatment and placebo was observed. Besides, mixture of different headache types resulted in high variability for a number of headache outcome measures. The most striking and quite uncommon feature of this study was a consensus method used by the investigators to ensure 'homeopathic quality' of prescriptions. The study by Whitmarsh et al [34] in 1997 inadequate description of drop-outs data, intervention, randomization procedure, blinding, confidence intervals and absence of ITT analysis, adjustment for multiple testing, and valid conclusion related to primary study objective. Differences between groups existed in spite of randomization at baseline. The study by Straumsheim et al [35] in 2000 also suffered from not mentioning CI, missing data, and ITT analysis and improper description of randomization procedure, blinding of outcome assessor, intervention procedure, primary objective, drop-outs, and correlated conclusion with primary study objective (Table 1).

Inter-rater reliability of different methodological qualities between the two reviewers was quite satisfactory for three studies – Straumsheim et al, 1997 (Spearman's $\rho$=0.733, P=0.000), Walach et al, 1997 (Spearman's $\rho$=0.793, P=0.000), and Whitmarsh et al, 1997 (Spearman's $\rho$=0.733, P=0.000), with the exception of the study by Brigo B, 1991 (Spearman's $\rho$=0.357, P=0.146).

**Synthesis of results:** Majority of the studies (three out of four, 75%) reported at least a trend in favor of the group getting homeopathic therapy. The overall meta-analysis confirmed the impression and yielded the pooled risk ratio (RR) of 1.58 (95% CI 0.8 to 3.1, Z=1.319, P=0.187 two-tailed, non-significant; Odds ratio 1.85; values >1 indicate results favoring homeopathy, <1 in favor of placebo)

(Figure 1). Other effect size measures also showed non-significant result (Table 2). Methodologically the best study (Walach et al, 1997) favored placebo over homeopathy with a RR of 0.857. The study by Brigo B in 1991 reported the most promising results in favor of homeopathy, but suffered from some methodological drawbacks. The $\chi^2$ test for heterogeneity ($\alpha$=0.05) was used to assess effect-size variance among trials.

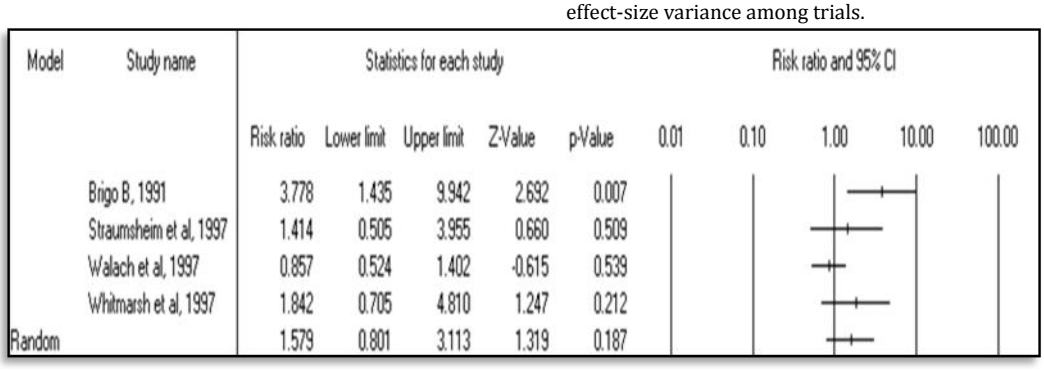


**Figure 1: Studies included in the meta-analysis**

**Table 1: Different effect size measures**

| Effect sizes | Value | Lower limit | Upper limit | Z value | P value |
|---|---|---|---|---|---|
| Odd's ratio | 1.849 | 0.8 | 4.5 | 1.355 | 0.175 |
| Log Odd's ratio | 0.615 | 0.3 | 1.5 | 1.355 | 0.175 |
| Log risk ratio | 0.457 | -0.2 | 1.1 | 1.319 | 0.187 |
| Risk difference | 0.110 | -0.0 | 0.3 | 1.395 | 0.163 |
| Standard difference in means | 0.339 | -0.2 | 0.8 | 1.355 | 0.715 |
| Hedge's g | 0.336 | -0.2 | 0.8 | 1.355 | 0.175 |
| Standard paired difference | 0.339 | -0.2 | 0.8 | 1.355 | 0.175 |
| Correlation | 0.167 | -0.1 | 0.4 | 1.369 | 0.171 |
| Fisher's Z | 0.169 | -0.1 | 0.4 | 1.369 | 0.171 |

