

# Effectiveness of Homeopathy in Immunology and Inflammation Disorders. A Literature Overview of Clinical Studies

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**Abstract:** Here we summarize the clinical research carried out in the past three decades to evaluate the effectiveness of homeopathy in conditions characterized by respiratory allergy, common upper respiratory tract infections, otorhinolaryngologic complaints, and rheumatic diseases. Most of initial evidence-based research, especially in allergy, was addressed to the question of whether homeopathic medicines used in high dilutions are placebos or possess specific effects, but this question has been often equivocated and is still a matter of debate. Collectively 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, in fibromyalgia and possibly in upper respiratory tract infections and allergic complaints. A general weakness of the evidence derives from the scarcity of independent confirmation of reported trials and from the presence of conflicting results, as in case of homeopathic immunotherapy of allergy and for asthma. In our opinion, since the homeopathic medicines are safe and under the light of few clinical and pre-clinical findings, their use could be regarded as a possible option in infections of upper airways, otitis, allergic rhinitis and asthma, provided that the homeopathic methodology of prescription is correct and not progressive. The suitable methods to evaluate homeopathy effectiveness, without altering the setting of the cure, are also discussed.

## Introduction

Homeopathic experience and literature have often been relegated to a self-contained, self-sufficient world which at the same time proves difficult to judge according to the categories of modern medicine. This situation today is slowly but steadily changing. Homeopathic clinical research has developed over the last twenty years with the increasingly greater use of modern medical methods (clinical trials, observational studies, statistic evaluations, computerized storage programs and instrumental or laboratory testing). Over two hundred clinical trials designed to verify the efficacy homeopathic treatments have been published, many (but not all) of which have led to positive results. The authors of a meta-analysis of the homeopathic clinical trials published up to 1991<sup>(1)</sup> wrote that the evidence was sufficient to make homeopathy a

treatment worthy of consideration in particular cases, although they also recommended further – and better quality studies – before drawing any definite conclusions. The results of another meta-analysis<sup>(2)</sup> also confirmed that homeopathic therapy has significant effects. However, it must be stressed that, although such analyses make it possible to exclude a generalized “placebo effect” as the only explanation of the results obtained by means of homeopathy, they are not sufficient to show that homeopathic treatment is surely efficacious<sup>(3-5)</sup>.

As in other medical disciplines, statistically significant result in favor of homeopathy could be reached by pooling all of the methodologically reliable studies in a given area, but this occurred very rarely, because few series have been conducted for single conditions and because the experimental approaches or the medicines

used are too heterogeneous to be able to conclude that any one protocol is efficacious. Some of these series document clinically useful effects and differences against placebo<sup>(2,6-9)</sup> and some series do not<sup>(10)</sup>, or their evidence is “promising” but insufficient for drawing conclusions<sup>(11)</sup>. In summary, the data are not strong enough to make a general recommendation to use homeopathy for first-line treatment of these conditions.

Recent controversies on the question of whether homeopathy is a placebo response<sup>(12-16)</sup> have shown that an approved answer of this dilemma is at present not possible, because the evaluation of the evidence and the inclusion or exclusion of papers from meta-analyses vary according to pre-selected criteria, that differ in different reviews, a sort of “bias” of the observer<sup>(17,18)</sup>. Moreover, there is a noteworthy confusion of what type of “homeopathy”

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is evaluated (e.g. use of low or high potencies) and when the homeopathy is accused for its lack of "plausibility"<sup>(1,12,19)</sup>, the different modalities are not suitably distinguished.

The aim of this lecture series is to provide an overview of the best of available homeopathic literature in the fields of immunoallergology and common inflammatory diseases. In this field, there is a body of pre-clinical research suggesting that homeopathic remedies may regulate the immune system at cellular and/or systemic levels<sup>(23,24)</sup>. There are also preliminary ex-vivo observations of significant changes of immune cells (CD4 lymphocytes) in people treated with high potencies of homeopathic medicines<sup>(25)</sup>.

Patients with diseases of the immune system like allergies and asthma, or with enhanced susceptibility to recurrent infections, or with chronic inflammatory diseases of the musculoskeletal system often have recourse to homeopathy as "alternative" medicine<sup>(26-34)</sup>, hoping to solve diseases that are not cured with conventional drugs, or as a "complementary" cure hoping to reduce the consumption of NSAIDs or other steroids that may have adverse effects, to relieve some symptoms and to improve quality of life. Unfortunately, there is paucity of evidence-based recommendations of the use of homeopathic remedies in these conditions.

Evidence-based medicine will have increasing impact also in the field of complementary and alternative medicine, but the systematic evaluation of the research evidence in homeopathy is an expectation that requires suitable methods of evaluation<sup>(35,36)</sup>. In this new and controversial field, the stringency of the tools utilized to systematically evaluate the scientific literature should be always accompanied by a consensus on the

clinical protocols that better reflect the modality of cure, the type of follow-up and the relevance of outcomes, which can be different from those of conventional medicine. Otherwise the results, instead of helping the judicious use of evidence in making clinical decisions, become only the source of new controversy, especially when disseminated by the media, as was in the Lancet's meta-analysis that was inappropriately boosted by the editorial title "*The end of homeopathy*"<sup>(37)</sup>.

