

Clinical research in homeopathy: systematic reviews and randomized clinical trials

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Abstract

Background: Systematic reviews and randomized clinical trials (RCT) are considered to have the highest level of evidence. Aim: To perform a descriptive review of systematic reviews and RCT on the effectiveness and efficacy of homeopathy. Methods: Data from the report published by Liga Medicorum Homeopathica Internationalis (LMHI) in 2014 were updated by means on a search conducted in database PubMed. Results: 7 systematic reviews with meta-analysis were located, 6 of them concluded that the effects of homeopathy are not compatible with placebo effect; only 1 systematic review arrived to the opposite conclusion, but was severely criticized due to methodological flaws. A total of 19 RCT were published along the analyzed period; 84.2% had at least one positive outcome. Conclusions: Based on the available evidences of the highest level it is not possible to assert that the effects of homeopathic are exclusively placebo effect. On the opposite, specific effects were detected in several studies.

Keywords

Homeopathy; Efficacy; Effectiveness; Systematic review; Meta-analysis; Randomized controlled trials

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Introduction

While we were writing the present article, homeopathy was officially equated to conventional medicine in Switzerland in the terms of mandatory coverage. This decision was made after a 6-year test period (2012-2017) of inclusion of various modalities of complementary and alternative medicine (CAM) upon the population's demand, following demonstration of their effectiveness. Indeed, 2/3 of the Swiss population voted to include CAM in the list of health care procedures paid by the government. However, the final decision had to take into consideration the objections raised by conventional medicine, according to which CAM is inefficacious and harmful [1].

The investigators entrusted the assessment of homeopathy within the Swiss government Complementary Medicine Evaluation Program (PEK) asked themselves: how to produce an answer satisfactory to society and at the same time complying with the requirements of scientific medicine? The answer was: through health technology assessment (HTA), which does not merely assess the efficacy of an intervention, as systematic reviews and meta-analyses do, but also and more especially its effectiveness in the real world, adequacy, safety and economy, i.e., a quite broader and information-rich scope. The conclusion was that there is sufficient evidence for preclinical (experimental) effectiveness and clinical efficacy of homeopathy, as well as for its safety and economy compared to conventional medicine [1].

It is safe to assume that this type of approach is the most judicious for assessment of health interventions. Yet, these studies demand much time (the just mentioned Swiss study needed 5 year preparation and 2-year execution) and funding, which is not easily available. Therefore, in their stead, investigators seek for evidences of effectiveness and clinical efficacy, for which various grading systems were developed. One of the most widely used among such systems, the one formulated by Oxford Centre for Evidence-based Medicine, establishes 5 levels of evidence (with some sublevels) being systematic reviews of randomized clinical trials (RCT) and individual RCT considered as the highest level [2]. Thus being, in the present study we analyzed systematic reviews and individual RCT to establish whether the clinical effects of homeopathy represent or not placebo effect.

The reference source was a previous analysis of such studies published until mid-2014 conducted by Liga Medicorum Homeopathica Internationalis (LMHI) [3]. We updated the data to include the ones published from mid-2014 to the present time through a search in database PubMed without language restrictions. The search was restricted to database PubMed to facilitate the access of the data to readers. For the same reason we did not consider less available sources, such as meeting proceedings and dissertations, among others.

Systematic reviews with meta-analysis

Up to this moment, 1,015 records are included in database CORE-Hom/HRI [4] corresponding to studies of any nature of homeopathic outcomes from RCT to observational studies. A large number of such studies were subjected to systematic

review with meta-analysis. From 1991 to the present time 7 large systematic reviews with meta-analysis were conducted, the results of which are described next.

The first systematic review was performed by Kleijnen et al. in 1991 [5]. These authors analyzed RCT published in any language assessing outcomes of homeopathic treatment in which participants were randomly allocated to groups intervention (homeopathy) or placebo. The studies were also subjected to analysis of methodological quality (emphasizing large sample size; randomization; double blinding; adequate description of patients' characteristics; accurate description of intervention; relevant and well described effect measures; and data presentation in a way to allow readers to verify data and analyses).

