

Lecture Series

Immunology and Homeopathy. 4. Clinical Studies—Part 2**Paolo Bellavite¹, Riccardo Ortolani², Francesco Pontarollo¹, Valeria Piasere¹, Giovanni Benato² and Anita Conforti³**¹Department of Scienze Morfologico-Biomediche, ²Association for Integrative Medicine 'Giovanni Scolaro' and³Department of Medicina e Sanità Pubblica, University of Verona, Piazza L.A. Scuro, 37134 Verona, Italy

The clinical studies on the effectiveness of homeopathy in respiratory allergy (18 randomized trials and 9 observational studies) are described. The literature of common immunologic disorders including also upper respiratory tract infections (URTI) and otorhinolaryngology (reported in part 1), is evaluated and discussed. Most of initial evidence-based research was addressed to the question of whether homeopathic high dilutions are placebos or possess specific effects, but this question has been often equivocal and is still a matter of debate. The evidence demonstrates that in some conditions homeopathy shows significant promise, e.g. *Galphimia glauca* (low dilutions/potencies) in allergic oculorhinitis, classical individualized homeopathy in otitis and possibly in asthma and allergic complaints, and a few low-potency homeopathic complexes in sinusitis and rhinoconjunctivitis. A general weakness of evidence derives from lack of independent confirmation of reported trials and from presence of conflicting results, as in case of homeopathic immunotherapy and of classical homeopathy for URTI. The suitable methods to evaluate homeopathy effectiveness, without altering the setting of cure, are also analyzed.

Keywords: allergy – asthma – evidence-based homeopathy – homeopathic immunotherapy – homeopathic medications – homeopathy – immunology – isopathy – rhinoconjunctivitis

Introduction

In the first part of this review (1) the evidence-based research on homeopathy in common upper respiratory tract infections (URTI) or in otorhinolaryngologic complaints has been described. We shall here describe studies performed in the field of allergology and, more specifically, in oculorhinitis (hayfever) and allergic asthma. The methods of analysis and the criteria of classification are the same as described in the first part of the review.

Finally, the global body of evidence regarding the effectiveness of the different therapeutic approaches, in the conditions considered in this review, is presented in the Discussion. Here, the classification of the therapeutic approaches is made according to a grade of evidence in six levels, which was developed by Natural Standard, an international research

collaboration that aggregates and synthesizes data on complementary and alternative therapies (<http://www.naturalstandard.com/index.asp>). A summary of these criteria is reported in Table 1.

Allergic Conditions

Allergies are the most common immunological diseases among general population, and increasing evidence suggests that incidence of allergic disorders is rising dramatically. The results of several studies indicated that patients before seeking homeopathic care for their allergic symptoms were unsatisfied within conventional health care system and that their choice was mostly motivated by assumption of few side-effects or by a wish to 'try everything' (2–7). Approximately 50% of asthma patients in the UK have used some form of complementary therapy for their asthma at some stage, and most of these patients have indicated that they derived at least some benefit (8).

For reprints and all correspondence: Paolo Bellavite, University of Verona, 37134 Verona, Italy. Tel: +39-045-8202978; Fax: +39-045-8202978; E-mail: paolo.bellavite@univr.it

© 2006 The Author(s).

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/2.5/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Table 1. Synthesis of the levels of evidence of therapeutic efficacy

Level of evidence	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis AND with supporting evidence in basic science, animal studies or theory
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, OR evidence of benefit from ≥ 1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/non-randomized trials AND with supporting evidence in basic science, animal studies or theory
C (unclear or conflicting scientific evidence)	Evidence of benefit from ≥ 1 small RCT(s) without adequate size, power, statistical significance or quality of design by objective criteria, OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness
D (fair negative scientific evidence)	Statistically significant negative evidence (i.e. lack of evidence of benefit) from cohort/case-control/non-randomized trials
E (strong negative scientific evidence)	Statistically significant negative evidence (i.e. lack of evidence of benefit) from ≥ 1 properly randomized adequately powered trial(s) of high-quality design by objective criteria
Lack of adequate evidence	Unable to evaluate efficacy due to lack of adequate available data. This is not equivalent to negative evidence

Several studies using homeopathy have reported beneficial effects from treating allergy-related conditions, other studies have not found benefits over placebo. A summary of these papers in chronological order is given in Table 2, here in the text they will be grouped according to different modalities of therapy that have been investigated.

Classic Individualized Homeopathy

According to this approach each patient received his/her single medicine ('simillimum'). In many reports using classic individualized prescription, there is an indication of most frequently used medicines.

In starting this brief analysis of results obtained in allergology, we cite a retrospective study, reported at a homeopathic conference (13), which included children treated with individualized homeopathy. The results appeared to be encouraging, since 44.2% of patients had a 'satisfactory reaction', 36.7% a 'manifest improvement', 18.3% a 'relative improvement' and 0.8% showing 'no reaction'. The remedies prescribed most frequently were *Lycopodium clavatum*, *sulphur*, *Pulsatilla* and *Silicea*.

Castellsagu (16), retrospectively evaluated a series of children who had suffered from allergic bronchial asthma, and who were treated with a single drug in accordance with classical homeopathic method. Twenty-two different drugs were prescribed (the most used were *sulphur*, *Calcarea carbonica*, *Lycopodium* and *Pulsatilla*), at different potencies. After 3 years of treatment, the results showed a complete cure in 58% of cases, improvements in 23% and failures in 19%. In brief, the results obtained in such a serious chronic disease are encouraging, but the open and uncontrolled nature of the trial makes it impossible to draw definite conclusions.

A further retrospective study evaluated patients suffering from bronchial asthma (both children and adults) and under individualized homeopathic treatment for more than 3 years (22). A statistically significant decrease in frequency and severity of attacks before and after treatment was reported. There was also a marked decrease in the use of conventional

medication. The most frequently prescribed remedies were *Arsenicum album*, *Nux vomica*, *sulphur*, *Pulsatilla* and *Silica*.

A communication in a conference of International Homeopathic Liga reported a trial on the effectiveness of classical individualized treatment of asthmatic people who were allergic to dermatophagoides (23). Symptoms and immunologic parameters were evaluated before and after an 8 months treatment. Significant decrease in number of exacerbations, of spirometric tests and immunologic markers was observed in active homeopathic group. A full report would permit a detailed evaluation of the trial.

A trial on individualized homeopathic therapy in asthma was published in a Mexican homeopathic journal (25). The study was double blind and controlled with placebo but the randomization was not specified. The main result was a reduction of asthma attacks after 4 months of therapy, with a significant difference in favor of homeopathy.

A pharmaco-economic study (not reported in Table 2 because it does not concern effectiveness) assessed the homeopathic treatment in allergic diseases in a health maintenance organization (4). The computerized medication charts of each patient were evaluated for conventional medication consumption 3 months before and 3 months after homeopathic intervention, with each patient serving as his or her own control. The results showed that 56% of patients reduced their use of conventional medication following homeopathic intervention. The most significant reduction was in anti-histamine use, followed by decreases in bronchodilator use and steroids, with an average saving of \$24 per patient in the 3 month period following homeopathic intervention.

Negative Trial, Questionable Method

The effects of individualized homeopathic remedies as an adjunct to conventional treatment were compared with placebo medication in children with mild to moderate asthma (33). There were no clinically relevant or statistically significant changes in active quality-of-life score. Scores of severity of