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?*"<sup>(38)</sup> and twenty years later a meta-analysis published in this field meaningfully had the title "*Are the clinical effects of homeopathy placebo effects?*"<sup>(12)</sup>. This clearly indicates that we haven't still an accepted answer, 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 can't be considered as inert placebos, but the distinction was ignored by the famed Lancet's meta-analysis<sup>(12)</sup> and its related editorial<sup>(37)</sup>.

Here, we have distinguished the publications in three major groups, each one of which holds a rationale for the employ of homeopathic remedies. A first group includes pathologies consisting in due to anomalous susceptibility to infections that may be, at least in part, due to inadequacy of efficiency of the immune system in the rejection of the extraneous aggressor. The second group includes pathologies due to hypersensitivity of the immune system, the most widespread of which is immediate hypersensitivity, or allergy, and

its major manifestations at the level of respiratory system. This hypersensitivity results typically from an overproduction of IgE and degranulation of mast cells when specific antigens combine with the antibody at the local site. The third group includes the chronic conditions due to rheumatic diseases or autoimmune pathologies in which one observes an immune response directed against auto-antigens, causing self-maintained lesions inside internal organs, skin, muscles and joints.

For each group of pathologies, the different homeopathic methods utilized, namely a) classical individualized homeopathy, b) isotherapy are dealt with in separate sub-chapters.

## Methods

This review reports all the literature on human subjects available to us in the considered fields from 1978 to 2006. Principal information sources were current reading of major CAM journals during the past fifteen years, screening of the monthly publication of complementary medicine index (British Library), of the databases of Central Council for research in Homeopathy (CCRH, [www.ccrhindia.org/](http://www.ccrhindia.org/)) and of Homeinform Information Service (British Homeopathic Library, <http://homeinform.soutron.com/>), literature searching using Medline, CAM on PubMed ([www.nlm.nih.gov/nccam/camon-pubmed.html](http://www.nlm.nih.gov/nccam/camon-pubmed.html)), Cochrane Database of Systematic Reviews and CAMbase, cross-referencing between published papers. We directly received several papers from Authors. We have also checked the existing systematic reviews and meta-analyses that cover trials of immunoallergology. The analysis includes controlled clinical trials (with and without randomization), observational studies and case series. All forms of homeopathic intervention are included.

When complementary and complex interventions such as acupuncture or homeopathy are considered, there is no consensus on the quality criteria used to classify the clinical data according to the importance of treatment outcomes, the scientific strength and the reliability<sup>(14,39,40)</sup>. As we will discuss later, the problems arise especially as regards the role of blinding and concealment, of follow-up indexes particularly in chronic cases, of healing markers, of primary and secondary outcomes, and in general of the validity of experimental vs. observational studies. Therefore, to allow a semi-quantitative ranking of homeopathic treatment studies, we have adopted the following three criteria.

First, we have classified the publications according to the type of study, using, with slight modifications, the classification system that has been developed by the National Cancer Institute for human studies of complementary and alternative medicine in cancer studies (<http://www.cancer.gov/cancertopic-spdq/levels-evidence-cam/HealthProfessional/page2>). According to this classification, the score in descending order of strength is reported in **Table 1**. The main modification with respect to the NCI classification is that we have included the randomized (non-blinded) equivalence studies, comparing two modalities of therapy, in level 1b and the non-randomized equivalence studies in level 2. Those types of studies have increasing importance in homeopathic literature.

A second criterion that may help in "weighing" each paper is the publication type, which we scored according to a classification where the top papers are those published in mainstream medical literature and the last level is provided by publications in books or conference proceedings (**Table 2**). Communications

reporting single cases or expert opinions were excluded. Although this order may be questionable for a number of reasons (especially as concerns the difference between mainstream and complementary/alternative medicine journals), we believe that it may facilitate the reader in judging the grade of evidence provided by each study.

Finally, the global body of evidence regarding the effectiveness of the different therapeutic approaches, in the conditions considered in this review, has been presented in the Discussion. Here the classification of the therapeutic approaches is made according to a grade of evidence in 6 levels that 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 3**.

Research with Fixed prescription of low potencies and complex formulations have not been included in this paper but the treated group had shown significant improvement. Certain interesting things found during these research works: It has been reported that some plant components of, e.g. *Euphorbium and Pulsatilla*, have a direct anti-viral (respiratory syncytial virus and herpes simplex virus type 1) effect in vitro<sup>(79)</sup>. No serious adverse effects were reported.

### Infections of upper airways and otorhinolaryngologic diseases

Homeopathic research in the otorhinolaryngologic field includes studies of acute and chronic rhinitis, otitis media, sinusitis, tonsillitis. Here the diseases of infectious origin are considered, while the allergic diseases are considered in the next section.

Various groups of homeopathic researchers have worked on these diseases, which are very frequent in the general population, with often (but not always) positive results. The unnecessary use of antibiotics in the initial treatment of acute otitis media and URI is currently being questioned. Homeopathy has been used historically to treat this illness, and it is interesting to see if there are methodologically rigorous trials to determine whether there is a positive treatment effect.