**Publication bias:** The basic issue of publication bias is that not all completed studies are published, and the selection process is not random (hence the 'bias'). Rather, studies that report relatively large treatment effects are more likely to be submitted and/or accepted for publication than studies which report more modest treatment effects. Since the treatment effect estimated from a biased collection of studies would tend to overestimate the true treatment effect, it is important to assess the likely extent of the bias, and its potential impact on the conclusions. Publication bias makes interpretation of meta-analysis difficult because the trials observed may be only a selected subset (e.g. the most positive) of all trials. It can be estimated by plotting standard error on the vertical axis as a function of effect size on the horizontal axis. Large studies appear toward the top of the graph, and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph, and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values. Assuming that publication bias has occurred in our data set despite efforts to collect all studies, various tests were performed to evaluate its presence. The general non-parametric selection model applied to the four studies confirmed that there was significant publication bias (Cochran's Q statistics: $\chi^2$=7.95 at df=3, P=0.002 two-tailed; adjusted value 20.37, $I^2$=85%, 84.89 to 86.53, inconsistency substantial/considerable/high) and suggested the bias was primarily due to under-reporting of studies with statistically insignificant effects and with negative effects. Publication bias was also evident by funnel plot almost asymmetry, asymmetric distribution of the studies about the combined effect size, and Egger's regression test [intercept (B0) 3.590, 95% CI -3.6 to 10.8, SE=1.676, $t_2$=2.142, P=0.083 one-tailed]. The classic fail-safe N of Harris Cooper (file drawer analysis of Robert Rosenthal) [z=1.99212, 2-tailed P=0.04636 ($\alpha$=0.05)] and the Orwin fail-safe N tests were applied to test whether the entire observed effect was due to an artifact of bias.

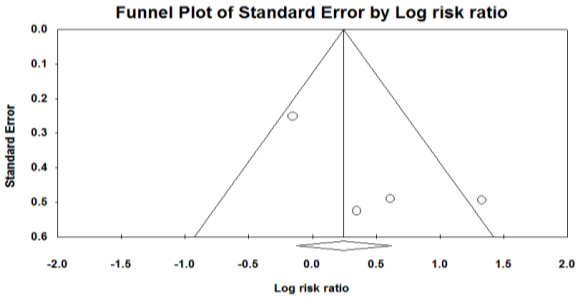


**Figure 2: Funnel plot of the homeopathic RCTs on headaches and migraine**

The classic fail-safe N is 1; i.e. one 'null' study would need to be located and included in order for the combined 2-tailed p-value to exceed 0.050; or there would be need to be 0.3 missing studies for every observed study for the effect to be nullified. The Orwin fail-safe N addresses the possibility that studies are missing from the analysis and that these studies, if included in the analysis, would shift the effect size toward the null. Calculated RR=1.278; criterion for trivial RR=1.000; mean RR in missing studies=1.000. Orwin's fail-safe N differs from the classic fail-safe N in two ways. First, the mean risk ratio in the new (missing) studies can be a value other than the nil value (currently, it is set to 1). Second, the criterion value is an effect size rather than a p-value. That is, the Orwin fail-safe N is the number of (missing) studies that, when added to the analysis, will move the combined risk ratio past a specified threshold (currently, 1).