Table 2. Homeopathic clinical studies of allergy and asthma

Reference and year	Condition (diagnosis)	Study type	Publication classification	Study group	Treatment(s)	Outcomes	Key results
Hardy (1984) (9)	Allergic oculorhinitis (house dust)	1a	2	70	Homeopathic immunotherapy (HIT) made with house dust potencies	Symptoms	HIT better than placebo
Wiesnauer and Gaus (1985) (10)	Allergic oculorhinitis	1a	1b	164	<i>Galphimia glauca</i> 6× dynamized versus placebo and <i>Galphimia glauca</i> 6× non-dynamized	Eye and nose symptoms	Trend to positive, not statistically significant; less symptoms in patients taking dynamized verum medicine than other groups HIT better than placebo
Reilly <i>et al.</i> (1986) (11)	Allergic oculorhinitis (hay fever)	1a	1a	144	<i>Pollen 30c</i> (HIT) versus placebo	Symptoms (VAS)	HIT better than placebo
Wiesnauer and Ludtke (1987) (12)	Allergic oculorhinitis	1a	3	132	<i>Galphimia 2c</i> versus placebo	Eye and nose symptoms	Significantly less eye symptoms in verum group
Mosquera (1990) (13)	Asthma	4	3	120 children	Individualized homeopathy bronchial asthma	General assessment	Improvement in most cases (uncontrolled)
Campbell <i>et al.</i> (1990); Reilly <i>et al.</i> (1994) (14,15)	Allergic asthma	1a	1a	28	Allopathy + allergen 30c (HIT) versus allopathy + placebo	Symptoms (VAS) and respiratory tests	Less symptoms in verum group than placebo, no difference in tests
Castellsagu (1992) (16)	Allergic asthma	4	1b	26 children	Individualized	Global evaluation	Improvement in most patients (uncontrolled)
Nolleveaux (1992) (17)	Allergic oculorhinitis	3	3	108	<i>Pollen 30c</i> , <i>Apis 15c</i> , <i>Lung histamine 15c</i>	Symptoms	Improvement in most patients (uncontrolled)
Wiesnauer and Ludtke (1995) (18)	Allergic oculorhinitis	1a	2	115	<i>Galphimia 4D</i> versus placebo	Eye and nose symptoms	Significant relief in verum group
Matusiewicz 1995, 1996, 1997 (19–21)	Allergic asthma	1a	2	40	Homeopathic complex <i>Engystol-N</i> versus placebo	Respiratory tests	Clinical improvement only in verum group
Eizayaga 1996 (22)	Allergic asthma	4	1b	62	Individualized	Symptoms scores	Significant decrease of symptoms after therapy (uncontrolled)
Lara-Marquez <i>et al.</i> (1997) (23)	Allergic asthma	1a	3	19	Individualized versus placebo	Symptoms, spirometry parameters and immunological markers	Verum better than placebo, significant changes of laboratory markers
Micciché <i>et al.</i> (1998) (24)	Allergic oculorhinitis	2	2	70 children	Homeopathic protocol based on three low-dilution drugs versus conventional therapy	Global evaluation	Trend to better improvement in the homeopathic group
Riveron-Garrote <i>et al.</i> (1998) (25)	Allergic asthma	1a	2	80	Individualized versus placebo	General symptoms and attack intensity	Higher reduction of asthma attacks in verum group

Table 2. Continued

Reference and year	Condition (diagnosis)	Study type	Publication classification	Study group	Treatment(s)	Outcomes	Key results
Hardy (1984) (9)	Allergic oculorhinitis (house dust)	1a	2	70	Homeopathic immunotherapy (HIT) made with house dust potencies	Symptoms	HIT better than placebo
Matusiewicz <i>et al.</i> (1999) (26)	Allergic asthma	1a	2	84	Homeopathic complex <i>Asthma H Inj. Pflugerplex</i> (subcutaneously)	Use of allopathic drugs, laboratory and spirometric tests	Slight decrease of conventional medication and infections; no change in spirometric tests
Weiser <i>et al.</i> (1999) (27)	Allergic rhinitis	1b	1b	146	Low-dilution homeopathic complex formulation <i>Luffa compositum</i> homeopathic complex versus chromolyn sodium	Symptoms and quality-of-life	Equivalence of homeopathy and allopathy
Taylor and Reilly (2000) (28)	Allergic rhinitis	1a	1a	50	Individual allergen 30c versus placebo (HIT)	Symptoms (VAS) and nasal air flux tests	Slightly better tests in verum group
Aabel <i>et al.</i> (2000) (29)	Allergic rhinitis	1a	1b	66	Homeopathic birch pollen <i>Betula</i> 30c versus placebo	Symptoms score	Slightly less symptoms during 10 days. Aggravation after taking verum
Aabel (2000) (30)	Allergic rhinitis	1a	1b	73	Homeopathic birch pollen <i>Betula</i> 30c versus placebo	Symptoms (VAS)	Verum worse than placebo
Aabel (2001) (31)	Allergic rhinitis	1a	1b	51	Homeopathic birch pollen <i>Betula</i> 30c versus placebo	Symptoms (VAS)	Similar improvement in verum and placebo
Lewith <i>et al.</i> (2002) (32)	Allergic asthma	1a	1a	242	Allergen (dust mite) 30c versus placebo (HIT)	Symptoms (VAS) and expiration flux (FEV)	No final therapeutic effect, initial aggravation
Frenkel and Hermoni (2002) (4)	Allergic asthma and other allergies	4	1b	48	Homeopathic care (various)	Conventional medication consumption	The homeopathic intervention led to reduction in the use of medications (uncontrolled)
White <i>et al.</i> (2003) (33)	Asthma (mild to moderate)	1a	1a	96 children	Individualized versus placebo	Quality-of-life, symptoms and tests	No changes of QOL, small not significant improvement of symptoms in verum group
Li <i>et al.</i> (2003) (34)	Allergic asthma	3	1a	12 children	HIT prepared from individual allergens versus placebo	Spirometric tests	No improvement after treatment (uncontrolled)
Kim <i>et al.</i> (2005) (35)	Allergic rhinitis	1a	1a	40	HIT prepared from common allergens versus placebo	Symptoms, quality-of-life questionnaires	Better clinical changes in verum group as compared with placebo
Witt <i>et al.</i> (2005) (36)	Allergic diseases including rhinitis and asthma	2	1b	178	Classic homeopathy versus conventional care	Symptoms, quality-of-life questionnaires, costs	Better outcomes in homeopathic group
Colin (2006) (37)	Ear, nose and throat allergies, allergic asthma	4	1b	147	Individualized and constitutional homeopathy	Global evaluation	Success rate of 87.6% (uncontrolled)

Study type and publication classification are according to Tables 1 and 2 of part 1 (1).

symptoms indicated relative improvements but the sizes of effects were small. The authors concluded that adjunctive homeopathic remedies are not superior to placebo in improving the quality of life of children with mild to moderate asthma. This is a study that raised high media coverage as a proof of inefficacy of homeopathy, but various authors have raised doubts that the parameters used were sensitive enough to differentiate between children who have no asthma and those who have only mild asthma (38–40). In fact, included patients had very mild or lacking symptoms, which hardly could be ameliorated. Therefore, this study should be interpreted with caution.

Effectiveness in 'Real World'

An observational study where outcome and costs of homeopathic therapy were compared with those of conventional treatment in routine care has been published (36). Since all children included in this study were affected by allergic diseases (homeopathic therapy: 54 atopic dermatitis, 20 allergic rhinitis, 17 asthma; conventional therapy: 64 atopic dermatitis, 11 allergic rhinitis, 12 asthma), the results of this subset of patients may be of interest for this review. Allergic children were treated either with classic homeopathic approach or with conventional therapies provided by doctors selected from an address list of general practitioners. The two groups were not randomized but their disease grade at baseline was similar. After 12 months of cure, symptom severity scores decreased more significantly in homeopathic group than in conventional group. There was also a trend to a better improvement of quality of life in the homeopathic group, but not statistically significant after diagnosis-specific adjustment.

A series of cases of respiratory allergy treated with individualized and constitutional homeopathy in a private homeopathic practice was recently reported (37). The author estimated an overall success rate of 87.6% for homeopathic treatment in these conditions. Only two cases of ear, nose and throat allergies out of a total of 105 showed no improvement, no patients deteriorated. Two cases with worsening and three without improvement were noted out of 42 cases of pulmonary allergies.

Homeopathic Immunotherapy

One of the most extensive lines of research in homeopathy was the attempt to utilize high dilutions of substances, known to cause allergy, to prevent or cure the same allergies. This is an application of the ancient isopathic principle (41) that has been also termed 'homeopathic immunotherapy (HIT)' (11,14,42). The chosen model, use of pollen in hay fever, actually comes from the work of a homeopath—Dr Charles Blackley—who, in the 1870s, first identified pollen as the cause of respiratory seasonal allergies (42).

To start the description of these results, it is worth citing a first report in a non-indexed journal by Hardy in 1984 (9). The authors showed a relief of oculorhinitis symptoms in

patients allergic to house dust by homeopathic potencies of house dust. The same approach characterized long-lasting and deep investigations by a group led by D. Reilly. A double-blind study, published as preliminary report in 1985 (43) and as a full paper in 1986 (11), compared the effects of placebo and of a 30c homeopathic preparation designed as *Pollen* because it contained a mixture of 12 pollens. The results were positive insofar as patients receiving the homeopathic treatment had significantly fewer symptoms and used half of anti-histamine rescue treatment than controls.

