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Clinical Trials of Homoeopathy

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individuals induces complaints resembling those of the patient, can be used to cure the patient.

Potentiation is a combination of dilution and shaking of a substance. A plant—for example, *Arnica montana*—is macerated and dissolved in alcohol. One part of this "mother tincture" is mixed with nine parts (D1 potency) or 99 parts (C1 potency) of 90% alcohol (the concentration of the alcoholic solution may vary between manufacturers) and then vigorously shaken. This process can be repeated many times, resulting in very high dilutions (potencies): D6 means one molecule of the original substance in 10^6 molecules of 90% alcohol; C6 means one molecule in 10^{12} molecules. In potencies of D24 or C12 and higher it is very unlikely that even a single molecule of the mother tincture is present. The idea is, however, that higher potencies work more strongly than lower potencies.

Using the similia principle the classical homoeopath tries to find a substance that fits the patient's complaints as much as possible. Unusual symptoms that do not fit the symptom complexes recognised by conventional medicine may be considered even more important than the regular symptoms. This is why homoeopathy is a highly individualised treatment, resulting in different treatments for patients who would receive an identical treatment in conventional medicine. In modern homoeopathy combinations of several or many homoeopathic substances are often used, especially in over the counter preparations. The classical homoeopath will never use this polypharmacy. Also, according to classical homoeopathy a similium must be used and not a potentiation of the causal agent (for example, pollen in hay fever or lead in lead poisoning), which is called isopathy. Phytotherapy is the administration of herbs or low potencies of herbs (D2 or so). These preparations may still have pharmacological effects, and therefore it is sometimes difficult to demarcate phytotherapy from modern homoeopathy, the fundamental difference being the applied low dose toxicology principle in homoeopathy. This description of homoeopathy indicates that it is not just another therapy but a distinct outlook in medicine, and several interpretations have developed, often contradictory to one another.

For this review we searched exhaustively for published reports to investigate the clinical evidence of the efficacy of homoeopathy, regardless of its (to us) implausibility. The positive and negative evidence was weighed against the methodological quality of the research.

Materials and methods

Trials were eligible if parallel index and control groups were included. Crossover designs were also eligible, but controlled studies in animal models were excluded.

Experiments were found by various strategies: a computer search (MEDLINE online 1966-90; keyword homeopathy); checking references extensively, in articles on clinical research and in textbooks[3-5]; checking the proceedings of conferences of homoeopathy; checking the contents of several journals of homoeopathy; personal communication with researchers; writing to and visiting major manufacturers of homoeopathic preparations; and visiting several libraries specialising in homoeopathy. This process of collection took place over a period of more than three years. Trials published in any language were eligible, without restrictions.

Classical homoeopathy uses individual diagnoses and treatments. From a homogeneous group given diagnoses in conventional medicine the patients suitable for homoeopathic treatment can be selected. This results in acceptable participants from both regular and homoeopathic points of view. Individual treatment is prescribed, and then the patients are randomly allocated to homoeopathic or placebo treatment. If necessary, the prescription may be changed in the course of time and, of course, patients who started on placebo stay on placebo.[6]

When the same homoeopathic drug or combination of homoeopathic drugs is given to all patients with a comparable regular diagnosis, trial methodology is the same as in regular medicine. This also goes for trials testing isopathy.

Because the effects of most homoeopathic treatments are meant to last for longer periods, the interpretation of crossover trials is complicated by carryover effects. The analysis will be very difficult, and consequently parallel experiments are preferable.