The systematic search retrieved 107 studies described in 96 articles; the overall methodological quality of the studies was low. For this reason, the authors chose to analyze only the articles with better methodological quality (score $\geq 60/100$).

Fourteen studies tested classical homeopathy (individualized treatment), 18 applied one and the same homeopathic treatment to all patients with a comparable diagnosis, in 26 more than 1 medicine was prescribed to each patient, and 9 were on isopathy (use of the same agent that causes disease subjected to dilution and agitation).

While 42 studies did not include sufficient data for assessment and interpretation of outcomes, their heterogeneity did not allowed for combined analysis. These flaws notwithstanding, the authors inferred that the positive results indicated statistically significant difference relative to the main outcomes between the groups. Thus they concluded: "Evidence is to a large extent positive"; there was no publication bias, i.e., the journal chosen had no relationship with the outcomes; and finally **"The amount of positive evidence even among the best studies came as a surprise to us. Based on this evidence we would be ready to accept that homeopathy can be efficacious, if only the mechanism of action were more plausible"** (our emphasis).

In 1996 Boissel et al. [6] published a report addressed to the Commission of European Communities; the data were re-analyzed in 2007 [7]. This study consisted of a systematic review with meta-analysis of RCT on any disease published or not until June 1998. The authors located 118 records, from which 16 (representing 17 comparisons) were included for analysis for a total of 2,617 patients.

The results were synthesized through the combination of the p values of the primary outcomes of each individual study. For the 17 comparisons combined p was 0.000036, however, with reduction to non-statistically significant level ($p= 0.08$) when the studies of poorer quality were progressively excluded in sensitivity analysis. Yet the authors concluded **"There is some evidence that homeopathic treatments are more effective than placebo"** (our emphasis).

The following systematic review was performed by Linde et al. in 1997 [8]. These authors considered RCT with sufficient information, after data extraction, to calculate outcome rates in both groups, i.e., intervention and placebo. As in Kleijnen et al.'s study [5] also they included studies with classical homeopathy (single individualized medicine), medicine(s) for definite conditions (here designated as 'clinical homeopathy'), medicine combinations ('homeopathic complex formulas') and isopathy. The quality of studies was assessed by means of Jadad's scale (good quality: > 3) and a *ad hoc* scale (good quality: > 5).

Systematic search located 186 records, which were reduced to 89 after application of the inclusion/exclusion criteria. The studies, published from 1945 to 1995, had 118 participants, on average, and corresponded to 24 different clinical conditions; 37% employed low potencies (1d to 8d, 1c to 4c), 22% medium potencies (9d to 23d, 5c to 11c) and 37% high dilutions (over 23d or 11c). 29% of the studies had high quality (Jadad's and *ad hoc* scales); 45% studies scored ≥ 3 on Jadad's scale and 38% \geq on the *ad hoc* scale.

The global odds ratio (OR) was 2.45 favorable to homeopathy (95% confidence interval – 95%CI: 2.05-2.93). To remind briefly, OR= 1 means that exposure does not influence the outcome odds, OR > 1 means that exposure is associated with higher outcome odds, and OR < 1 means that exposure is associated with lower outcome odds [9]. In turn, OR for the studies with high quality was 1.66 (95%CI: 1.33-2.08), being the results patently favorable to homeopathy. In addition neither sensitivity nor subgroup analysis eliminated the statistical significance of the results. OR of the studies with positive results decreased by 27% when publication bias was considered, however, once again without loss of statistical significance.

The authors concluded that **“The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo”** (our emphasis) and that “We believe that a serious effort to research homeopathy is clearly warranted despite its implausibility”.