The same group published the results of a study on patients with severe atopic asthma requiring daily administrations of bronchodilators, most of whom were being treated with steroids (14). Patients received a placebo for 4 weeks and were then randomly divided into two groups, one of which continued the placebo, whereas the other was treated with a 30c homeopathic preparation of the main allergen to which each patient was sensitive. The patients revealed a statistically significant difference in favor of the active treatment. These studies, enriched by further statistical analyses and a meta-analysis of all of patients, were published in 1994 (15) and showed an extremely high probability ($P = 0.0004$) that the homeopathic effect was not due to a placebo effect. The time-course of symptoms improvement of this trial series is reported in Fig. 1. A clear difference can be seen between HIT and placebo, but the effect may be considered quite small for therapeutic purposes.

A trial of the homeopathic medication *Lung histamine 5c* used prophylactically in children with asthma also reported promising results in reducing the frequency of attacks (44), but the design of study did not allow persuasive evidence (42). An uncontrolled study conducted in Belgium observed the effect of *Pollen 30c* (prepared from a mixture of 12 grass pollens) combined with *Apis mellifica 15c* and *Lung histamine 15c*, in allergic oculorhinitis (17). The regimen was one tablet per day and progress was monitored for 6 months by registering nasal and ocular symptoms as well as by doctor's assessment. From 69 to 86% of patients—according to the parameter evaluated—showed clinical improvements.

Further Multicenter Studies

Reilly's group has subsequently organized a multicenter study on patients affected by allergic rhinitis (28). The study involved administration of a 30c potency of the main allergen or (in control group) an indistinguishable placebo. The results demonstrated a significant improvement in nasal air flow in treated patients in comparison with those receiving placebo ($P = 0.0001$). Subjective symptoms improved but not in a statistically significant manner. It is interesting to note that the group treated with homeopathic preparations of allergen more frequently reported an initial worsening, that is well known in homeopathy. This study offered further proof that high homeopathic dilutions cannot be assimilated to a simple placebo. However, as underlined by the authors themselves, this does not mean that their proposed HIT is an efficacious

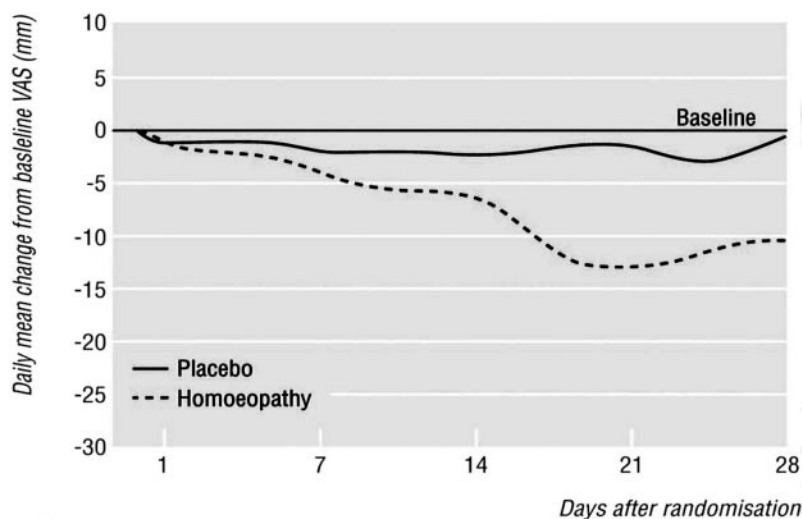


Figure 1. Effect of homeopathic immunotherapy (HIT) on visual analogue scale (VAS) scores averaged over four trials. On average, there was a mean reduction of the visual analogue scale score of 10.9 mm in the homoeopathy group compared with 1.1 mm in the placebo group ($P < 0.001$). Reproduced with permission from Taylor et al, reference 28.

homeopathic therapy for chronic rhinitis (also because classic homeopathy requires individualized treatment).

Unsuccessful Replications

A study of HIT, with essentially negative results, was published in 2002 by an independent group led by G. Lewith (32). Patients with asthma and positive skin prick tests for house dust mite entered the trial. After a 4 week baseline assessment, participants were randomized to receive oral HIT, made with their specific allergen, or placebo, and then assessed over 16 weeks by means of three visits and diary assessments every other week. There was no difference in most final outcomes between placebo and HIT, but there was a different pattern of change during the trial in diary assessments concerning morning peak expiratory flow, visual analogue scale and mood. In brief, the homeopathic medicine caused a slight but statistically significant worsening during the early phases of treatment than placebo, while at the end of experimental period the effectiveness of HIT was not significantly different from placebo. This study sparked a considerable discussion in the same Journal (45). In a subsequent paper, some of the authors of the past negative trial of HIT have discussed their data of the same trial using complexity theory (46). This is an evidence for a different oscillation in outcome (both physiological and subjective) of verum treatment with respect to placebo (see Fig. 2). The authors suggest that such time dynamics are consistent with a complexity theory interpretation of how the body functions as a whole and speculate that these oscillatory phenomena require a different trial methodology from that currently employed.

A series of double-blind, randomized, placebo-controlled trials on preventive and therapeutic effectiveness of pollen of *Betula* (HIT) were conducted by a Norwegian group. In the first study (29), the effect of the homeopathic remedy *Betula*

30c versus placebo for adult patients with birch pollen allergy was tested. No statistically significant difference between groups was found, except for a brief period when those receiving verum having fewer and less serious symptoms. For some days these differences were statistically significant. Surprisingly, the verum group also reported some aggravation after medication, more than did placebo group, a result in agreement with that of previously mentioned trials (28,32). The second study (30) involved children and gave uncertain results, according to the authors possibly because the pollen count was very low during treatment period and only 3 days were high enough to provoke allergic symptoms. This time the verum-treated patients fared worse than placebo group; they used more rescue medication and had higher symptom scores during these 3 days. The authors suggested that the findings may document a putative 'aggravation response', but certainly do not support the usefulness of the tested homeopathic prophylaxis for this condition. The third paper (31) with similar protocol with addition of a crossover of treatments showed a consistent response in both verum and placebo groups, with no consistent clinical advantage of HIT.

Other authors communicated, in a letter (34), to have obtained negative findings in an open study in which they assessed the effects of HIT in children with stable asthma. This could be because of the small sample size ($n = 12$) or because the lack of efficacy of remedy.

New Positive Findings

A recent double-blind trial showed significantly positive effects of HIT of seasonal allergic rhinitis (35). The drug was prepared from common allergens (tree, grass, weed species) specific to Southwest region of US, which was compared with placebo. Study outcomes included allergy-specific symptoms using the rhinoconjunctivitis quality-of-life questionnaires.

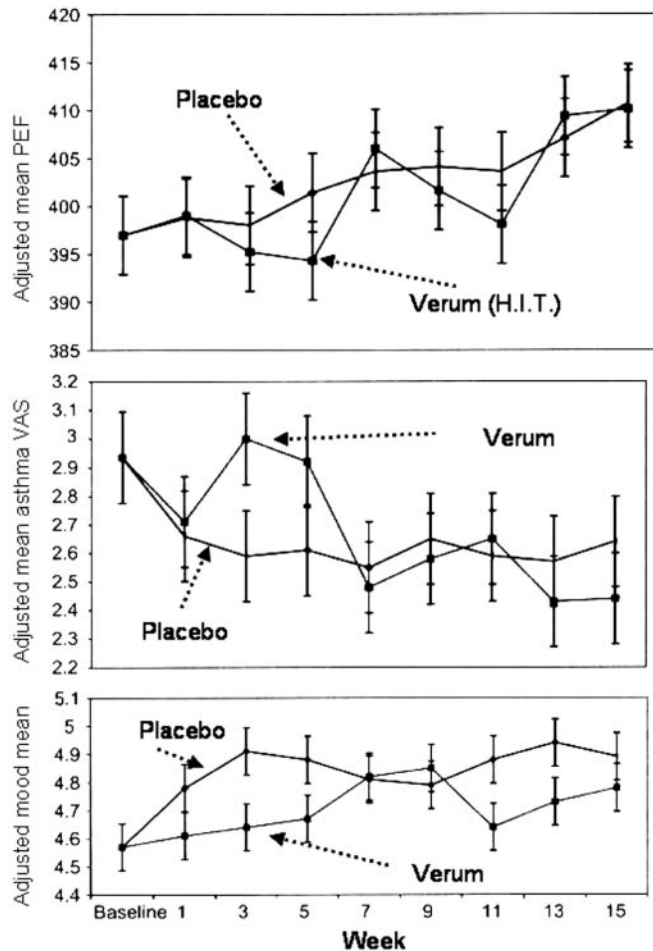


Figure 2. Oscillatory effects in a homeopathic clinical trial. Although the study failed to show a clinical improvement at the end of the trial period, there was nevertheless a significant difference between active treatment compared to placebo: the pattern of data indicate that verum, compared to placebo, approximates to an oscillation. PEF, peak of expiratory flow; VAS, visual analogue scale. Reproduced with permission from Hyland and Lewith, reference 46.