To explore the possibility that an increasing likelihood of bias (an increasing number of methodological shortcomings) is reflected in the results of the trials, criteria for a methodological assessment of the experiments were established. We put much weight on the number of participants. In most indications for homoeopathic treatment subjective symptoms are the main outcome phenomenon. Substantial improvements of patients in the control group can be expected, and fairly large groups, which are comparable at baseline for prognostic factors, are needed for valid assessment of the efficacy. In trials with limited numbers of participants one cannot be confident that randomisation will equally divide known and unknown confounders over the experimental and control groups. As well, publication bias may be less likely for experiments with large numbers of participants: the effort and costs entailed will increase the likelihood that a paper is submitted for publication. Thus a main argument for our emphasis on relatively large numbers of participants was not the likelihood of type II error, which also depends on the estimated size of the effect, but mainly our worry about incomparability at baseline of the groups and the likelihood of publication bias.

Other major criteria for methodological soundness were randomisation and double blindness. When prognostic factors of the illness, other than the intervention under study, are insufficiently known, random allocation to the contrasted treatments is useful to ensure a comparable prognosis. Double blindness is important for keeping the intervention exactly the same in the contrasted groups except for the homoeopathic treatment, and for an unbiased assessment of the effects. This is especially important if it concerns the relief of subjective symptoms, as is often the case in homoeopathic treatment.

Starting from a maximum score of 100 points, we divided these among seven methodological criteria.

(1) *Patient characteristics adequately described: 10 points*—Description of the syptoms and, if appropriate, of their duration and severity.

(2) *Number of patients analysed: 30 points*—One hundred or more patients per group analysed=30 points, 50-99 patients per group=20 points, and 25-49 patients per group=10 points. A crossover trial with 70 participants (35 given active treatment and 35 given placebo in each period) would score 10 points. In trials assessing the prophylactic effects of homoeopathy the number of patients with the outcome phenomenon was used.

(3) *Randomisation: 20 points*—Twenty points if the method of randomisation was described and correct, 10 points if the method was not described or if some form of pseudorandomisation was applied. If there were fewer than 25 participants per group, half the score was given unless there was prestratification (matching) on relevant items and a table showing comparable baseline characteristics.[7]

(4) *Intervention well described: 5 points*—Adminis-

tration (doses, duration) and origin (method of manufacture) of homoeopathic preparations.

(5) *Double blinding: 20 points*—Twenty points if the placebo was described as indistinguishable, 10 points if double blinding was only mentioned.

(6) *Effect measurement relevant and well described: 10 points*—Measurement of the effect must be sensible and reproducible. Five points each for relevance and adequate description.

(7) *Presentation of the results in such a manner that the analysis can be checked by the reader: 5 points*—Depending on measurement of the effect, at least the mean(s) and standard deviation, standard error, or confidence interval in each group must be mentioned, or the number of patients with a certain outcome (for example, if rates or proportions were used).

Sometimes only part of the score was given if the description was unclear, or if only some of several interventions, measurements of outcome, or data presentations met the criteria. In the second criterion we chose to use the number of patients analysed instead of the number randomised because in many publications drop outs were not accounted for. Often the number of patients admitted was not even mentioned. In the seventh criterion we did not demand confidence intervals for the comparisons between groups because then virtually no trials would score the criterion, with only a few exceptions.[2 8 9]

All articles were scored by at least two of us, and differences, which were mainly caused by reading errors or by unclear descriptions in the publications, were resolved by discussions. Most of these differences occurred in patient characteristics and descriptions of measurement of the effect; in these cases the relevance and sensibility had to be judged. The largest difference was 13 points.

Assessment of articles using these criteria provides a score that gives an indication of the methodological quality of each trial. This quality is an important factor in weighing the conclusions of different trials and, of course, on the impact on the reader's opinion of all the evidence presented. We have selected well established methodological criteria,[10] and our assessment can be checked by the reader (table I).

Results

Table I shows some methodological characteristics of the better trials (those scoring 55 points or more).[2 8 11-31] Some good studies have been reported, but overall the methodological quality was disappointing. Patient characteristics were described adequately in 56 trials. More than half of the publications (63) were of trials in which fewer than 25 patients per group were treated. Sixty eight trials were randomised, but only 17 described the method of randomisation. The intervention was adequately or reasonably well described in 80 trials. Seventy five were double blind, but the placebo was described as indistinguishable in only 31 trials. In 67 publications the effect measurement was judged to have been sensible and well described. Sufficient data for the reader to check the analysis were given in 65 trials.