We also report a relevant study on post-chemotherapy stomatitis, which is caused both by direct mucosal damage and by infections due to immunocompromise. We have omitted the trials on influenza both because the limited space of this lecture and the existence of systematic reviews covering the topic<sup>(21,41)</sup>. A summary of these studies in chronological order is reported in (**Table 4**) and a brief outline of each protocol with the main results of the different homeopathic strategies is given as follows.

### Classic Individualized Homeopathy

The first report of classical homeopathy dates in 1997 when *Friese et al.*<sup>(43)</sup> reported an open study comparing the results obtained in otitis media in children, treated using two different medical approaches. They compared classical unitary homeopathic remedies (*Aconitum, Apis mel., Belladonna, Lachesis, Pulsatilla, Silicea, Lycopodium, Chamomilla and Capsicum*) prescribed after an individual homeopathic case analysis (repertorisation), with conventional therapy based on antibiotics, mucolytics and antipyretics in a group of children. The duration of pain was two days in the homeopathic group and three days in the conventional therapy group (n.s.) and the duration of therapy was four and ten days respectively. The latter difference

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was statistically significant ( $p < 0.01$ ), but it should be noted that the duration of antibiotic therapy for these conditions can't be shorter than a week, so this comparison may not reflect the clinical outcomes. Relapses were experienced by respectively 29.3% and 43.5% of the subjects, with a mean number of relapses of 0.41 vs. 0.70 ( $p = 0.39$ ). In brief, this pragmatic study comparing homeopathic with conventional therapy showed that the results were similar, but with a trend in favor of the former.

In an open, prospective, multi-centre study, Kruse<sup>(44)</sup> evaluated a group of children with otitis media for six weeks, controlling the results against conventional therapy. The homeopathy group was treated with single remedies like *Aconitum* 30X,<sup>1</sup> *Apis* 6X, *Belladonna* 30X, *Capsicum* 6X, *Chamomilla* 3X, *Lachesis* 12X and other remedies; the reference group was treated with antibiotics (amoxicillin, erythromycin, etc.), secretolytics (ambroxol, acetylcysteine), antipyretics (paracetamol, etc.) and sympathomimetics such as nasal sprays. In the homeopathic group, 70.7% of the children who completed the study did not experience any recurrence; in the allopathic group, 64% of the children completing the study remained relapse free (n.s.). The average duration of pain in the two groups was respectively three days and four days (n.s.). Therefore, also this study suggested a similar effectiveness of the homeopathic and conventional treatments, with a positive trend in favor of the former.

*De Lange et al.*<sup>(45)</sup> carried out a double-blind, randomized study which they evaluated the frequency, duration and severity of rhinitis, pharyngitis and tonsillitis in a group of children. The homeopathic prescription included "constitutional" remedies for preventive purposes and remedies for the treatment of acute phases. The year-long therapy was continuously adjusted on an individual basis, and the data were collected by means of diaries kept by the parents and attending physicians. The results showed that the homeopathic therapy was slightly but not significantly better than placebo: the mean number of infective episodes was 7.9/year in the treated group and 8.4/year in the control group. The children in the active group experienced episodes that were generally shorter and less severe, and were disease-free for 53% of the days (as against 49% in the placebo group); the percentage of children not requiring antibiotics was 62% vs. 49% in homeopathy and conventional therapy respectively. Adenoidectomy was performed in 16% of the treated subjects vs. 21% of the controls. The results of a questionnaire concerning the children's global well-being showed a slight preference for the homeopathic treatment (4.81 vs. 4.17 points). The authors concluded that the differences between the two treatments were interesting but small; the main reason for the lack of statistical significance was that a considerable improvement in both groups was

observed during the year of observation, something that may have masked a small specific effect of the homeopathic treatment. The paper was criticized by homeopathic expert clinicians<sup>(53)</sup> and methodologists<sup>(18)</sup> maintaining that in that study homeopathy had to prove benefit additional to conventional therapy. If homeopathy was effective, control children would need more antibiotics and tonsillectomy, and this was the case; such surplus of conventional therapies could have created false negative results.

The purpose of the observational study of Frei and Thurneysen<sup>(47)</sup> was to find out how many children with acute otitis media are relieved of pain with individualized homeopathic treatment. A group of children with this condition received a first individualized homeopathic medicine in the pediatric office. If pain-reduction was not sufficient after 6 h, a second (different) homeopathic medicine was given. After a further 6 h, children who had not reached pain control were started on antibiotics. Pain control was achieved in 39% of the patients after 6 h, another 33% after 12 h. Compared with literature's data, the authors stated that the resolution rate is 2.4 times faster than in untreated cases. The six more frequently prescribed remedies were *Pulsatilla*, *Belladonna*, *Sulphur*, *Phosphorus*, *Calcium carbonicum*, *Lycopodium*.