The subjects reported no adverse effects during the 4 weeks intervention period.

Fixed Prescription of Low-Potencies

The treatment of allergic patients using low potencies (4 \times or 6 \times) extract from the plant *G. glauca* has been investigated for many years by Wiesenauer's group (10,18,47). In a double-blind, randomized study of patients with seasonal allergic rhinitis, Wiesenauer and Gaus (10) used *G. glauca* 6 \times without individual homeopathic prescriptions. After 1 month of treatment, an improvement in eye symptoms was observed in 80% of patients in the homeopathic group, in 65% of patients in the placebo group and in 66% of patients in the group receiving the dilution alone, without dynamization. The data were promising but there was not clear cut statistical difference.

Two years later, Wiesenauer and Ludtke (12) published the results of another double-blind, randomized, placebo-controlled study of the effects of *G. glauca* in allergic rhinitis. After 1 month of treatment, there were clear improvements in the experimental group in terms of eye symptoms and nasal symptoms. As in the 1985 study, the authors confirmed the efficacy of *Galphimia* in seasonal allergic rhinitis, and suggested that it should be used only after homeopathic identification of sensitive individuals in order to minimize the number of non-responders. Wiesenauer subsequently continued the experiments and his group has published a number of papers concerning the efficacy of *G. glauca*, the most effective potency being the 4 \times (18,48,49).

Complex Formulations

A group of investigators tested the effectiveness of two homeopathic complexes in bronchial asthma. In the first clinical trial the complex *Engystol-N* (tablets) was studied (19–21). Patients were randomly assigned to verum or placebo groups, under blind conditions. During observation period, those treated with homeopathic complex showed greater improvement of respiratory function. In another paper (26), they described a double-blind, randomized, placebo-controlled study of patients with allergic bronchial asthma already being treated with steroids, bronchodilators and other drugs. One vial of complex *Asthma H Inj. Pflugerplex* (a mixture of low dilutions of many homeopathic plants and minerals) was administered subcutaneously every week for 9 months. The administration of *Triamcinolone* decreased in treated group and increased in placebo group. The treated group also showed a significant reduction in contracted infections and in cationic protein levels, a marker of local inflammation. There was no change in spirometric parameters (FEV and FVC), possibly because patients were advised to take the lowest cortisone dose compatible with the absence of cough and resting dyspnea.

Micciché *et al.* (24) carried out an open study of children with allergic oculorhinitis comparing conventional anti-histaminic and cortisone treatment with a homeopathic protocol based on three drugs (*Doliosobios* No. 15, an organotherapeutic, *Mn-Cu Oligodrop* and *Histaminum 4c*) initiated after the start of pollen season in order to evaluate their acute phase efficacy. After 2 months of treatment, 30 out of 35 children in homeopathic group were cured, 2 received only a slight benefit and 3 were switched to conventional treatment because of relapses. In conventional treatment group, 21 out of 35 children were cured, 7 showed a slight improvement and 7 had to discontinue treatment because of toxic effects. As in other reports from 'equivalence' studies, the effectiveness of homeopathy is clearly demonstrated when it is compared with conventional therapies. However, the validity of results is limited by the fact that this was not a randomized study.

Weiser *et al.* (27) have reported a study of seasonal allergic rhinitis, using a complex product (*Luffa compositum*) in nasal spray formulation. The homeopathic remedy consisted of a

fixed combination made up of *Luffa operculata* and *G. glauca* (in 4×, 12×, 30× potencies), plus *histamine* and *sulfur* (in 12×, 30×, 200× potencies). There was a reference group of patients without homeopathic therapy who were treated only with standard intranasal therapy based on *chromolyn sodium*. The results of the study demonstrate a quick and lasting effect of the treatment, which produced a nearly complete remission of hay fever symptoms. Adverse systemic effects did not occur. Local adverse events appeared in 3 patients among a total of 146. In conclusion, the authors suggested that, for the treatment of hay fever, the homeopathic nasal spray is as efficient and well tolerable as conventional therapy with *chromolyn sodium*.

Systematic Reviews of Allergy and Asthma

A meta-analysis of seven randomized clinical trials (RCT) to assess the efficacy of homeopathic preparations of *G. glauca* in treatment of allergic rhinitis was published by Ludtke and Wiesenauer (50). The data are consistently in favor of a statistically significant effect of the low-dose homeopathic medicine over placebo, particularly in relief of eye symptoms. Verum estimate of success is reported of ~80%. The validity of these experimental studies was confirmed also by independent meta-analyses (51,52).

The review of Kleijnen *et al.* (53) and the meta-analysis of Reilly of his own studies (28) suggested that HIT was effective in the treatment of rhinitis. There have been a few reviews of randomized, controlled trials published regarding the use of homeopathy for asthma treatment. Six trials were included in a recent review (54,55). These trials were of variable quality and the results of the studies are conflicting in terms of effects on lung function. The authors underlined that standardized treatments in these trials are unlikely to represent common homeopathic practice where treatment tends to be individualized. More and larger trials are therefore urgently needed to assess properly the role of homeopathy in management of asthma, but experts (51,56,57) suggested that as well as randomized trials, there is a need for observational data to document the different methods of homeopathic prescribing and how patients respond. Further studies could assess whether individuals respond to a 'package of care' (i.e. the effects of medication as well as consultation, which is considered a vital part of individualized homeopathic practice) rather than the homeopathic medicine against placebo alone.

Discussion

While complementary medicine and homeopathy are becoming an increasingly prominent part of health care practices, there is paucity of controlled studies concerning their effectiveness. Traditional knowledge has been accumulating for over 200 years, but only in past few decades modern research methods such as RCT, rigorous observational studies and equivalence studies comparing homeopathy with conventional standard therapies have been applied.

Few well-designed studies have been reproduced by independent research teams for two main reasons: lack of sufficient funding and lack of a sufficient number of well-trained homeopaths who are qualified and interested in research. As a matter of fact, the debate on efficacy of homeopathy is still very hot, as shown by a series of reviews (51,52,58,59) and chiefly by the controversial meta-analysis published by the *Lancet* (60,61) and by the significant expert reactions to the latter (62–64).

Even though the number of papers published in peer-reviewed journals is increasing, the results of many clinical studies on effectiveness of homeopathy are characterized by low standards of methodology (52,53,65). The major problems in most trials were the description of allocation concealment, imprecise outcomes and the reporting of drop-outs and withdrawals. Other concerns are publication bias (tendency to publish more positive than negative trials, a problem that is also present in conventional medicine) and lack of independent replications of most conducted studies.

This review summarizes the trial data for or against homeopathy as a treatment for a series of diseases due to disorders of immune system and/or dysregulation of local inflammatory processes. We are confident that the reported studies represent a large majority of available literature in this field, although some omission cannot be excluded. Clearly, the few dozens of papers reported are highly heterogeneous in terms of disease conditions, drug used and experimental designs.

There was great heterogeneity in the nature of the homeopathic intervention applied: mostly fixed combinations or complexes, several individualized homeopathy with single remedies, some isotherapy studies in allergy. In Table 3 the studies concerning the disorders of immune system considered in this review are grouped according to clinical condition and type of homeopathic treatment; the clinical evidence of the major groups of treatments was classified according to criteria that have been reported in Table 1.

The best evidences of effectiveness appearing in the top two rows of Table 3 and are *G. glauca* (low potencies) in allergic oculorhinitis, classical individualized homeopathy for otitis, *Euphorbium compositum* for rhinitis–sinusitis, *Traumeel* in post-chemotherapy stomatitis. The use of homeopathy in those conditions is indirectly supported also by evidence in basic science, animal studies or theory [(89,90) and P. Bellavite, R. Ortolani, F. Pontarollo, G. Pitari, A. Conforti, unpublished data]. In grade C (unclear or conflicting evidence) there are many studies, because positive results reported by some authors were not replicated by others. The classical individualized therapy of allergy and asthma was shown to be effective in a number of studies and not effective only in one trial, but several positive trials were of lower quality and published in non-indexed journals; so, as a caution, we considered the scientific evidence as still unclear according to the criteria of Table 1. The number of homogeneous trials is too small to attempt pooling and meta-analysis.