It is difficult to compare the quality of trials that score more or less the same, and in the lower range the results of all studies may be seriously biased because of several methodological shortcomings. Consequently, we present in detail the results of only the best trials (those scoring 60 points or more) (table II).[2 11-24]

In 14 experiments some form of classical homoeopathy was tested.[22 32-44] Only one of these scored more than 60 points. In a randomised double blind trial Brigo gave one or sometimes two of eight chosen drugs (belladonna, gelsemium, ignatia, cyclamen, lachesis, natrium muriaticum, silicea, or sulphur in a C30 potency) to 30 patients with migraine headache; 30 controls received a placebo. After four months the patients treated with homoeopathy fared much better than the controls on severity of attacks: on a 10 cm visual analogue scale the severity changed from 9·1 to 2·9 in the homoeopathic group and from 8·4 to 7·8 in the control group. Similar differences were found for the frequency and the duration of the attacks.[22]

In about half of the controlled trials (58 studies) the same single homoeopathic treatment was given to a group of patients with comparable conventional diagnoses. Combinations of homoeopathic treatments (polypharmacy) were tested in 26 studies, and isopathy in nine. Only one trial compared dilutions with potencies (a positive trend was found in favour of the potency)[13] and in a few trials different potencies or different homoeopathic substances were compared with each other.[12 15 24 66 79]

Twenty eight trials were published before 1980, 38 in the period 1980-4 and 41 from 1985 onwards. Forty two trials were published in English, 34 in German, 30 in French, one in Italian, and one in Portuguese. Several trials were published in more than one language (for example, Italian and French); in those cases we chose the reference of the most comprehensive and most easily obtainable publication.

According to conventional diagnoses, several groups

TABLE I—*Scoring of methodological characteristics of clinical trials of homoeopathy*

	Characteristics of patients (max=10)	Number analysed (max=30)	Randomisation (max=20)	Intervention (max=5)	Double blinding (max=20)	Measurement of effect (max=10)	Presentation of data (max=5)	Total score (max=100)
GRECHO 1989[11]	10	30	10	5	20	10	5	90
Reilly *et al* 1986[1]	10	20	20	5	20	10	5	90
Ferley *et al* 1989[3]	10	30	10	5	20	8	5	88
Wiesenauer *et al* 1985[13]	5	20	20	5	20	10	5	85
Arnal-Laserre 1986[14]	10	10	20	5	20	10	5	80
Wiesenauer and Gaus 1986[15]	10	20	10	5	20	10	5	80
Zell *et al* 1988[16]	10	10	20	5	20	10	5	80
Valero (Raphanus sativus) 1981[17]	10	20	20	5	10	10	5	80
Aulagnier 1985[18]	10	30	10	5	10	10	0	75
Wiesenauer *et al* 1983[19]	5	10	20	5	20	10	5	75
Bordes and Dorfman 1986[20]	10	10	10	5	20	10	5	70
Valero (Pyrogenium) 1981[17]	10	10	20	5	10	10	5	70
Ferley *et al* 1987[21]	8	10	10	5	20	10	5	68
Brigo 1987[22]	10	10	20	3	10	10	5	68
Maiwald *et al* 1988[23]	10	20	15	5	0	10	5	65
Wiesenauer *et al* 1989[24]	5	10	10	5	20	10	0	60
Bignamini *et al* 1987[25]	10	0	10	3	20	10	5	58
Chevrel *et al* 1984[26]	10	10	10	3	10	10	5	58
Gassinger *et al* 1981[27]	10	10	20	3	0	10	5	58
Ritter 1966[28]	5	20	10	3	10	5	5	58
Wiesenauer and Gaus 1987[29]	10	0	10	5	20	10	3	58
Lewith *et al* 1989[30]	10	0	5	5	20	10	5	55
Savage 1977[31]	10	0	5	5	20	10	5	55