An interesting multicentre, prospective, observational study in a real world medical setting compared the effectiveness of homeopathy with conventional medicine<sup>(48)</sup>. Thirty investigators with conventional medical licenses at six clinical sites in four countries enrolled a series of patients with at least one of the following three complaints: upper respiratory tract complaints including allergies; lower respiratory tract complaints including allergies; or ear com-

<sup>1</sup>Homeopathic remedies are solutions of substances diluted and succussed ("dynamized" or "potentized" according to traditional terminology) in 1:100 serial dilutions (centesimal, c) or 1:10 serial dilutions (decimal, x), or in other types of serial dilutions like Korsakovian (K), 1/50,000 (LM), continuous flux, etc. According to the Avogadro's law and as an approximate reference value, assuming a 1 Mole/l concentration of pharmacologically active principles in the starting solution (mother tincture), dilutions lower than 12c or 24x (here referred as "low potencies") should contain a consistent number of molecules of the active principle. This means that the allegation of being "placebos" can not be always based on the purported absence of drug molecules as it is often done.

plaints. Four hundred and fifty-six patient visits were compared: 281 received homeopathy, 175 received conventional medicine. The response to treatment (healing or a major improvement after 14 days of treatment) was 82.6% among the patients receiving homeopathy and 68% among those receiving conventional medicine. The adverse events in the conventional therapy group were 22.3% vs. 7.8% in the homeopathy group. Seventy-nine percent of the patients treated with homeopathy were very satisfied as against 65.1% of those receiving conventional treatment. Since the trial was not randomized, no statistical comparison between groups could be done. In any case, homeopathy appeared to be at least as effective as conventional medical care in the treatment of patients with these three conditions.

A randomized double-blind placebo control pilot study was conducted<sup>(49)</sup> in children with otitis media. Subjects having middle ear effusion and ear pain and/or fever for no more than 36 h entered into the study. They received either an individualized homeopathic medicine or a placebo administered orally three times daily for 5 days, or until symptoms subsided. Outcome measures included the number of treatment failures after 5 days, 2 weeks and 6 weeks. Diary symptom scores during the first 3 days and middle ear effusion at 2 and 6 weeks after treatment were also evaluated. There were fewer treatment failures in the group receiving homeopathy after 5 days, 2 weeks and 6 weeks, with differences of 11.4%, 18.4% and 19.9%, respectively, but these differences were not statistically significant. Diary scores showed a significant decrease in symptoms at 24 and 64 h after treatment in favor of homeopathy ( $P < 0.05$ ).

An equivalence trial was performed by *Steinsbekk et al*<sup>(50)</sup>, who

investigated whether individualized treatment by homeopaths is effective in preventing childhood URTI. Children recruited by post from a group previously diagnosed with URTI, were randomly assigned to receive either homeopathic care for 12 weeks or to conventional health care. There was a significant difference in median total symptom score in favor of homeopathic care (24 points) compared to the control group (44 points) ( $p = 0.026$ ). The days with symptoms were 8 and 13 in the homeopathic group and the reference group respectively ( $p = 0.006$ ). On the other hand, negative results were obtained by the same group<sup>(51)</sup> in a double-blind placebo controlled randomized trial.

A study to compare effectiveness and costs of two treatment strategies ('homeopathic strategy' vs. 'antibiotic strategy') used in routine medical practice by allopathic and homeopathic GPs in the treatment of recurrent acute rhinopharyngitis in children was published<sup>(52)</sup>. Data from a large series of patients, clinically observed for 6 months, were analyzed and grouped according to type of drug prescribed and the episodes of acute rhinopharyngitis, complications, and adverse effects. Direct medical costs (medical consultations, drug prescriptions, further tests) and indirect medical costs (sick-leave) were also evaluated. The results showed that the 'homeopathic strategy' yielded significantly better results than the 'antibiotic strategy' in terms of number of episodes of rhinopharyngitis (2.71 vs. 3.97,  $P < 0.001$ ), number of complications (1.25 vs. 1.95,  $P < 0.001$ ), and quality of life (global score: 21.38 vs. 30.43,  $P < 0.001$ ), with lower direct medical costs in favor of homeopathy (€88 vs. €99,  $P < 0.05$ ). The authors suggested that homeopathy may be a cost-effective alternative to antibiotics in the treatment of recurrent infantile

rhinopharyngitis. Of course, these conclusions should be confirmed or proven to be wrong with randomized studies on homogeneous groups of patients.

### Systematic Reviews

No systematic reviews on the effectiveness of homeopathy in these conditions have been published. A review on all the complementary and alternative medicines for URTI in children just mentioned homeopathy, as a modality of prevention and treatment that is not adequately supported by clinical trials<sup>(53)</sup>.

### Allergic Conditions

Allergies are the most common immunological diseases among the general population, and increasing evidence suggests that the 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 the conventional health care system and that their choice was mostly motivated by the assumption of few side-effects or by a wish to "try everything"<sup>(27,29,34,56-58)</sup>. 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<sup>(59)</sup>.

We shall here describe the studies that have been carried out in the field of allergology and, more specifically, oculorhinitis (hayfever) and allergic asthma. 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 5), here in the text they will be grouped according the different modalities of therapy that have been investigated.