**Table 2: Overview of randomized trials of classical homeopathy in headaches and migraine**

| Reference | Methods: 1. Allocation to groups 2. Blinding 3. Concealment of allocation 4. Selection bias after allocation 5. Duration of observation | Patients: 1. Number included/analyzed 2. Condition 3. Demographics 4. Setting | Interventions: 1. Homeopathy 2. Control | Results (homeopathy vs. control): 1. Overall assessment 2. Patients assessed globally as improved (n) | Jadad score (max=5), Internal validity score (max=6), MQI score % |
|---|---|---|---|---|---|
| Brigo B, 1991 | 1. Randomized | 1. 60/60 | 1. Eight pre-defined | 1. Significant | 3, 5, 38.5 |

| | | | | | |
|---|---|---|---|---|---|
| | 2. Double<br>3. ?<br>4. No drop-outs<br>5. 4 months | 2. Migraine<br>3. 83% female, mean age 39 years<br>4. Italy | remedies (patients included only if similimum was among these eight) in 30cH, four doses at 2-weeks intervals<br>2. Placebo | positive result in favour of homeopathy<br>2. 24/30 (80%) vs. 4/30 (13%), P<0.001 | |
| Walach et al, 1997 | 1. Randomized<br>2. Double<br>3. Independent person (notary)<br>4. None (ITT analysis)<br>5. 3 months | 1. 98/92<br>2. Chronic headaches (tension, migraine)<br>3. 66% female, age 24-64 years<br>4. Germany | 1. Individualized similimum and dosage<br>2. Placebo | 1. Trend in favour of placebo<br>2. 25/61 (41%) vs. 19/37 (51%); slight decrease of headache frequency and medication use in both groups | 5, 6, 64.3 |
| Whitmarsh et al, 1997 | 1. Randomized<br>2. Double<br>3. ?<br>4. None<br>5. 4 months | 1. 63/60<br>2. Migraine<br>3. 92% female, age 19-59 years<br>4. UK | 1. Eleven pre-defined remedies (patients included only if similimum was among these eleven) in 30cH, two tablets twice weekly<br>2. Placebo | 1. No statistically significant difference between groups<br>2. 11/32 (34%) vs. 5/31 (16%); slight improvement in both groups | 4, 4, 25 |
| Straumsheim et al, 2000 | 1. Randomized<br>2. Double<br>3. ?<br>4. Unlikely<br>5. 4 months | 1. 73/68<br>2. Migraine<br>3. 82% female, age 28-65 years<br>4. Norway | 1. Individualized similimum (chosen from 60 available remedies) and individualized dosage<br>2. Placebo | 1. Similar outcomes in both groups<br>2. 8/35 (23%) vs. 5/33 (15%); similar decrease of attack frequency and medication use, intensity almost same as in baseline | 3, 5, 57.1 |

The classic case of publication bias is the case depicted by the funnel plot. Large studies tend to be included in the analysis regardless of their treatment effect whereas small studies are more likely to be included when they show a relatively large treatment effect. Under these circumstances there will be an inverse correlation between study size and effect size. Begg and Mazumdar suggested that this correlation can serve as a test for publication bias. Concretely, they suggest that we compute the rank order correlation (Kendall's tau b) between the treatment effect and the standard error (which is driven primarily by sample size). A significant correlation suggests that bias exists but does not directly address the implications of this bias. Conversely, a non-significant correlation may be due to low statistical power, and cannot be taken as evidence that bias is absent. In this case Kendall's tau b (corrected for ties, if any) is 0.167, Z=0.339; 2-tailed P value 0.734 (based on continuity-corrected normal approximation).

Duval and Tweedie's trim and fill method imputes the missing studies in the funnel plot, analyzes them, and recomputes the

combined effect. The method initially trims the asymmetric studies from the right-hand side to locate the unbiased effect (in an iterative procedure), and then fills the plot by re-inserting the trimmed studies on the right as well as their imputed counterparts to the left the mean effect. Under the random effects model, the point estimate and 95% confidence interval for the combined studies is 1.579 (0.8 to 3.1). Using Trim and Fill, the Cochran's Q adjusted point estimate of risk ratio becomes 0.983 (95% CI of 0.5 to 1.9). Thus correction for publication bias decreases the RR by 37.75% and again remains statistically insignificant.