Eighty four controlled trials scored <55 points.[1 17 69]

TABLE II—*Characteristics and results of best trials*

	Score for methodology (max=100)	Indication (No of patients/No of controls)	Intervention	Results (No of patients/No of controls)
Polypharmacy:				
Ferley *et al* 1989[9]	88	Treatment of influenza (237/241)	Anas barbariae hepatis, cordis extractum C200 *v* placebo	Recovery rate within 48 hours (17·1%/10·3%)
Arnal-Laserre 1986[10]	80	Duration of delivery (53/40)	Actea racemosa C5, arnica C5, caulophyllum C5, gelsemium C5, pulsatilla C5 *v* placebo	Duration of delivery: (5·1/8·5 hours); "dystocie" [problems with dilatation] (11·3%/40%)
Zell *et al* 1988[16]	80	Ankle sprains (33/36)	D2-D6 combination of 14 substances *v* placebo	No of patients without pain after 10 days: (28/13)
Aulagnier 1985[11]	75	Bowel movements after abdominal operation (100/100)	Opium C9, raphanus C9, arnica C9 *v* placebo	Days until first flatus (2·5/3·2); days until first faeces (4·0/4·9)
Bordes and Dorfman 1986[12]	70	Dry cough (30/30)	C3 combination of 10 substances *v* placebo	Very good or good result after 1 week (20/8)
Ferley *et al* 1987[13]	68	Prevention and treatment of influenza (588/594)	D1-D6 combination of 10 substances *v* placebo	Incidence (6·5%/7·2%); duration of symptoms (7·0/6·8 days)
Maiwald *et al* 1988[15]	65	Influenza (88/82)	Aconitum D4, bryonia D4, lachesis D12, eupatorium perfoliatum D3, phosphorus D5 *v* acetyl salicylic acid 1500 mg days 1-4, 500 mg days 5-10	Positive result within 4 days (29%/23%)
Wiesenauer *et al* 1989[14]	60	Sinusitis (45, 38, 35/34)	(1) Luffa operaculata D4, kalium bichromicum D4, cinnabaris D3 (2) Kalium bichromicum D4, cinnabaris D3 (3) Luffa operaculata D4; *v* (4) placebo	Combination score of 6 symptoms (no difference between the 4 groups)
Same formula in all patients:				
GRECHO 1989[17,18]	90	Bowel movements after abdominal operation (4 groups of 150)	(1) Opium C15 (2) Opium C15, raphanus C5 *v* (3) Placebo (4) No treatment	Time until first faeces: (1) 96 hours (2) 99 hours (3) 94 hours (4) 95 hours Similar results for first peristaltic sounds and first flatus
Wiesenauer and Gaus 1985[19]	85	Pollinosis (50/55, 59)	(1) Galphimia glauca D6 *v* (2) Galphimia glauca dilution 10^{-4} (3) Placebo	Improvement of nasal symptoms after 2, 4 weeks: (1) 60%, 78% (2) 40%, 51% (3) 41%, 58% Similar results for ocular symptoms
Valero 1981[20]	80	Postoperative infections (54/74)	Raphanus C7 *v* placebo	No of patients with infection (15/20)
Valero 1981[21]	70	Bowel movements after abdominal operation (43/37)	Pyrogenium C7 *v* placebo	Time until first flatus (53·3/58·6 hours)
Wiesenauer *et al* 1983[22]	75	Pollinosis (41/45)	(1) Galphimia glauca D4 *v* (2) Placebo	Improvement of symptoms after 2, 4 weeks: (1) 83%, 81% (2) 47%, 57%
Comparison of several homoeopathic treatments:				
Wiesenauer and Gaus 1986[23]	80	Pollinosis (62, 56, 54, 63)	Galphimia glauca (1) C2 (2) C4 (3) D4 (4) LM4	Improvement of nasal symptoms after 2, 4 weeks: (1) 67%, 83% (2) 71%, 79% (3) 67%, 82% (4) 69%, 85% Improvement of ocular symptoms after 2, 4 weeks: (1) 64%, 83% (2) 73%, 88% (3) 65%, 82% (4) 76%, 89%
Isopathy:				
Reilly *et al* 1986[1]	90	Pollinosis (74/70)	Pollen C30 *v* placebo	Change in 100 mm visual analogue scale symptom score after 5 weeks (−17·2 mm/−2·6 mm)
Classical homoeopathy:				
Brigo 1987[24]	68	Migraine (30/30)	8 possible homoeopathic remedies C30 *v* placebo	Change in 10 cm visual analogue scale symptom score after 4 months (−6·2 cm/−0·6 cm). Similar results for frequency and duration of attacks