### Classic Individualized Homeopathy

In starting this brief analysis of the results obtained in the field of allergology, we cite a retrospective study by M. Mosquera Pardo, reported at a homeopathic conference<sup>(63)</sup>. The study included children who were 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<sup>(65)</sup> retrospectively evaluated a series of children who had suffered from allergic bronchial asthma for between 18 months and 11 years, and who were treated with a single drug in accordance with the classical homeopathic method. Twenty-two different drugs were prescribed (the most used were *Sulphur*, *Calcarea carbonica*, *Lycopodium* and *Pulsatilla*), at different potencies (mainly 200 K). After three years of treatment, the results showed a complete cure in 58% of cases, improvements in 23% and failures in 19%. Of the cured cases, 53% needed only one homeopathic drug, 27% required 2-4 remedies, and 20% required 5-9 different drugs. The time to cure was 2-6 months in 33.3% of cases, one year in 33.3%, 1-3 years in 20% and more than three years in 13.3%. 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 three years<sup>(66)</sup>. A statistically sig-

nificant decrease in the frequency and severity of attacks before and after the treatment was reported. There was also a marked decrease of the use of conventional medication. The most frequently prescribed remedies were *Arsenicum album*, *Nux vomica*, *Sulphur*, *Pulsatilla*, and *Silica*.

In 1997 a communication in a conference of International Homeopathic Liga (LMHI) reported a double-blind, randomized, placebo controlled trial the effectiveness of classical individualized treatment of asthmatic people who were allergic to dermatophagoides<sup>(67)</sup>. Symptoms and immunologic parameters were evaluated before and after 8-months treatment. Significant decrease in the number of exacerbation and of spirometric tests was observed in the active homeopathic group. Asthmatic patients showed at baseline higher levels of interleukin-4 produced by non-stimulated Peripheral Blood Mononuclear Cells (PBMC) cultures, as compared to controls. After treatment, there was a decrease in the spontaneous production of interleukin-4 by PBMC on the active homeopathic group that was not observed in the placebo group. Complex differential changes of other variables (IL-5, Interferon-Gamma, and soluble CD23) were also reported. These results suggest that homeopathic treatment was effective and had concomitant immune regulatory effects in the patients with active vs. placebo treatment. Unfortunately this interesting and promising communication was not followed, to the best of our knowledge, by a full report that would permit a detailed evaluation of the trial.

A trial on individualized homeopathic therapy in asthma was published in a Mexican homeopathic journal<sup>(68)</sup>. 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 difference in favor of homeopathy vs. placebo ( $p < 0.05$ ).

A pharmaco-economic study (not reported in (Table 4) because it does not report data of effectiveness) assessed the effect of integrative homeopathic treatment in allergic diseases on conventional medication consumption in a health maintenance organization<sup>(67)</sup>. Forty-eight patients were treated for allergic diseases with homeopathic and conventional medications. The computerized medication charts of each patient were evaluated for conventional medication consumption three months before and three months after the homeopathic intervention, with each patient serving as his or her own control. The results showed that 56% of the patients reduced their use of conventional medication following the homeopathic intervention. The most significant reduction was in antihistamine use (a 70% reduction), followed by decreases in bronchodilator use (55%) and steroids (50%). The patients who used also conventional medications for their allergic disorders reduced their medication expenses by an average of 60%, with an average saving of \$24 per patient in the 3-month period following the homeopathic intervention.

In a randomised, double blind, placebo controlled trial the effects of individualized homeopathic remedies as an adjunct to conventional treatment were compared with placebo medication in children with mild to moderate asthma<sup>(73)</sup>. The main outcome measure was the active quality of living subscale of the Childhood Asthma Questionnaire administered at baseline and follow up at 12 months. There were no clinically relevant or statistically significant

changes in the active quality of life score. Scores of severity of symptoms indicated relative improvements but the sizes of the effects were small. There were no differences between the groups for other measures. 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 the 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<sup>(77-79)</sup>. In fact, included patients had very mild or lacking symptoms, which hardly could be ameliorated and expected peak flow value in the treatment group was already over 100% at the beginning of the study. Therefore, this study should be interpreted with caution and will not permit a definitive judgment about the role of adjunctive homeopathic treatment in asthma.

An observational study where the outcome and costs of homeopathic therapy were compared with those of conventional treatment in routine care has been published<sup>(76)</sup>. Since all the 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. Briefly, the results after 12 months of cure indicated that the symptom severity

scores (assessed both by patients and by physicians) 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. Overall costs were higher in homeopathic care than conventional care (€1049 vs. €366), but the difference between groups was not statistically significant.

### Homeopathic Immunotherapy

One of the most extensive lines of research in homeopathy was the attempt to utilize high dilutions of substances known to cause the allergy (antigens) to prevent or cure the same allergies. This is an application of the ancient isopathic principle<sup>(22)</sup>, that has been also termed "homeopathic immunotherapy (HIT)"<sup>(38,64,80)</sup>. Isopathy does not match the full expression of Hahnemann's rules, according to which the treatment is adapted to the whole characteristic of the patients. Nevertheless, the study of HIT offered a simple model of comparing the action of ultra-diluted and dynamized substances with that of placebo on the immune system.

To start the description of these results, it is worth citing a first report in a non-indexed journal by *Hardy* in 1984<sup>(60)</sup>. The authors were able to show a relief of oculorhinitis symptoms of in patients allergic to house dust by homeopathic potencies. The same approach characterized the long-lasting and deep investigations of isopathic treatment of respiratory allergies by the Glasgow group led by *D. Reilly*. A double-blind study, published as preliminary report by the *British Homeopathic Journal* in 1985<sup>(81)</sup> and as a full paper by *The Lancet* in 1986<sup>(38)</sup>, 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 the patients receiving the homeopathic treatment had significantly fewer symptoms and used half of the anti-histamine rescue treatment than the controls. This study, given the good methodology, the novelty of the approach and the prestige of the journal in which it was published, was followed by literature reverberations and by a series of predictable criticisms. By the way, it is noteworthy that the chosen model, the 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<sup>(80)</sup>.