**DISCUSSION& CONCLUSION**

**Summary of evidence:** A total of four RCTs on headaches and migraine were included in our meta-analysis. The study by Brigo B yielded the most positive results favoring homeopathy, but methodologically was the poorest of all. On the contrary, methodologically the highest scoring trial by Walach et al revealed negative outcomes for homeopathy. The overall meta-analysis produced a pooled risk ratio of 1.58 (95% CI 0.8 to 3.1), though favoring homeopathy, yet statistically insignificant (P=0.187). Asymmetry was suspected on account of asymmetry of funnel plot. Cocharn's Q statistic was applied to test the presence of heterogeneity, if any, among the studies considered in the analysis. It showed significant heterogeneity ($\chi_3^2$=7.95, P=0.002). The measure of inconsistency was high ($I^2$=85%, 95% CI 84.89 to 86.53%). When corrected for publication bias, RR became 0.98 (95% CI 0.5 to 1.9), i.e. negative result for homeopathy. Finally it can be concluded that evidence is still insufficient to support or refute the use of homeopathy for managing headaches and migraine.

**Limitations:** Migraine has a notoriously high rate of placebo response. Any individual taking interest in migraine sufferings is likely to demonstrate some therapeutic improvement by virtue of apparent interest. However, CAM approaches including homeopathy can demonstrate clinical results clearly [19]. The mechanism by which homeopathy worked could be described as 'systemic'. However, the evidence base contains too few trials as well as trials resulting in contradictory findings which preclude any definitive summary [38].

The broad nature of the question asked in meta-analysis makes it difficult to use conventional meta-analysis techniques, like Peto or Mantel-Haenszel. These conventional methods estimate the size of treatment effects and then pool these estimates. They rely on the assumption that there is an underlying common treatment effect size across the combined trials. The pooled treatment effect size only has a clear meaning when all the trials included in the meta-analysis enrolled similar patients and endpoints. A frequent criticism of meta-analysis is that a common estimate is obtained for heterogeneous trials, combining apples, oranges and cabbages. As we have combined similar trials in terms of using individualized

homeopathic treatment in a single disease (headache and migraine) using similar end-point of global improvement in number of patients in either group, the assumption of a common underlying treatment effect size used in this meta-analytical technique seems to be appropriate. Combination of significance levels (sum of logs, sum of Z, weighted sum of Z, sum of t, mean Z, mean P, count test and logit procedure), as suggested by Cucherat M et al [7] would have been another valid statistical approach. The rational for this choice would be that all the trials would have explored the same broad question, i.e. "is homeopathic treatment efficacious?" If the results are interpreted with sufficient precaution and conservativeness (least optimistic results), this approach would provide a way to combine results from very dissimilar trials with differing outcomes and statistical tests.

Credible homeopathic research, both true to its philosophy and withstanding the scrutiny of reductionist experimental research as well, is an emerging field, though it is clearly in its infancy. After conducting the trials on headaches and migraine during 1991-2000, no trial has been reported till 2013, clearly indicating an acute dearth of homeopathic trials. Therefore, this study is restricted by chances of potential flaw or premature negative bias of making conclusion from the limited quantity of trials currently available in peer-reviewed literature. Inadequate reporting has inadvertently introduced a source of error in the trials. Generalizability of application of homeopathic therapy remains undecided as this review pertains to relative efficacy of homeopathy in headaches and migraine.