of indications emerged: diseases of the respiratory system (19 trials on respiratory infections, five trials on hay fever, and one on asthma); gastrointestinal complaints (seven trials); and pain from several sources (27 trials, of which six were of rheumatological diseases). Table III presents the outcome of all 107 trials. In 42 we thought that insufficient data were given to check the authors' interpretation of the outcome(s). Consequently the results reflect not our conclusions but the inference made by the authors of the publications, who to us seem sometimes to be a little overoptimistic. In most cases, however, a positive result indicates that there was a statistically significant difference in the main outcome(s) between the contrasted groups, whereas a negative result means that no significant difference was found ($p>0·05$). We could not pool the results statistically because of the heterogeneity of the studies.

The evidence is to a large extent positive: of the better studies 15 trials showed positive results whereas in seven trials no positive effect could be detected (in one trial only homoeopathic treatments were compared with each other). The trials with a methodological score below 55 points showed an even clearer trend: in most publications positive results were reported (66 positive, 17 negative). Overall, of the 105 trials with interpretable results, 81 indicated positive results whereas in 24 trials no positive effects of homoeopathy were found compared with (mostly) placebo controls. In the two other trials only homoeopathic treatments were compared to each other.

Discussion

In the methods section we indicated that it is possible to perform trials on the efficacy of homoeo-

pathy, including classical homoeopathy, in a way that is acceptable for both sceptical physicians and enthusiastic homoeopaths. Criticisms of these methods, often suggesting that special methodology and statistics are needed for the evaluation of homoeopathy, are in our opinion based on lack of knowledge of research methodology.

A problem in our methodological assessment is that limited description of the methods and the results in the publication may lead to a lower score. We believe, however, that a detailed description of this information is as important as using good methodology in practice. It could be argued that other criteria should be used for the methodological assessment and that this kind of assessment is rather subjective. As stated before, we have selected well established criteria. The reader could apply different weights to the criteria to see whether substantial changes would occur in our methodological ranking, but we think that this will not be the case.

Double blinding, even if the placebo is described as indistinguishable, has to be checked by asking the patients in which group they believe that they were during the trial. Blindness must be checked early in the trial, before the treatment is expected to take effect, because positive effects would break the code. It is easy to state that a trial was double blind, but patients have many ways to break the code. This might explain small differences in favour of homoeopathy. Double blinding was not checked in any trial of homoeopathy.

TABLE III—*Clinical trials of homoeopathy grouped according to diagnoses from conventional medicine*