The following year Line and Melchart published a new review [10] which exclusively included individualized homeopathic studies. The authors considered randomized or quasi-randomized clinical trials comparing individualized homeopathic treatment to placebo, no treatment or other treatment. The quality of studies was assessed through a checklist and 2 scores. Studies with sufficient data were jointly subjected to quantitative meta-analysis.

This review analyzed 32 articles that met the inclusion criteria; 28 involved comparison to placebo, 2 to other treatment and 2 to both, for a total of 1,778 patients and variable quality. Among the placebo-controlled studies, 19 had sufficient data for inclusion in meta-analysis, which indicated that homeopathy was more effective than placebo (pooled rate ratio 1.62; 95%CI: 1.17-2.23). However, when analysis was restricted to the studies with better quality significant effect was not detected. The authors concluded **“The results of the available randomized trials suggest that individualized homeopathy has an effect over placebo”** (our emphasis).

In 2005 was published a meta-analysis performed by Shang et al. [11] which analyzed 110 homeopathic RCT (44% clinical homeopathy, 32% complex formulas, 16% classical homeopathy, 1% isopathy and 1 non-classifiable study) matched to 110 conventional medicine RCT per diagnostic category (diseases). On the first and main analysis, which included all the selected RCT, more homeopathic studies had high methodological quality (19% vs. 8%) and in both groups the studies with smaller samples and poorer methodological quality reported more beneficial therapeutic effects. Heterogeneity was lower among the homeopathic RCT, which could not be attributed to chance. Bias was similar in both groups.

Upon restricting analysis to the studies with better quality - larger sample size, being 8 homeopathic and 6 conventional medicine studies, OR was 0.88 (95%CI: 0.65-1.19) for the homeopathic RCTs and 0.58 (95%CI: 0.39-0.85) for the conventional medicine

ones – in this case, $OR < 1$ was defined as beneficial effect. Considering the presence of bias, the authors concluded “there was weak evidence for a specific effect of homeopathic remedies, but strong evidence for specific effects of conventional interventions. **This finding is compatible with the notion that the clinical effects of homeopathy are placebo effects**” (our emphasis).

The last 2 meta-analyses were chaired by Mathie in 2014 and 2017 [12,13] comprising RCT with individualized and non-individualized homeopathy, respectively, for any clinical condition. The former analyzed 32 RCT for 24 different clinical conditions, and the latter 75 RCT for 48 different conditions, with median $n = 43.5$ and $n = 62.5$ patients per study, respectively. In both cases, studies with high methodological quality were very few, just 3 in each review.

In the 2014 review, 22 RCT had data extractable for meta-analysis. Pooled OR was 1.53 (95%CI: 1.22-1.91; $p < 0.01$) favorable to homeopathy. There was no evidence of publication bias. In analysis of the group of RCT with reliable evidence, pooled OR was 1.98 (95%CI: 1.16-3.38; $p = 0.013$). According to the authors, the results indicate that “**Medicines prescribed in individualized homeopathy may have small, specific treatment effects**” (our emphasis).

In the 2017 review, 54 RCT had data extractable for meta-analysis. The overall standardized mean difference (SMD) was -0.33 (95%CI: -0.44 to -0.21; $p < 0.001$) falling to 0.16 (95%CI: -0.31 to -0.02) following adjustment for publication bias. It is worth to observe that SMD is an effect measure used when several studies assess one same outcome, but in different ways, for which reason the results ought to be standardized on a uniform scale before they can be pooled [14]. When improvement is associated with lower scores on the outcome measure, $SMD < 0$ denotes how much efficacious the analyzed treatment is compared to placebo, and reciprocally $SMD > 0$ denotes how much less efficacious the analyzed treatment is compared to placebo [15].

Following adjustment for publication bias, the authors concluded that the results led to **rejection of the null hypothesis, i.e., that across the entire range of clinical conditions that have been researched, the main outcome of treatment using a non-individualized homeopathic medicine cannot be distinguished from that using placebo** (our emphasis). In subgroup analysis (RCT with the best quality) pooled SMD fell to a non-significant value, -0.18 (95%CI: -0.46 to 0.09), which indicates that **non-individualized homeopathy was not different from placebo on the basis of reliable evidence** (our emphasis).