Another clear shortcoming is that extraction and assessments were made by two reviewers only, though inter-rater reliability was assessed and found to be satisfactory. The quality assessments and the results of the quantitative meta-analysis should be interpreted with caution. The methodological assessment, though explicit, involved subjective judgments. These quality scoring methods are useful in evaluating the robustness of results of a meta-analysis when corrected for possible sources of bias. However, for a more in-depth assessment, these scores are too crude, too formal and depend too much on reporting. To date, and given the often insufficient detail in reporting, a valid and reliable assessment of methodological quality remains elusive. In particular, the reliability of data collection can hardly be assessed unless it is guaranteed that Good Clinical Practice (GCP) guidelines have been followed.

It was not possible to assess the 'homeopathic' quality of trials. There is no consensus about what good quality homeopathy means. Several schools of homeopathy exist making it often difficult to obtain a consensus about what treatment should be given in a particular situation. It was therefore impossible to judge with certainty whether, in a given trial, the patients received the most suitable substances for their symptoms. Hence we did not try to assess the conformity of the homeopathic treatment given.

The trials measured a variety of outcomes. For practical reasons, we favored the outcomes used in the meta-analysis which could be dichotomized. Thus the results of some trials might not be well reflected in our meta-analysis, giving rise to an excessively negative interpretation trend. With these shortcomings in mind, the results of this quantitative analysis should only be seen as a crude indicator of the trend of the results in the single trials.

Although the development of methodologies for randomized clinical trials of individualized homeopathy is promising, some inherent problems are claimed to be obvious. Patients routinely seeking homeopathic care rarely agree to participate; consequently, the sample is not representative (which can be seen both as advantage and disadvantage). Patients in the placebo group also undergo homeopathic history taking that might contribute considerably to a possible treatment effect, decreasing the likelihood of identifying differences between the groups. However, this 'empathy' or consultation bias is nullified when applied equally to either group. Often, selection of correct remedy becomes difficult at once and/or change of remedy becomes required when clinical picture changes. In a double-blind trial, the homeopath is not sure if the responses, changes, or lack of responses are due to a failure to find the correct remedy, a symptoms shift, lack of efficacy or simply because the patients are in the placebo group. This problem can be solved by reporting any deterioration as 'adverse event' by the prescriber, and analyzing the data by finer differentiation as 'homeopathic aggravation', 'medicinal aggravation', or 'disease aggravation' by the analyst after unblinding of the code allocated at the end of the study. We also recommend serious randomized pilot studies before planning and conduct of any full-fledged randomized trial, so that major decisions are not based on empirical data. Also, replicating promising earlier studies independently seems a logical way both to reduce the risk of making relevant errors and to provide more convincing evidence for individualized homeopathy – if the promising results can be confirmed. Careful selection of headache subjects according to explicit inclusion and exclusion criteria following the IHS classification guidelines [40] should be employed. Researchers should be warned of being too optimistic both in terms of feasibility and results. Otherwise, skeptical readers will interpret existing negative replications as further evidence that homeopathy is merely placebo and that positive findings are likely to be irreproducible (and, therefore, artifacts). From a purely clinical point of view, if the result of a trial is not able to be replicated by other clinicians in other centers or countries, it has little practical value and is even less likely to be accepted as saying something that approaches the truth. Thus lack of reproducibility of trials seems to be one of the major problems of homeopathic research. Alongside, it is likely that case studies and observational studies are also realistic tools and can provide preliminary evidence and insight into structures and processes. Pragmatic research is another promising way to critically evaluate homeopathic therapy with other forms of therapies and is gradually becoming widespread. Sufficiently large sample sizes are a precondition for conclusive results. Guidelines and expert recommendations on the conduct of clinical trials with limited resource and infrastructure as in individualized homeopathy are available [41-46]. We should stay close to real homeopathic practice and should try to produce robust results with methodological rigor and thereby show the true effects of this therapy.

## CONCLUSIONS

Given the insufficient quality and quantity of research literature, this review concludes that there is no clear evidence that homeopathy is superior to placebo in treatment of headaches and migraine. Further confirmatory independent replications are warranted provided the trials are rigorous and systematic.

## CONFLICT OF INTEREST STATEMENT

None declared.

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