	Indication	Score (max=100)	Result
Diseases of the vascular system:			
Bignamini *et al* 1987[25]	Hypertension	58	Negative
Wiesenauer and Gaus 1987[17]	Hypotension	58	Positive
Savage 1977[11]	Stroke	55	Negative
Gauthier 1983[13]	Flushing	53	Negative
Savage and Roe 1978[46]	Stroke	53	Negative
Hitzenberger *et al* 1982[14]	Hypertension	48	Negative
Dorfman *et al* 1988[47]	Venous perfusion	35	Positive
Hadjicostas *et al* 1988[48]	Bleeding	35	Positive
Master 1987[42]	Hypertension	13	Positive
Respiratory infections:			
Ferley *et al* 1989[1]	Influenza	88	Positive
Bordes and Dorfman 1986[49]	Coughing	70	Positive
Ferley *et al* 1987[10]	Influenza	68	Negative
Maiwald *et al* 1988[12]	Influenza	65	Positive
Wiesenauer *et al* 1989[16]	Sinusitis	60	Negative
Gassinger *et al* 1981[17]	Common cold	58	Positive
Lewith *et al* 1989[50]	Influenza	55	Negative
Lecocq 1985[45]	Respiratory infections	50	Positive
Lewis 1984[19]	Whooping cough	49	Negative
Schmidt 1987[18]	Bronchitis	45	Positive
Chakravarty *et al* 1977[44]	Tonsillitis	38	Positive
Mössinger 1985[51]	Otitis media	38	Positive
Davies 1971[52]	Influenza	35	Positive
Mössinger 1973[53]	Pharyngitis	35	Positive
Mössinger 1982[54]	Common cold	35	Negative
Hourst 1982[55]	Respiratory infections	28	Positive
Mössinger 1976[56]	Pharyngitis	25	Positive
Masciello and Felesi 1985[57]	Influenza	18	Positive
Bungetzianu 1988[58]	Influenza	0	Negative
Other infections:			
Valero 1981[59]	Postoperative infection	80	Negative
Valero 1981[59]	Postoperative infection	50	Positive
Ustianowski 1974[60]	Cystitis	45	Positive
Mössinger 1980[61]	Furuncles	43	Positive
Subramanyam *et al* 1990[62]	Filariasis	38	Positive
Carey 1986[63]	Vaginal discharge	35	Positive
Castro and Noguiera 1975[64]	Meningitis	13	Positive
Diseases of the digestive system:			
Ritter 1966[65]	Gastritis	58	Positive
Rahlfs and Mössinger 1979[66]	Irritable colon	50	Positive
Owen 1990[67]	Irritable colon	35	Positive
Rahlfs and Mössinger 1976[68]	Irritable colon	35	Positive
Mössinger 1976[69]	Abdominal complaints	23	Negative
Mössinger 1974[70]	Cholecystopathy	15	Positive
Mössinger 1976[71]	Abdominal complaints	13	Negative
Pollinosis:			
Reilly *et al* 1986[4]	Pollinosis	90	Positive
Wiesenauer and Gaus 1985[15]	Pollinosis	85	Positive
Wiesenauer and Gaus 1986[72]	Pollinosis	80	*
Wiesenauer *et al* 1983[73]	Pollinosis	75	Positive
Reilly and Taylor 1985[74]	Pollinosis	50	Positive
Reilly *et al* 1990[9]	Asthma	35	Positive
Recovery of bowel movements after surgery:			
GRECHO 1989[75,76]	Ileus	90	Negative
Aulagnier 1985[77]	Ileus	75	Positive
Valero 1981[59]	Ileus	70	Positive
Chevrel *et al* 1984[78]	Ileus	58	Positive
Valero 1981[59]	Ileus	50	Positive