In synthesis, there are many promising studies supporting clinically demonstrable activity of homeopathic medicines

Table 3. Summary of the levels of evidence of clinical homeopathic studies in immunoallergology

Level of evidence	Infections of upper airways and ear–nose–throat diseases	Allergy and asthma
A (strong scientific evidence)	–	<i>Galphimia glauca</i> (low potencies) IN ALLERGIC OCULORHINITIS (10) , (12) , (18) , (49) , (50) , (51)
B (good scientific evidence)	CLASSICAL INDIVIDUALIZED HOMEOPATHY IN OTITIS (66) , (67) , (68) , (69) , (70) Euphorbium compositum IN RHINITIS–SINUSITIS (71) , (72) , (73) , (74) <i>Traumeel-S</i> IN POST-CHEMOTHERAPY STOMATITIS (75)	–
C (unclear or conflicting scientific evidence)	CLASSICAL INDIVIDUALIZED HOMEOPATHY FOR URTI: →Effective: (69) , (76) ; →Not effective: (77) , (78) , (79) . HOMEOPATHIC COMPLEX FORMULATIONS: <i>Eupatorium</i> (80) <i>L52</i> (81) , <i>Drosera</i> (82) , <i>Grippheel</i> (83) , (84)	HOMEOPATHIC IMMUNOTHERAPY (ISOTHERAPY): →Effective: (9) , (11) , (17) , (15) , (28) , (29) , (35) ; →Not effective: (31) , (30) , (46) , (32) , (34) CLASSICAL INDIVIDUALIZED HOMEOPATHY: →Effective: (8) , (13) , (16) , (22) , (23) , (25) , (36) , (37) ; →Not effective: (33) . HOMEOPATHIC COMPLEX FORMULATIONS: <i>Luffa compositum</i> (27) ; <i>Asthma H Inj. Pflugerplex</i> (26) ; <i>Engystol-N</i> (20) , (19) , (21) .
D (fair negative scientific evidence)	<i>Engystol-N</i> injection (85) Homeopathic complex <i>Luffa</i> + <i>Cinnabaris</i> + <i>Kalium bichromicum</i> (86)	–
E (strong negative scientific evidence)	–	–
Lack of adequate evidence	<i>Lymphomyosot</i> (87) , <i>Phytolacca americana</i> + <i>Guajacum officinale</i> + <i>Capsicum annum</i> , <i>Sinusitis PMD</i> (88)	Homeopathic protocol based on <i>Doliosobios</i> No. 15, <i>Mn-Cu Oligodrop</i> and <i>Histaminum</i> (24)

The characters of reference numbers indicate the type of study and of publication: boldface indicates randomized controlled trial or meta-analysis covering the topic; italics indicate non-randomized controlled trial; normal case indicates uncontrolled, observational and retrospective studies; underlines indicate PubMed indexed journals.

in immunoallergology but the database of high-quality homeopathic research in various fields is very small. Most studies here reviewed suggest that homeopathic medicines in high dilutions, prescribed by trained professionals, are safe and are unlikely to provoke severe adverse reactions, in agreement with previous reports (91–93).

Placebo and Effectiveness, Different Questions

Clinical research on homeopathy has been initially focusing on the question of placebo. The first relevant RCT published by top medical journals came out in 1986 with the title ‘Is homeopathy a placebo response?’ (11) and 20 years later a meta-analysis published in this field meaningfully had the title ‘Are the clinical effects of homeopathy placebo effects?’ (61) (Fig. 3). This clearly indicates that we still do not have a consensus, but possibly also because the question is not correct, and this is the case for those medicines that contain low dilutions, i.e. ponderal doses, of active principles. The latter medicines by definition cannot be considered as inert placebos, but the distinction was ignored by the famed *Lancet*’s meta-analysis (61) and its related editorial (60).

On evaluating the evidence in favor and against clinical effectiveness of a therapy, it should be pointed out that the placebo question is exceedingly important but is not equivalent to the question of whether a therapeutic approach is clinically effective. The evidence of specific activity of a drug

over placebo is usually achieved in double-blind RCT. Epidemiologists agree that this ‘artificial’ setting may have high internal validity but often fails to reproduce the ‘real life’ application of the method. Patients and physicians need also an answer to the empirical question of whether and how much the homeopathic therapy, considered as a whole system of cure, may help to decrease symptoms, improve quality of life and may substitute other, often more toxic, forms of therapy. More pragmatic studies aimed at ‘improving’ instead of ‘proving’ homeopathy have been suggested (45,51,94).

To Blind or Not to Blind

The blinding procedure that is often related to the problem is utilized in clinical research. This procedure has been so widely employed in evidence-based research on conventional drugs that there is the tendency to consider it as the gold standard for any clinical research. However, randomized trials have important limitations in interventions that require particular skills (95) and finding the correct homeopathic *simillimum* depends on in-depth anamnesis and atmosphere of trust, which is disrupted by randomization (96). In homeopathy, the parameters of evaluation follow specific rules that imply consideration of the totality of a patient’s symptoms which includes the disease’s symptoms and a continuous follow-up that often requires careful evaluation of response by the clinician, and often change of medicine, particularly in chronic

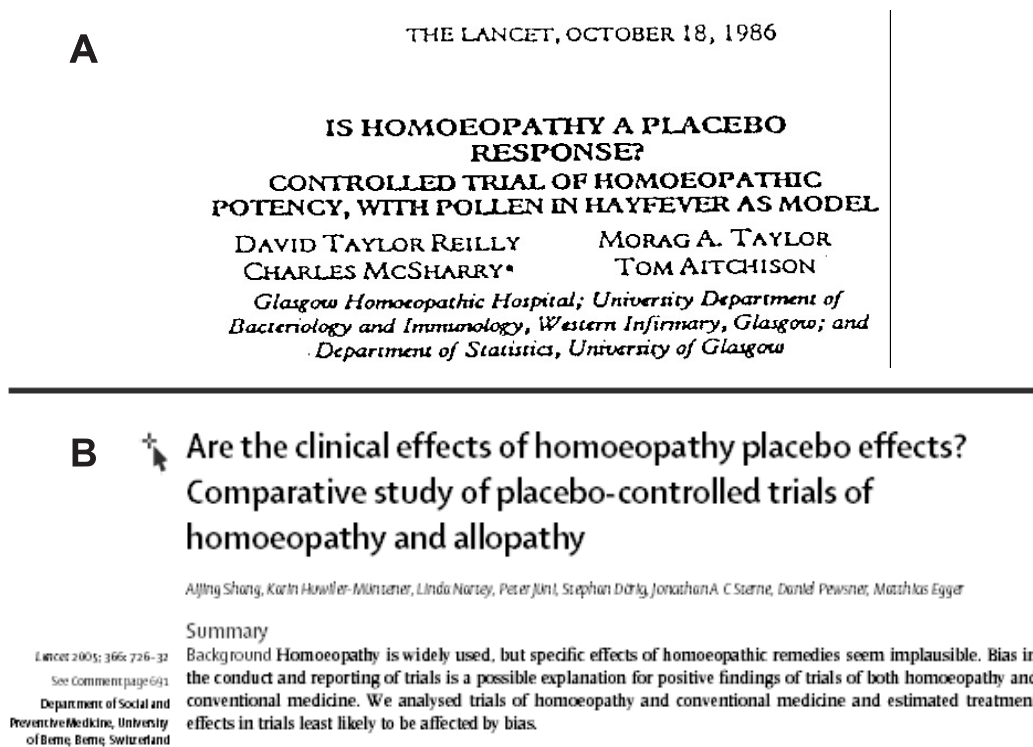


Figure 3. Titles of *Lancet's* two publications on homeopathic trials. Reproduced with permission from *Lancet* 1986;2:881–6 (A) and from *Lancet* 2005;366:726–32 (B).

cases. To successfully discriminate between complex responses to a homeopathic treatment it is important to know the characteristics of the substance given to the patient and the healing steps of this modality.

We consider the great importance that is given by classic homeopathy to the interactions such as those between patient–doctor–medicine and environment–body–mind (97,98). It has been suggested that, according to the theory of ‘entanglement’ (99–102), the remedy would act in the context of a tripartite relationship with the patient and the practitioner. What may be the physical basis of such an entanglement is still a matter of speculation, but this point forces us to take into account the ‘context’ of cure (e.g. patient–physician interactions) and therefore to seriously question the double blinding for testing homeopathy: this method by definition would disrupt those interactions (103).