The same group published the results of a study on patients with severe atopic asthma requiring daily administrations of bronchodilators, most of who were being treated with steroids<sup>(64)</sup>. Without any change in their basic therapy, the patients received a placebo for four 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 recorded the intensity of symptoms every day using a visual analogue scale for the following four weeks. Analysis of the end-of-study judgments of the patients revealed a statistically significant difference in favor of the active treatment. These studies of *Reilly's* group, enriched by further statistical analyses and a meta-analysis of all of the patients, were published in 1994<sup>(20)</sup>. An analysis of symptom intensity during the course of treatment revealed that the homeopathic immunotherapy was superior to placebo ( $p=0.003$ ). The treated group showed a similar trend towards an improvement in respiratory function and the results of bronchial reactivity tests, but this

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was not statistically significant. The meta-analysis of all three previous studies as a whole showed an extremely high probability ( $p=0.0004$ ) that the homeopathic effect was not due to a placebo effect.

Reilly's group has subsequently published a multicentre, randomized and double-blind study on patients attending hospital otorhinolaryngologic department for their chronic allergic rhinitis<sup>(6)</sup>. The study involved the administration of a 30c potency of the main allergen or (in the control group) an indistinguishable placebo. The results demonstrated a significant improvement in nasal air flow in the 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 the allergen more frequently reported the initial worsening, that is well known in homeopathy. This study offers further proof that high homeopathic dilutions cannot be assimilated to a simple placebo.

A replication study of HIT, with essentially negative results, was published in 2002 by an independent group led by G. Lewith<sup>(72)</sup>. Patients with asthma and positive skin prick tests for house dust mite entered the trial. After a 4-week baseline assessment, the 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 homeopathic immunotherapy, but there was a different pattern of change during the trial in three of the diary assessments: morning peak expiratory flow ( $P=0.025$ ), visual analogue scale

( $P=0.017$ ) and mood ( $P=0.035$ ). By week three, there was a significant deterioration in the visual analogue scale ( $P=0.047$ ) and mood ( $P=0.013$ ) in the homeopathic immunotherapy group. 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 (*Brit. Med. J.*). The reply of Reilly, the author of previous (positive) studies on homeopathic immunotherapy, stated that the Lewith's study was not actually a reply of their work, because the patient population, the drug administration, and the outcome measures were different<sup>(82)</sup>. In any case, the different patterns of change between HIT and placebo during the course of the study are unexplained, but seem to confirm a statistically significant "homeopathic aggravation" and symptoms oscillations that, being obtained using high allergen dilutions/dynamisations, are consistent with an immunologic effect of the medicine that is different from that of placebo.

In a subsequent paper, some of the Authors of the last negative trial of homeopathic immunotherapy have discussed their data of the same trial using complexity theory<sup>(83)</sup>. This is an evidence for a different oscillation in outcome (both physiological and subjective) of verum treatment with respect to placebo. 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, ran-

domized, placebo-controlled trials on the preventive and therapeutic effectiveness of pollen of *Betula* (HIT), were conducted by a Norwegian group. In the first study<sup>(69)</sup>, the effect of the homeopathic remedy Betula 30c vs. placebo for adult patients with birch pollen allergy was tested. No statistically significant difference between the 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 the medication, more than did the placebo group, a result in agreement with that of previously mentioned trials<sup>(8,72)</sup>. The second study<sup>(70)</sup> involved children and gave uncertain results, according to the authors possibly because the pollen count was very low during treatment period and only three days were high enough to provoke allergic symptoms. This time the verum treated patients fared worse than the placebo group; they used more rescue medication and had higher symptom scores during these three 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<sup>(71)</sup> with similar protocol with addition of a cross-over of treatments showed a consistent response in both verum and placebo groups, with no consistent clinical advantage of HIT.

A double-blind trial showed positive effects of homeopathic immunotherapy of seasonal allergic rhinitis<sup>(75)</sup>. The drug was prepared from common allergens (tree, grass, weed species) specific to the Southwest region of the US, which was compared with placebo. Study outcomes included allergy-specific



symptoms using the rhinoconjunctivitis quality-of-life questionnaires. The outcomes were positive ( $p < 0.05$ ) and subjects reported no adverse effects during the 4-weeks intervention period.

### Systematic Reviews

A meta-analysis of 7 randomized clinical trials to assess the efficacy of homeopathic preparations of *Galphimia glauca* in the treatment of allergic rhinitis was published by Ludtke and Wiesenauer<sup>(6)</sup>. The data are consistently in favor of a statistically significant effect of the low-dose homeopathic medicine over placebo, particularly in the relief of eye symptoms. Verum estimate of success is reported of about 80%. The validity of these experimental studies was confirmed also by independent meta-analyses<sup>(2,4)</sup>.