A considerable number of reviews of homeopathy for specific clinical conditions were performed. One analysis of such studies up to mid-2014 was published by LMHI [3]. The reviews found favorable results for homeopathy in: upper airway infections and allergies, childhood diarrhea, influenza, postoperative ileus, rheumatic disorders, allergic rhinitis, vertigo and anxiety. This analysis is available online, readers might access it at <http://www.lmhi.org/downloads/articles/lmhi-sc-framework-2014-june-15-2015.pdf>. Next we updated the data from 2014 to the present time.

Boehm et al. [16] surveyed the literature on homeopathy for fibromyalgia and located 10 case reports, 3 observational studies, 1 non-randomized clinical trial and 4 RCT. The latter were subjected to meta-analysis, which found that homeopathy was effective to reduce the tender point count (SMD: -0.42; 95%CI: -0.78 to 0.05; $p = 0.03$), pain

intensity (SMD: -0.54; 95%CI: -0.97 to -0.10; $p= 0.02$) and fatigue (SMD: -0.47; 95%CI: -0.90 to -0.05; $p= 0.03$) compared to placebo. On those grounds the authors concluded there is **“sufficient basis for discussing the possible benefits of homeopathy for patients suffering from fibromyalgia syndrome”** (our emphasis).

Banerjee et al. [17] analyzed RCT assessing the effects of any modality of homeopathic treatment on allergic rhinitis published until December 2015. Primary outcomes were: improvement of symptoms and global quality of life score. The authors located 11 records, 6 corresponding to isopathy, which were not considered adequate for inclusion in meta-analysis. The overall quality of the studies was low; only 3 studies with variable quality were included for meta-analysis. **The results evidenced favorable results for homeopathy in the improvement of nasal** (relative risk – RR: 1.48; 95%CI: 1.24-1.77 and RR: 1.27; 95%CI: 1.10-1.46, respectively) **and eye** (RR: 1.55; 95%CI: 1.22-1.80 and RR: 1.37; 95%: 1.21-1.56) **symptoms at 2 and 4 weeks** (our emphasis). However, the authors observe that the low or uncertain methodological quality of the evidences demand caution upon drawing sound conclusions.

Interestingly, also the occurrence of adverse effects of homeopathic treatment was subjected to systematic review and meta-analysis. In 2016, Stub et al. [18] analyzed RCT published from 1995 to 2011. The authors located 41 studies, for a total of 6,055 patients; 39 studies were included for meta-analysis. Adverse effects were reported in 68% of the studies ($n= 28$) without significant difference compared to the control group (OR: 0.99; 95%CI: 0.86-1.14). In other words, as the authors stated, adverse effects are commonly reported in studies on homeopathy, being that **the proportion of patients with adverse effects is similar among the ones treated with homeopathy and conventional medicine** (our emphasis).

Recent randomized controlled trials

To complete the present summary description of clinical studies on homeopathy, we next describe RCT published from 2014 to the present time, and thus not included in the LMHI report (Table 1).

Table 1. Homeopathic RCT published from 2014 to the present time

Author/year	Model	Outcomes	Results
Teixeira et al., 2017 [19]	Estrogen 6cH, 18c, 24cH vs. placebo	Reduction of global and partial scores (VAS) of endometriosis-related pelvic pain, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and quality of life (SF-36)	POSITIVE Reduction of global score in group homeopathy ($p < 0.001$); reduction in partial scores for dysmenorrhea ($p < 0.001$), noncyclic pelvic pain ($p < 0.009$) and cyclic bowel pain ($p < 0.001$); group placebo did not show any improvement. Group homeopathy exhibited significant improvement on BDI and 3 SF-36 domains (physical pain, vitality and mental health); group placebo did not show any improvement