Estrangin 1979[79]	Ileus	48	Negative
Castelin 1979[79]	Ileus	20	Positive
Rheumatological disease:			
Shipley *et al* 1983[21]	Osteoarthritis	50	Negative
Fisher *et al* 1989[22]	Fibromyalgia	45	Positive
Gibson *et al* 1980[80]	Rheumatoid arthritis	40	Positive
Audrade *et al* 1988[81]	Rheumatoid arthritis	38	Negative
Fisher 1986[23]	Fibrositis	38	Positive
Gibson *et al* 1978[24]	Rheumatoid arthritis	33	Positive
Trauma or pain:			
Zell *et al* 1988[26]	Ankle sprains	80	Positive
Brigo 1987[82]	Migraine	68	Positive
Bourgois 1984[83]	Haematoma	53	Positive
Casanova 1981[84]	Myalgia	45	Positive
Pinsent *et al* 1986[85]	Dental extraction	45	Positive
Berthier 1985[86]	Dental extraction	40	Positive
Albertini *et al* 1984[87]	Dental neuralgia	38	Positive
Campbell 1976[88]	Bruising	38	Negative
Hildebrand and Eltze 1983[89]	Myalgia	38	Positive
Hildebrand and Eltze 1983[89]	Myalgia	38	Positive
Hildebrand and Eltze 1983[89]	Myalgia	38	Positive
Hildebrand and Eltze 1983[89]	Myalgia	38	Positive
Leaman and Gorman 1989[90]	Minor burns	38	Negative
Geiger 1968[91]	Oedema	35	Positive
Kubista *et al* 1986[92]	Mastalgia	35	Positive
Michaud 1981[93]	Oedema	35	Positive
Mergen 1969[94]	Oedema	33*	
Caspar and Foerstel 1967[95]	Oedema	28	Positive
Campbell 1976[88]	Bruising	28	Positive
Khan 1985[96]	Hallux valgus	15	Positive
Anonymous 1980[97]	Cystitis	13	Positive
Mental or psychological problems:			
Delauney 1985[98]	Behaviour in children	48	Positive
Carlini *et al* 1987[99]	Insomnia	45	Negative
Heulluy 1985[100]	Depression	45	Positive
Ponti 1986[101]	Travel sickness	40	Positive
Tsiakopoulos *et al* 1988[102]	Vertigo	35	Positive
Vu Din Sao and Delauney 1983[103]	Nervous tension	30	Positive
Dexpert 87[104]	Seasickness	25	Positive
Alibeu and Jobert 1990[105]	Agitation	23	Positive
Davies 1988[106]	Aluminium deficiency	23	Negative
Master 1987[107]	Aphasia	23	Positive
Other diagnoses:			
Arnal-Laserre 1986[108]	Duration of delivery	80	Positive
Skaliodas *et al* 1988[109]	Diabetes	50	Positive
Coudert-Deguillaume 1981[110]	Duration of delivery	45	Positive
Kennedy 1971[111]	Postoperative complications	43	Negative
Paterson 1943[112]	Gas poisoning	41	Positive
Basu 1980[113]	Myopia	35	Positive
Hariveau 1987[114]	Cramps (dialysis)	35	Positive
Kirchhoff 1982[115]	Lymphoedema	33	Positive
Kienle 1973[116]	Respiratory insufficiency	30	Positive
Paterson 1943[112]	Gas poisoning	28	Positive
Ventoskovskiy and Popov 1990[117]	Complications of delivery	22	Positive
Schwab 1990[118]	Skin diseases	20	Positive
Schwab 1990[118]	Skin diseases	20	Positive
Mössinger 1976[71]	Crumps (legs)	13	Negative
Khan and Rawal 1976[119]	Verruca plantaris	0	Positive