According to these premises, one can assume that in homeopathic cure a complex *interaction* of these mechanisms occurs: (i) a small physical action of extremely low-dose remedy, (ii) the activation of centers responding to ‘placebo effect’ due to beliefs, expectations of the patient and (iii) the endogenous healing mechanisms (99,100,104–108). If this is the case, the therapeutic effect is due not to the *sum* of these factors but to their *product* and any procedure decreasing or shutting down one of them (as blinding undoubtedly does) may markedly affect homeopathic cure, much more than allopathic drug effect. As a consequence of the interference with everyday routine homeopathic practice, more false

negative findings are expected in homeopathic double-blind studies than in allopathic ones (109).

Observational Research

Observational research of uncontrolled homeopathic practice documents consistently strong therapeutic effects and sustained satisfaction in patients (59). An observational study showed that over 70% of patients attending a homeopathic hospital out-patient unit recorded positive changes in a wide range of chronic diseases (110). Superimposable to this finding is the report showing that 7 out of 10 patients visiting a Norwegian homeopath reported a meaningful improvement in their main complaint 6 months after the initial consultation (111). Similar or even higher percentages of patients declaring their satisfaction with homeopathic cure were reported by others (112–116). Interestingly, a study was undertaken to investigate the preferences of patients with asthma for various treatment modalities showed that the extent to which the doctor treated the patient as a whole person was also a statistically significant attribute for the choice of homeopathic therapy versus conventional therapy, even if clinical results are perceived as equivalent (8).

So, we are in the situation that if we adopt the strict criteria of evidence-based medicine, which were initially developed for chemical drugs, the analysis of published literature on homeopathy finds little evidence of superiority of homeopathic medicines over placebo. If we accept observational

studies and equivalence studies as valuable tools of investigation, we find many proofs of effectiveness of homeopathy. In any case this is valuable information from a pragmatic standpoint because it enables the decision based on other factors like patient's personal preference, adverse effects, availability and costs. The integration of RCT, observational prospective studies and pharmacoeconomic analyses are the future of research in this field.

Conclusions and Prospects

In summary, there is an efficacy/effectiveness paradox (similar to that found in several other areas of complementary medicine research) with a weak evidence in favor of homeopathy when studies are done in randomized and double-blind conditions, but yet there is documented effectiveness in equivalence studies comparing homeopathy and conventional medicine and documented usefulness in general practice (59): the therapy is useful when applied in open practice and produces substantial effects, even in patients with chronic diseases (117,118). This paradox leads to two conclusions: (i) additional clinical research, both experimental and observational, including studies using different designs, is necessary for further research development in homeopathy and (ii) it is conceivable that the discrepancies are due to lack of a consistent theory concerning the action mechanism of homeopathy (59), so that additional basic research and innovative approaches to this problem are urgently warranted.

Nevertheless, the growing public interest in homeopathy (probably due more to a 'liking' for this therapeutic system as a whole and the use of small doses rather than to any scientific certainty concerning its effectiveness) allows us to hope that also this section of medicine will also receive greater attention from the competent authorities and the scientific world. Rigorous clinical studies examining effectiveness of homeopathy like other complementary and alternative medicines are needed (119). It will be necessary to adapt research methodologies to the homeopathic field in order to respect the complexity of its diagnostic procedure, but it is equally necessary to ensure that protocols include objective measurements of clinical and laboratory parameters, as well as adequate control groups of untreated subjects or subjects treated with conventional therapies.

References

- Bellavite P, Ortolani R, Pontarollo F, Piasere V, Benato G, Conforti A. Immunology and homeopathy. 4. Clinical studies—part 1. *Evid Based Complement Alternat Med* 2006;3:293–301.
- Schafer T, Riehle A, Wichmann HE, Ring J. Alternative medicine in allergy. *Allergy* 2002;57:694–700.
- Jorgensen V, Launso L. Patients' choice of asthma and allergy treatments. *J Altern Complement Med* 2005;11:529–34.
- Frenkel M, Hermoni D. Effects of homeopathic intervention on medication consumption in atopic and allergic disorders. *Altern Ther Health Med* 2002;8:76–9.
- Schafer T. Epidemiology of complementary alternative medicine for asthma and allergy in Europe and Germany. *Ann Allergy Asthma Immunol* 2004;93:S5–10.
- Launso L, Rieper J. General practitioners and classical homeopaths treatment models for asthma and allergy. *Homeopathy* 2005;94:17–25.
- Passalacqua G, Compalati E, Schiappoli M, Senna G. Complementary and alternative medicine for the treatment and diagnosis of asthma and allergic diseases. *Monaldi Arch Chest Dis* 2005;63:47–54.
- Ratcliffe J, van Haselen R, Buxton M, Hardy K, Colehan J, Partridge M. Assessing patients' preferences for characteristics associated with homeopathic and conventional treatment of asthma: a conjoint analysis study. *Thorax* 2002;57:503–8.
- Hardy J. A double-blind placebo controlled trial of house dust potencies in the treatment of house dust allergy. *Br Hom Res Group Comm* 1984;11:75–6.
- Wiesenaue M, Gaus W. Double-blind trial comparing the effectiveness of the homeopathic preparation *Galphimia* potentiation D6, *Galphimia* dilution 10⁻⁶ and placebo on pollinosis. *Arzneimittelforschung* 1985;35:1745–7.
- Reilly DT, Taylor MA, McSharry C, Aitchison T. Is homeopathy a placebo response? Controlled trial of homeopathic potency, with pollen in hayfever as model. *Lancet* 1986;2:881–6.
- Wiesenaue M, Ludtke R. *The Treatment of Pollinosis with Galphimia glauca D4—A Randomized Placebo-Controlled Double Blind Clinical Trial*. Edition forschung, vol. 3, Stuttgart: Hippocrates Verlag, 1987, 235–43.
- Mosquera Pardo MF. Bronchial asthma in childhood: management by means of homeopathia. Proceedings of the 2nd OMHI Congress. 1990, 156–66.
- Campbell JH, Taylor MA, Beattie N, McSharry C, Aitchison T, Carter R, et al. Is homeopathy a placebo response? A controlled trial of homeopathic immunotherapy in atopic asthma. *Am Rev Resp Dis* 1990;141:A24.
- Reilly DT, Taylor MA, Beattie NG, Campbell JH, McSharry C, Aitchison TC, et al. Is evidence for homeopathy reproducible? *Lancet* 1994;344:1601–6.
- Castellsagu API. Evolution of 26 cases of bronchial asthma with homeopathic treatment. *Br Homeopath J* 1992;81:173–5.
- Nolleveaux MA. Interet de la prescription d'APP (Apis 15 cH, Pulmo-Histaminum 15 cH, Pollantium 30 cH) dans la rhinite allergique. Observations cliniques en pratique journaliere. *Homeopath Fr* 1992;80:24–33.
- Wiesenaue M, Ludtke R. The treatment of pollinosis with *Galphimia glauca* D4—a randomized placebo-controlled double-blind clinical trial. *Phytomedicine* 1995;2:3–6.
- Matusiewicz R. Efficacia de *Engystol* en l'asma bronquial corticopendente. *Med Biol* 1996;5:176–80.
- Matusiewicz R. Wirksamkeit von *Engystol* N bei Bronchialasthma unter kortikoidabhängiger Therapie. *Biol Med* 1995;24:242–6.
- Matusiewicz R. The homeopathic treatment of corticosteroid dependent asthma: a doubleblind, placebo-controlled study. *Biomed Ther* 1997;4:117–22.
- Eizayaga FX, Eizayaga J. Homeopathic treatment of bronchial asthma. *Br Hom J* 1996;85:28–33.
- Lara-Marquez ML, Pocino M, Rodriguez F, Carvallo GE, Ortega CF, Rodriguez C. Homeopathic treatment for atopic asthma lung function and immunological outcomes in a randomized clinical trial in Venezuela. Proceedings of the 52nd LMHI Congress. Seattle, USA, 1997, 73.
- Micciché G, Trapani GF, Lucamante M, Lanza C, Tanga L, Gallese A, Grasso RM, Totino T. Le oculoriniti allergiche in età pediatrica. *Cah Biother* 1998;1/2:13–8.
- Riveron-Garrote M, Fernandez-Argulles R, Moron-Rodriguez F, Campistrou-Labaut JL. Ensayo clinico controlado aleatorizado del tratamiento homeopático del asma bronquial. *Bol Mex Hom* 1998;31:54–61.
- Matusiewicz R, Wasniewski J, Sterna Bazanska A, Hulsberg M. Behandlung des chronischen Asthma bronchiale mit einem homeopathischen komplexmittel. *Erfahrungsheilkunde* 1999;48:367–74.
- Weiser M, Gegenheimer LH, Klein P. A randomized equivalence trial comparing the efficacy and safety of *Luffa comp.*-Heel nasal spray with cromolyn sodium spray in the treatment of seasonal allergic rhinitis. *Forsch Komplementarmed* 1999;6:142–8.
- Taylor MA, Reilly D, Llewellyn-Jones RH, McSharry C, Aitchison TC. Randomised controlled trial of homeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *Br Med J* 2000;321:471–6.
- Aabel S, Laerum E, Dolvik S, Djupesland P. Is homeopathic 'immunotherapy' effective? A double-blind, placebo-controlled trial with the