Sorrentino et al., 2017 [20]	<i>Arnica montana</i> 1000K vs. placebo	Blood/serum drainage volume, drainage duration, perceived pain and hematomas, days of treatment after total mastectomy for breast cancer	MIXED Reduced bleeding and seroma formation (p= 0.03); no difference in the remainder of outcomes
Chaiet et al., 2016 [21]	<i>Arnica montana</i> vs. placebo	Ecchymosis extension and intensity after rhinoplasty with	POSITIVE Intervention groups exhibited 16.2%, 39.2% and 20.4% reduction of ecchymosis extension on days 2/3, 7 and 9/10 after surgery, being statistically significant for day 7 (p= 0.097); lesion intensity increased 13.1% on day 1, followed by 10.9% and 36.3% reduction on days 7 and 9/10, being statistically significant for day 9/10 (p= 0.074)
Alizadeh Charanabi et al., 2016 [22]	Individualized homeopathy vs. placebo	Pain intensity (VAS) and quality of life (SF-36); use of conventional analgesics for moderate-to-severe menstrual pain	NEGATIVE All outcomes improved in both groups, without significant difference
Jacobs et al., 2016 [23]	Commercial homeopathic syrup vs. placebo, 3 days	Change in upper airway symptoms 1 h after intake; pooled score (nasal discharge, cough, congestion and sneezing) assessed twice/day along 3 days on a 4-point scale among children 2 to 5 years old	MIXED No difference in symptoms 1 hour after intake. Sneezing, cough and pooled score exhibited significant improvement in group homeopathy on the first 2 assessments
Vilhena et al., 2016 [24]	9 pre-selected homeopathic medicines vs. placebo	Prevention of excess weight gain during pregnancy among women with mental disorders	MIXED No difference in BMI at baseline and pregnancy week 40. 5 min Apgar significantly higher in group homeopathy
Pedrero-Escala et al., 2016 [25]	Adjuvant homeopathic formula vs. placebo, 3 months	Clinical progression (pneumatic otoscopy, tympanometry) of children (2 months to 12 years old) with otitis media with effusion treated with mucolytic agents and inhaled steroids	MIXED No difference in the proportion of cured cases or frequency of adverse effects. Incidence of acute respiratory disorders was lower in group homeopathy (p= 0.009)
van Haselen et al., 2016 [26]	On demand conventional symptomatic treatment vs. homeopathic formula (Influcid®) +	Cure of fever and upper respiratory symptoms and Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21), among children	POSITIVE Group homeopathy required less symptomatic medication. Symptoms cured significantly faster (p= 0.0001). Proportion of children without fever on day 3 was higher. Significant