The review of Kleijnen *et al.*<sup>(1)</sup> and the meta-analysis of Reilly of his own studies<sup>(8)</sup> 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. In 1991 an overview of all the complementary and alternative therapies used for asthma<sup>(84)</sup> including homeopathy concluded that this modality must be regarded as unproven despite the fact that is widely used; in 1996 a similar study<sup>(85)</sup> concluded that the preliminary evidence suggests that homeopathy may be of help in asthma, associating HIT and classical homeopathy, but that larger controlled studies are needed. A specific meta-analysis on asthma was published in 2000 and regarded three trials<sup>(86)</sup>. The authors found that two of the three studies were positive, although two were thought to be of suboptimal quality. Six trials were included in a review<sup>(10,87)</sup>. These trials were found to be 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.

A review on all the complementary therapies in the management of asthma<sup>(79)</sup> included a brief consideration of homeopathic trials and confirmed that there is insufficient evidence to reliably assess the possible role of homeopathy in treatment for this condition. More and larger trials are therefore urgently needed to assess properly the role of homeopathy in the management of asthma, but experts<sup>(2,10,86,87)</sup> suggested that as well as randomised 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 effect of the medication as well as the consultation, which is considered a vital part of individualized homeopathic practice) rather than the homeopathic medicine against placebo alone.

### Arthro-Rheumatic Diseases

Despite a growing interest in uncovering the basic mechanisms of arthritis, medical treatment remains symptomatic. Current medical treatments do not consistently halt the long-term progression of these diseases, and surgery may still be needed to restore mechanical function in large joints. Patients with rheumatic syndromes often seek alternative therapies, with homeopathy being one of the most frequent, together with acupuncture<sup>(33,88,89)</sup>. On patients' self-perceived efficacy homeopathy achieved higher scores in osteoarthritis, while satisfaction was lower with rheumatoid arthritis and connective

tissue diseases<sup>(89)</sup>. The literature in this area is summarized in (Table 6).

### Classical Individualized Homeopathy

Retrospective studies and case histories suggested that recovery or clinical improvement may be achieved by homeopathic care in conditions like osteoarthritis, ankylosing spondylitis and rheumatoid arthritis<sup>(98)</sup>. Literature of clinical trials in this field began in 1978 when a Scottish group led by Gibson published a study on the homeopathic treatment of rheumatoid arthritis conducted at the Glasgow Homeopathic Hospital<sup>(90)</sup>. In this pilot study, a group of patients with rheumatoid arthritis were treated with classic homeopathy; a group was treated with high doses of salicylate. Both groups were compared with a third group of patients who received placebo. The patients who received homeopathy did better than those who received salicylate. The design of the trial was not randomized nor double blind, so that it was not possible to distinguish between the effects due to the physicians and the effects due to the drugs. In a subsequent study, the same group evaluated individualized homeopathic therapy against placebo<sup>(91)</sup> in double-blind conditions. Each patient of the verum group received his or her own prescribed remedy, while the others were treated with placebo. The results after three months of therapy showed an improvement in the symptoms (mainly spontaneous pain, stiffness in the joint, prenil strength) of 83% of the treated patients, as against only 22% of those receiving placebo. On the other hand, no differences between verum and placebo groups were observed with regard to laboratory variables.

A trial characterized by thoroughly negative results was conduct-

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ed in patients with osteoarthritis<sup>(92)</sup> who were divided into three groups: one received *Rhus toxicodendron* 6x, second fenoprofen, and the third placebo. The results showed that only the group treated with fenoprofen showed a significant improvement in symptoms in comparison with placebo.

The negative result of the last mentioned trial suggests that the tested medicine can't be effective when prescribed on the basis of the disease diagnosis and in the absence of individualization of the prescription. These methodological issues have been addressed in subsequent trials carried out in Great Britain. For example, in a double-blind trial involving patients suffering from fibrositis (primary fibromyalgia)<sup>(93)</sup>, the doctor had a choice between the three homeopathic drugs likely to be active in this condition: *Arnica montana*, *Rhus toxicodendron* and *Bryonia alba*: no difference was found between the groups treated with the remedies and those treated with placebo. A similar trial involving patients with fibromyalgia was carried out in the Department of Rheumatology of St. Bartholomew's Hospital, London<sup>(94)</sup>. The diagnosis was reached on the basis of the conventional diagnostic criteria defined by Yunus, and the patients then had their homeopathic history taken: only those for whom the remedy *Rhus toxicodendron* 6C (poison ivy) was indicated were included in the trial. This was a double-blind, placebo-controlled, cross-over study. The results were positive in favor of the homeopathic treatment, which led to a reduction in pain symptoms and improvement in general conditions. This experience indicates that the problem of disconnection between "conventional" diagnosis and homeopathic prescribing that should be individualized can be solved by

including in the trial a sub-group of patients who, according to classical homeopathic guidelines, are susceptible to a single medicine.

Another approach is to include all the patients, irrespective of the remedy prescribed, and to evaluate the homeopathic cure itself, not the effectiveness of single remedies. In such a double-blind randomized trial, carried out on patients with active rheumatoid arthritis<sup>(95)</sup>, the approach was similar to that of *Gibson's group*<sup>(91)</sup> with the difference that here patients were allowed to reduce the dosage of analgesic and prednisone if they improved. Patients were treated for six months; all patients were monthly interviewed by an expert homeopathic physician and the selected homeopathic medicine was maintained or changed according to the patient's response. Patients were assessed every month by a blinded evaluator. In patients treated with homeopathy, there was a significant intragroup improvement, comparing trial outset and end of treatment, in 3 of 5 observed variables, namely 15-meter walking time, articular index and functional class. With placebo, only one variable improved significantly, that was articular index. Both groups showed a significant decrease of the daily dose requirement of prednisone. The overall assessment by physicians confirmed an improvement in both groups (59% and 44% of patients in verum and placebo respectively), but there was no statistically significant difference. Adverse effects were scarcely and comparably reported in both groups.