- isopathic remedy Betula 30c for patients with birch pollen allergy. *Br Homeopath J* 2000;89:161–8.
30. Aabel S. No beneficial effect of isopathic prophylactic treatment for birch pollen allergy during a low-pollen season: a double-blind, placebo-controlled clinical trial of homeopathic Betula 30c. *Br Homeopath J* 2000;89:169–73.
 31. Aabel S. Prophylactic and acute treatment with the homeopathic medicine, Betula 30c for birch pollen allergy: a double-blind, randomized, placebo-controlled study of consistency of VAS responses. *Br Homeopath J* 2001;90:73–8.
 32. Lewith GT, Watkins AD, Hyland ME, Shaw S, Broomfield JA, Dolan G, Holgate ST. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial. *Br Med J* 2002;324:520.
 33. White A, Slade P, Hunt C, Hart A, Ernst E. Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomised placebo controlled trial. *Thorax* 2003;58:317–21.
 34. Li AM, Bush A, Wilson NM. Homeopathy in childhood asthma. *Thorax* 2003;58:826.
 35. Kim LS, Riedlinger JE, Baldwin CM, Hilli L, Khalsa SV, Messer SA, et al. Treatment of seasonal allergic rhinitis using homeopathic preparation of common allergens in the southwest region of the US: a randomized, controlled clinical trial. *Ann Pharmacother* 2005;39:617–24.
 36. Witt C, Keil T, Selim D, Roll S, Vance W, Wegscheider K, et al. Outcome and costs of homeopathic and conventional treatment strategies: a comparative cohort study in patients with chronic disorders. *Complement Ther Med* 2005;13:79–86.
 37. Colin P. Homeopathy and respiratory allergies: a series of 147 cases. *Homeopathy* 2006;95:68–72.
 38. Dantas F. Homeopathy in childhood asthma. *Thorax* 2003;58:826.
 39. Fisher P, Chatfield K, Mathie R. Homeopathy in childhood asthma. *Thorax* 2003;58:827.
 40. Gyorik SA, Brutsche MH. Complementary and alternative medicine for bronchial asthma: is there new evidence? *Curr Opin Pulm Med* 2004;10:37–43.
 41. Bellavite P, Conforti A, Piasere V, Ortolani R. Immunology and homeopathy. 1. Historical background. *Evid Based Complement Altern Med* 2005;2:441–52.
 42. Poitevin B. Review of experimental studies in allergy: clinical studies. *Br Homeopath J* 1998;87:89–99.
 43. Reilly DT, Taylor MA. Potent placebo or potency? A proposed study model with its initial findings using homeopathically prepared pollens in hayfever. *Br Homeopath J* 1985;74:65–75.
 44. Boucinhas JC, DeMadeiros Boucinhas ID. Prophylaxie des crises d'asthme bronchique chez l'enfant par l'usage de Poumon histamine 5 CH. *Homeopath Fr* 1990;78:35–9.
 45. Reilly D. Randomised controlled trials for homeopathy. When is useful improvement a waste of time? Double positive paradox of negative trials. *Br Med J* 2002;325:4.
 46. Hyland ME, Lewith GT. Oscillatory effects in a homeopathic clinical trial: an explanation using complexity theory, and implications for clinical practice. *Br Homeopath J* 2002;91:145–9.
 47. Wiesenauer M, Haussler S, Gaus W. Pollinosis-therapie mit *Galphimia glauca*. *Fortschr Med* 1983;101:811–4.
 48. Wiesenauer M, Gaus W, Haussler S. Behandlung der Pollinosis mit *Galphimia glauca*. Eine Doppelblindstudie unter Praxisbedingungen. *Allergologie* 1990;13:359–63.
 49. Wiesenauer M, Ludtke R. A metaanalysis of the homeopathic treatment of pollinosis with *Galphimia glauca*. *Forsch Komplementarmed* 1996;3:230–4.
 50. Ludtke R, Wiesenauer M. A meta-analysis of homeopathic treatment of pollinosis with *Galphimia glauca*. *Wien Med Wochenschr* 1997;147:323–7.
 51. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350:834–43.
 52. Jonas WB, Kaptchuk TJ, Linde K. A critical overview of homeopathy. *Ann Intern Med* 2003;138:393–9.
 53. Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homeopathy. *Br Med J* 1991;302:316–23.
 54. McCarney RW, Lasserson TJ, Linde K, Brinkhaus B. An overview of two Cochrane systematic reviews of complementary treatments for chronic asthma: acupuncture and homeopathy. *Respir Med* 2004;98:687–96.
 55. McCarney RW, Linde K, Lasserson TJ. Homeopathy for chronic asthma. *Cochrane Database Syst Rev* 2004; CD000353.
 56. Lewith GT, Watkins AD. Unconventional therapies in asthma: an overview. *Allergy* 1996;51:761–9.
 57. Linde K, Jobst KA. Homeopathy for chronic asthma. *Cochrane Database Syst Rev* 2000; CD000353.
 58. Cucherat M, Haugh MC, Gooch M, Boissel JP. Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials. HMRAG. Homeopathic Medicines Research Advisory Group. *Eur J Clin Pharmacol* 2000;56:27–33.
 59. Walach H, Jonas WB, Ives J, Wijk RV, Weingartner O. Research on homeopathy: state of the art. *J Altern Complement Med* 2005;11:813–29.
 60. Editorial. The end of homeopathy. *Lancet* 2005;366:690.
 61. Shang A, Huwiler-Müntener K, Nartey L, Jüni P, Dörig S, Sterne JAC, et al. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet* 2005;366:726–32.
 62. McCarthy M. Critics slam draft WHO report on homeopathy. *Lancet* 2005;366:705–6.
 63. Bell IR. All evidence is equal, but some evidence is more equal than others: can logic prevail over emotion in the homeopathy debate? *J Altern Complement Med* 2005;11:763–9.
 64. Fisher P. Homeopathy and The Lancet. *Evid Based Complement Alternat Med* 2006;3:145–7.
 65. Linde K, Jonas WB, Melchart D, Willich S. The methodological quality of randomized controlled trials of homeopathy, herbal medicines and acupuncture. *Int J Epidemiol* 2001;30:526–31.
 66. Friese KH, Kruse S, Ludtke R, Moeller H. The homeopathic treatment of otitis media in children—comparisons with conventional therapy. *Int J Clin Pharmacol Ther* 1997;35:296–301.
 67. Kruse S. Otitis media bei Kindern. Stuttgart: Edition Forschung, Hippokrates Verlag, 1998.
 68. Frei H, Thurneysen A. Homeopathy in acute otitis media in children: treatment effect or spontaneous resolution? *Br Homeopath J* 2001;90:180–2.
 69. Riley D, Fischer M, Singh B, Haidvogel M, Heger M. Homeopathy and conventional medicine: an outcomes study comparing effectiveness in a primary care setting. *J Altern Complement Med* 2001;7:149–59.
 70. Jacobs J, Springer DA, Crothers D. Homeopathic treatment of acute otitis media in children: a preliminary randomized placebo-controlled trial. *Pediatr Infect Dis J* 2001;20:177–83.
 71. Sprenger F. The therapy of rhinitis. *Biol Ther* 1989;7:60–3.
 72. Connert WD, Maiwald J. The therapy of rhinopathy as associated with previous abuse of nasal spray and with vasomotor influences. *Biol Ther* 1991;9:182–6.
 73. Weiser M, Clasen BP. Controlled double-blind study of a homeopathic sinusitis medication. *Biol Ther* 1994;13:4–11.
 74. Ammerschlager H, Klein P, Weiser M, Oberbaum M. Treatment of inflammatory diseases of the upper respiratory tract—comparison of a homeopathic complex remedy with xylometazoline. *Forsch Komplementarmed Klass Naturheilkd* 2005;12:24–31.
 75. Oberbaum M, Yaniv I, Ben Gal Y, Stein J, Ben Zvi N, Freedman LS, et al. A randomized, controlled clinical trial of the homeopathic medication *Traumeel S* in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. *Cancer* 2001;92:684–90.
 76. Steinsbekk A, Fonnebo V, Lewith G, Bentzen N. Homeopathic care for the prevention of upper respiratory tract infections in children: a pragmatic, randomised, controlled trial comparing individualised homeopathic care and waiting-list controls. *Complement Ther Med* 2005;13:231–8.
 77. de Lange de Klerk ES, Blommestein J, Kuik DJ, Bezemer PD, Feenstra L. Effect of homeopathic medicines on daily burden of symptoms in children with recurrent upper respiratory tract infections. *Brit Med J* 1994;309:1329–1332.
 78. Steinsbekk A, Bentzen N, Fonnebo V, Lewith G. Self treatment with one of three self selected, ultramolecular homeopathic medicines for the prevention of upper respiratory tract infections in children. A double-blind randomized placebo controlled trial. *Br J Clin Pharmacol* 2005;59:447–55.
 79. Trichard M, Chaffuerin G, Nicoloyannis N. Pharmacoeconomic comparison between homeopathic and antibiotic treatment strategies in recurrent acute rhinopharyngitis in children. *Homeopathy* 2005;94:3–9.