	conventional treatment, 7 days		reduction on WURSS-21 score (p< 0.00011)
Siqueira et al., 2016 [27]	Isopathic formula vs. InluBio (H3N2 30x) vs. placebo	Number of URI episodes along 1 year among children 1 to 5 years old	POSITIVE Significant different between the 2 isopathy groups and placebo (p< 0.001). 30.5% of the children in group placebo exhibited 3 or more URI episodes/year vs. 1/year in group InluBio and none in group isopathic formula
Zafar et al., 2016 [28]	<i>Chamomilla</i> vs. pentazocine vs. placebo	Labor pain in healthy women	NEGATIVE No significant difference between the groups
Morris et al., 2016 [29]	Standard physical therapy vs. homeopathic formula + standard physical therapy, 6 weeks	Pain intensity (VAS); Oswestry Disability Index; lumbar spine range of motion; analgesics; patients from both genders, 45-75 years old, receiving physical therapy for osteoarthritis	MIXED Pain improvement, daily functioning and range of motion significantly better in group homeopathy. No difference in use of analgesics
Macias-Cortes et al., 2015 [30]	Individualized homeopathy vs. fluoxetine vs. placebo	Depression in peri- and postmenopausal women, Hamilton Rating Scale for Depression, Beck Depression Inventory (BDI), Greene scale, response rate (50% reduction from baseline score), remission rate after 6-week treatment	MIXED Homeopathy and fluoxetine improved the score on Hamilton scale compared to placebo. No treatment changed BDI score. Only homeopathy improved score on Green scale compared to placebo (p= 0.02); no difference in remission rate; response rate significantly higher in groups homeopathy and fluoxetine (p= 0.0)
Frass et al., 2015 [31]	Adjuvant individualized homeopathy	Overall state of health, subjective well-being in cancer patients under standard anticancer treatment	POSITIVE Significant improvement of overall state of health (p< 0.005) and subjective well-being (p< 0.001) in group homeopathy
Koley et al., 2015 [32]	Individualized homeopathy vs. placebo	3 VAS (pain, stiffness, function loss), score on Osteoarthritis Research Society International after 2-month treatment of patients with knee osteoarthritis	NEGATIVE Significant reduction of scores in both groups (p< 0.05) without difference between them
Peckham et al., 2014 [33]	Standard care vs. homeopathy + standard care vs. supportive listening + standard care	Severity of inflammatory bowel syndrome (IBS) after 26-week treatment	MIXED Interim ANCOVA adjusted for IBS severity, age and occupation did not detect difference; post-hoc test revealed significant difference favorable to homeopathy

			compared to standard care; 62.5% of patients in homeopathy arm exhibited clinically relevant changes on IBS severity score (vs. 25.0% in arm standard care alone)
Danno et al., 2014 [34]	<i>China rubra</i> 7cH + quinine vs. quinine alone; non-blind allocation	Frequency of quinine adverse effects in women with < 3 months pregnancy and malaria	POSITIVE Lower proportion of patients with adverse effects in <i>China rubra</i> group on days 0 and 6 (53.9% and 23.3%, respectively); the proportion of patients with adverse effects did not change in control group (58.9% and 82.5%); 72.4% of patients in group intervention and 97.2% of patients in control group reported at least 1 adverse effect (p< 0.0001)
Chand et al., 2014 [35]	Standard anti TB treatment + individualized homeopathy vs. standard anti TB treatment + placebo	Homeopathy as adjuvant for multidrug resistant pulmonary TB; sputum conversion, weight gain, ESR, Hb, chest x-ray	MIXED No difference in conversion rate; greater weight gain (p= 0.071), ERS reduction (p= 0.068) and Hb increase (p= 0.068) in group homeopathy; greater proportion of radiological improvement (p= 0.002); cure rate increased by 11.4%
Chauhan et al., 2014 [36]	Individualized homeopathy vs. placebo, 18 months	TSH and antithyroid antibodies (TOPAb) in children with subclinical hypothyroidism and autoimmune thyroiditis	POSITIVE Greater proportion of TSH and TOPAb return to normal values in group homeopathy (p< 0.006; p< 0.05); 8 children in placebo group (10.5%) progressed into clinical hypothyroidism
Malapane et al., 2014 [37]	Homeopathic formula vs. placebo, 6 days	Wong-Baker FACES Grading scale, changes in signs of symptoms, among children 6 to 12 years old with acute viral tonsillitis	POSITIVE Significant improvement in group homeopathy in: tonsillitis-related pain, pain on swallowing, pharyngeal erythema and inflammation, tonsil size

TB, tuberculosis; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; VAS, visual analog scale; BMI, body mass index; URI, upper respiratory infection; TSH, thyroid-stimulating hormone

Discussion

Six out of the 7 available meta-analyses are favorable to homeopathy, while only Shang et al.'s [11] attributed the clinical effects of homeopathy to placebo effect. Shang et al.'s study had disproportionate repercussion, leading to assert that the "end of homeopathy" had come [38]. Yet, that study was the target of hard criticism, which is reminded here briefly. For a detailed analysis of the methodological flaws of Shang et

al.'s review we recommend Eizayaga's paper [39] available in Portuguese and Spanish in this journal at <http://aph.org.br/revista/index.php/aph/article/view/262/327>.