*Comparison of homoeopathic treatments.

Although the number of trials is impressive, many questions remain. Virtually no evidence exists about the correct choice of the remedy and the potency to be used (different potencies or homoeopathic substances should be compared in controlled trials). Hahnemann's principles have been brought into practice in innumerable ways, as is indicated by the differences among the trials presented here. The process of producing preparations (the percentage of alcohol in the solution, the number of times that the substance must be shaken during potentiation, etc) and their composition (especially when herbs are used) differ greatly among manufacturers. Also, there is no plausible explanation of the mechanisms through which homoeopathy would act. Substances that contain only the solvent can have no pharmacological actions according to our present knowledge of physics and chemistry. If a homoeopath is asked his or her opinion about these mechanisms, the most likely reply is "I do not know." In practice, if a treatment works knowledge of the mechanisms of action is not necessary, and numerous examples from regular medicine can be cited in which the mechanisms are hardly understood or not at all. However, to assume that an infinitesimally diluted substance in an alcoholic solution has pharmacological effects would mean that essential concepts of modern physics would have to be dismissed.

An important problem in reviewing the literature is publication bias. Especially with a controversial subject such as homoeopathy, several problems may exist. More trials with positive results might have been submitted and accepted by "alternative" journals, whereas small trials with negative results might not have been submitted or might have been rejected. On the other hand trials with positive results might have been rejected and negative trials more readily accepted by "regular" journals. About one third of the trials were published in each of regular journals, alternative journals, and by other means of communication (proceedings, reports, dissertations, books). No relation between the result and the place of publication was seen. Negative results were reported in alternative journals 12 times, in regular journals seven times, and in other publications five times. When talking to authors of trials we identified at least six trials for which no manuscript had been submitted for publication. It is difficult to discover the true reasons for failure to submit an article for publication, but we think that the (possibly negative) results may have been an important factor in these cases.

Nevertheless, much evidence is available. We tried to decrease the effects of publication bias by extensively checking every possible source for publications or reports of trials. We wrote to many researchers and also visited several of them to learn whether there were any unpublished trials and to get further details of the published ones. We used strict criteria to select the best trials and based our main conclusions on the results of these. 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 homoeopathy can be efficacious, if only the mechanism of action were more plausible. The way in which the belief of people changes after the presentation of empirical evidence depends on their prior beliefs and on the quality of the evidence.[105 106] Critical people who did not believe in the efficacy of homoeopathy before reading the evidence presented here probably will still not be convinced; people who were more ambivalent in advance will perhaps have a more optimistic view now, whereas people who already believed in the efficacy of homoeopathy might at this moment be almost certain that homoeopathy works.

A trial of very high quality was that of the Groupe de Recherches et d'Essais Cliniques en Homéopathie, initiated by the French Ministry for Social Affairs and performed by a group consisting of regular and homoeopathic researchers.[11 12] After the earlier publication of several trials in which homoeopathy was shown to decrease the time to recovery of bowel movements after abdominal surgery, this hypothesis was retested in a rigorous trial comparing four groups of 150 patients (two groups were treated with opium C15 and raphanus C5, one group with indistinguishable placebo, and one group was not treated). No differences at all were found. Will more of such trials for other indications show the same results and refute the existing evidence?

The weight of the presented evidence will probably not be sufficient for most people to decide definitely one way or the other. The question arises, What further evidence would be needed? Investigations in animal or plant models may increase the belief of sceptical people before they have read the evidence from clinical trials, but if no positive results are found homoeopaths may claim that homoeopathy only works in humans. We did not assess the evidence from such investigations; Scofield concluded in 1984 in a comprehensive review article that "despite the great deal of experimental and clinical work there is only little evidence to suggest that homoeopathy is effective. This is because of bad design, execution, reporting or failure to repeat experimental work."[107] If more (well performed) controlled trials in humans are demanded, cooperation between sceptical investigators and homoeopaths is likely to make the trial results more convincing for many readers. The question is how many of such trials would be needed to draw definitive conclusions? The evidence presented in this review would probably be sufficient for establishing homoeopathy as a regular treatment for certain indications. There is no reason to believe that the influence of publication bias, data massage, bad methodology, and so on is much less in conventional medicine, and the financial interests for regular pharmaceutical companies are many times greater. Are the results of randomised double blind trials convincing only if there is a plausible mechanism of action? Are review articles of the clinical evidence only convincing if there is a plausible mechanism of action? Or is this a special case because the mechanisms are unknown or implausible?

In our opinion, additional evidence must consist of a few well performed controlled trials in humans with large numbers of participants under rigorous double blind conditions. The results of the trials published so far, and the large scale on which homoeopathy is brought into practice, makes such efforts legitimate.

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