80. Gassinger CA, Wunstel G, Netter P. A controlled clinical trial for testing the efficacy of the homeopathic drug eupatorium perfoliatum D2 in the treatment of common cold. *Arzneimittelforschung* 1981;31:732–6.
81. Lecoq PL. L-52. Les voies thérapeutiques des syndromes grippaux. *Cah Biother* 1985;87:65–73.
82. Bordes LR, Dorfman P. Evaluation de l'activité antitussive du sirop Drosetux: Etude en double aveugle versus placebo. *Cah Otorhinolaryngol* 1986;21:731–4.
83. Maiwald VL, Weinfurter T, Mau J, Connert WD. Therapy of common cold with a homeopathic combination preparation in comparison with acetylsalicylic acid. A controlled, randomized double-blind study. *Arzneimittelforschung* 1988;38:578–82.
84. Rabe A, Weiser M, Klein P. Effectiveness and tolerability of a homeopathic remedy compared with conventional therapy for mild viral infections. *Int J Clin Pract* 2004;58:827–32.
85. Heilmann A. A combination injection preparation as a prophylactic for flu common colds. *Biol Ther* 1994;7:249–53.
86. Wiesenauer M, Gaus W, Bohnacker U, Haussler S. Efficiency of homeopathic preparation combinations in sinusitis. Results of a randomized double blind study with general practitioners. *Arzneimittelforschung* 1989;39:620–5.
87. Zenner S, Metelmann H. Therapeutic use of lymphomyosot, result of a multicentric use observation study on 3512 patients. *Biol Ther* 1990;8:49–69.
88. Wiesenauer M. Comparison of solid and liquid forms of homeopathic remedies for tonsillitis. *Adv Ther* 1998;15:362–71.
89. Bellavite P, Conforti A, Pontarollo F, Ortolani R. Immunology and homeopathy. 2. Cells of the immune system and inflammation. *Evid Based Complement Altern Med* 2006;3:13–24.
90. Bellavite P, Conforti A, Ortolani R. Immunology and homeopathy. 3. Experimental studies on animal models. *Evid Based Complement Alternat Med* 2006;3:171–86.
91. Dantas F, Rampes H. Do homeopathic medicines provoke adverse effects? A systematic review. *Br Homeopath J* 2000;89:S35–8.
92. Fisher P, Dantas F, Rampes H. The safety of homeopathic products. *J R Soc Med* 2002;95:474–6.
93. Endrizzi C, Rossi E, Crudeli L, Garibaldi D. Harm in homeopathy: aggravations, adverse drug events or medication errors? *Homeopathy* 2005;94:233–40.
94. van Haselen R, Fisher P, Dantas F. Improving the success of homeopathy 2, London, 15–16 April 1999. Taking homeopathic research into the next millennium. *Br Homeopath J* 1999;88:191–4.
95. Kotaska A. Inappropriate use of randomised trials to evaluate complex phenomena: case study of vaginal breech delivery. *Br Med J* 2004;329:1039–42.
96. Kiene H, Kienle GS, Schon-Angerer T. Bias in meta-analysis. *Homeopathy* 2006;95:54.
97. Swayne J. *Homeopathic Method*, New York: Churchill Livingstone, 1998.
98. Bellavite P, Pitari G, Italiano M. Homeopathy and placebo. *Homeopathy* 2006;95:51.
99. Milgrom LR. Patient–practitioner–remedy (PPR) entanglement. Part 1: a qualitative, non-local metaphor for homeopathy based on quantum theory. *Homeopathy* 2002;91:239–48.
100. Walach H. Entanglement model of homeopathy as an example of generalized entanglement predicted by weak quantum theory. *Forsch Komplementarmed Klass Naturheilkd* 2003;10:192–200.
101. Hyland ME. Does a form of 'entanglement' between people explain healing? An examination of hypotheses and methodology. *Complement Ther Med* 2004;12:198–208.
102. Walach H. Entangled-and tied in knots! Practical consequences of an entanglement model for homeopathic research and practice. *Homeopathy* 2005;94:96–9.
103. Milgrom LR. Are randomized controlled trials (RCTs) redundant for testing the efficacy of homeopathy? A critique of RCT methodology based on entanglement theory. *J Altern Complement Med* 2005;11:831–8.
104. Bell IR, Baldwin CM, Schwartz GE. Translating a nonlinear systems theory model for homeopathy into empirical tests. *Altern Ther Health Med* 2002;8:58–66.
105. Torres JL. Homeopathic effect: a network perspective. *Homeopathy* 2002;91:89–94.
106. Bellavite P. Complexity science and homeopathy. A synthetic overview. *Homeopathy* 2003;92:203–12.
107. Bell IR, Lewis DA, Lewis SE, Brooks AJ, Schwartz GE, Baldwin CM. Strength of vital force in classical homeopathy: bio-psycho-social-spiritual correlates within a complex systems context. *J Altern Complement Med* 2004;10:123–31.
108. Hyland ME. Entanglement and some heretical thoughts about homeopathy. *Homeopathy* 2005;94:105–6.
109. Weatherley-Jones E, Thompson EA, Thomas KJ. The placebo-controlled trial as a test of complementary and alternative medicine: observations from research experience of individualised homeopathic treatment. *Homeopathy* 2004;93:186–9.
110. Spence DS, Thompson EA, Barron SJ. Homeopathic treatment for chronic disease: a 6-year, university-hospital outpatient observational study. *J Altern Complement Med* 2005;11:793–8.
111. Steinsbekk A, Ludtke R. Patients' assessments of the effectiveness of homeopathic care in Norway: a prospective observational multicentre outcome study. *Homeopathy* 2005;94:10–6.
112. Attena F, Del Giudice N, Verrengia G, Granito C. Homeopathy in primary care: self-reported change in health status. *Complement Ther Med* 2000;8:21–5.
113. Thompson EA, Reilly D. The homeopathic approach to symptom control in the cancer patient: a prospective observational study. *Palliat Med* 2002;16:227–33.
114. Muscari-Tomaioli G, Allegri F, Miali E, Pomposelli R, Tubia P, Targhetta A, et al. Observational study of quality of life in patients with headache, receiving homeopathic treatment. *Br Homeopath J* 2001;90:189–97.
115. Van Wassenhoven M, Ives G. An observational study of patients receiving homeopathic treatment. *Homeopathy* 2004;93:3–11.
116. Witt CM, Luedtke R, Baur R, Willich SN. Homeopathic medical practice: long-term results of a cohort study with 3981 patients. *BMC Public Health* 2005;5:115.
117. Guthlin C, Lange O, Walach H. Measuring the effects of acupuncture and homeopathy in general practice: an uncontrolled prospective documentation approach. *BMC Public Health* 2004;4:6.
118. Robinson T. Responses to homeopathic treatment in National Health Service general practice. *Homeopathy* 2006;95:9–14.
119. Cooper EL. Complementary and alternative medicine, when rigorous, can be science. *Evid Based Complement Alternat Med* 2004;1:1–5.

Received March 6, 2006; accepted June 9, 2006