Linde and Jonas [40] stressed 2 among various "fundamental problems" in the presentation and discussion of results. First, the authors did not report the excluded studies nor assessed the methodological quality and OR of all the RCT included in the study, as well as the 8 studies included in the final analysis. Then, considering the approach followed in pooled analysis, restriction to the larger studies led to false-negative results. In addition, since the final analysis was based on only 8 and 6 studies (possibly non-matched per disease) the outcome might be easily due to chance.

In turn, Walach et al. [41] point to the argument that small study bias impregnates any clinical study, which might represent a "mortal blow" to homeopathy, since the OR of the larger studies converge around zero. These authors again stress that the analyzed studies were not described, which is necessary to establish whether they were truly representative as stated by Shang et al. Contrariwise, the 6 studies with conventional interventions were carefully selected.

Fisher et al. [42] put the matching of the studies according to quality into question, as the methodological quality was better in the homeopathy studies. Then, Shang et al.'s conclusions were based on mere 8 and unknown clinical trials, which led Fisher et al. to ask what the results would have been were the 21 homeopathic studies with high quality to have been included. In addition, Dantas [43] stresses the fact that Shang et al.'s argument asserting that study size might be a more precise measurement of study quality than the standards assessment techniques is groundless.

Synthetically, the problems in Shang et al.'s meta-analysis might be summarized as follows, according to Eizayaga [39]: 1) biased grounds: homeopathy is implausible, and thus its results must have other causes; 2) study size is the determinant of study quality; 3) the effects detected in homeopathic RCT might be explained by a combination of methodological flaws and bias, which does not account for the results of conventional RCT; 4) arbitrary selection of studies, with major imbalance, which makes them non-comparable, in addition to including 3 conventional interventions that later on were banned by the Food and Drug Administration (USA); 5) arbitrary sub-selection in the final meta-analysis, while the initial criterion established by the authors (matched RCT) was dismissed; 6) when the authors finally communicated the 8 homeopathic RCT used, they were found not to be representative of homeopathy.

A total of 19 RCT on homeopathy published from 2014 to the present time were located in database PubMed. The single source available for comparison is a review from 2015 by Mathie et al. [44] which covered the period from 1995 to 2015 to compare it to the state of the art in 1994 [45].

The annual rate detected in the present review (5.43 studies/year) is smaller compared to Mathie et al.'s [22], 10-12/year, possibly because we restricted the search to database PubMed and only included controlled studies (placebo, no treatment or other treatment).

A little more than one-third of the studies tested individualized homeopathy (n= 7, 36.8%); the vast majority used non-individualized homeopathy/complex formulas, 1 study tested isopathy [27] and another semi-individualized homeopathy (pre-selection

of 9 medicines) [24]. In Mathie et al.'s review [44], almost half of the studies used individualized homeopathy (45.30%).

In the present review, only 15.79% (3/19) of the studies reported negative results; all the others had positive (n= 8, 42.10%) or mixed (n= 8, 42,10%) results. In Mathie et al.'s study [44], 44.44% (16/36) of the studies reported positive results; 30.55% (11/36) reported negative results and 25.0% (9/36) were inconclusive. These data point to possible occurrence of publication bias, which naturally can only be assessed in future systematic reviews with bias analysis. There was not considerable difference between results and homeopathic approach (individualized, non-individualized, semi-individualized or isopathy).

Conclusions

On the basis of the available evidences, considering the ones of highest level (systematic reviews and RCT) only, one might not assert that the effects of homeopathy are exclusively placebo effect. Contrariwise, specific effects were detected. Inasmuch as the mechanism of action of homeopathy is becoming increasingly plausible (see the other articles included in the present dossier), the remaining doubts on its efficacy and effectiveness will be gradually dispelled.

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