A negative study of the effectiveness of homeopathy (individualized prescriptions) in rheumatoid arthritis has been published<sup>(96)</sup>. This was a 6-month randomized, cross-over, double-blind, placebo-controlled, single-centre study set in a teaching

hospital rheumatology out-patient clinic. The participants of the study had definite or classical rheumatoid arthritis and were receiving non-steroidal anti-inflammatory drugs. In addition to the conventional treatment, patients received either individualized homeopathic treatment in potencies of 6c and/or 30c, or identical matching placebos. The main outcome measures were visual analogue scale pain scores, objective indexes of stiffness and laboratory erythrocyte sedimentation rate (ESR). There were many drop-outs from the trial. Placebo and active homeopathy had different effects on pain scores; mean pain scores were significantly lower after 3 months' placebo therapy than 3 months' active therapy ( $P=0.032$  by Wilcoxon rank sum test). Articular index, ESR and morning stiffness were similar with active and placebo homeopathy. In conclusion, this trial found no evidence that active homeopathy improves the symptoms of RA, in patients attending a routine clinic who are stabilized on conventional anti-inflammatory treatment.

A double-blind, randomized trial to assess the effectiveness of individualized classical homeopathy in the treatment of fibromyalgia was carried out in Arizona<sup>(97)</sup>. Patients (mean age 49 yr, 94% women) received either homeopathic remedy in 1LM (1/50,000) potency or placebo. Participants on active treatment showed significantly greater improvements in tender point count and tender point pain, quality of life, global health and a trend toward less depression compared with those on placebo. This trial was paralleled by a series of interesting analyses aimed at characterizing some factors that may be correlated with the therapeutic outcome:

1. Homeopaths rated each patient's vital force in a five-point scale, with 1 = very weak to 5 = very strong and this parameter was correlated better with perceived

- mental function, energy, and positive dimensions of the individual, beyond absence of disease<sup>(99)</sup>.
2. The possibility of changing the group for an optional cross-over trial was offered and the analysis of responses allowed distinguishing subgroups of different responders. Individual difference factors predicted better and poorer responders with fibromyalgia to specific and non-specific effects of homeopathic and placebo treatments<sup>(100)</sup>.
  3. Fibromyalgia patients showed evidence of sensitizability in pain pathways and electroencephalographic (EEG) alterations and the homeopathic treatment group significantly increased in global alpha-1 and alpha-2 during a test based on laboratory elicitation by temporolimbic olfactory stimulation or sniffing, while the placebo group decreased<sup>(101)</sup>.
  4. Baseline and 3-month difference scores for initial prefrontal electroencephalographic alpha frequency cordance (a correlate of functional brain activity) showed that people who better responded to therapy exhibited significantly more negative initial difference scores at prefrontal sites<sup>(102)</sup>. These findings suggest that EEG changes of specific areas of brain may be a biomarkers of the individualized homeopathic medicines.

### Systematic Reviews

A review of research have concluded that there is a body of evidence to suggest that homeopathic medicines, either individually prescribed or used in a homeopathic formula, can provide relief for people with rheumatic disease<sup>(89)</sup>. A systematic review of the clinical evidence for and against the effectiveness of homeopathic medicines in the treatment of patients with osteoarthritis has been published<sup>(11)</sup> in which the authors

conclude that, although the small number of randomized clinical trials conducted so far favor homeopathic treatment, they do not allow any firm conclusion as to the effectiveness of homeopathic remedies in the treatment of osteoarthritis patients.

Fibromyalgia has been the object of two reviews of complementary and alternative treatments<sup>(146,147)</sup>, whose conclusions were that the evidence of efficacy of homeopathy was limited due to the existence of only one quite old, non replicated, RCT<sup>(94)</sup>, but at that time the careful trial of Bell and coworkers was not published yet<sup>(97)</sup>. A general review of the state of the art of homeopathic research<sup>(6)</sup> summarized six existing randomized clinical trials and found that four of them had high quality and positive outcomes. According to these authors the clinical evidence, particularly in osteoarthritis and fibromyalgia, is "promising", and more research in this area is warranted.

### Discussion

While complementary medicine and homeopathy are becoming an increasingly prominent part of the health care practices, there is paucity of controlled studies concerning their effectiveness. While traditional knowledge has been accumulating for over 200 years, only in the past few decades modern research methods such as randomized clinical trials, rigorous observational studies, and equivalence studies comparing homeopathy with conventional standard therapies have been applied. It is therefore not true that there are no serious controlled trials on homeopathic medicine, though it must be admitted that such trials are too few to allow any very firm conclusions to be drawn.

Few well-designed studies have been reproduced by independent research teams for two main reasons: the lack of sufficient funding and the

lack of a sufficient number of well-trained homeopaths who are qualified and interested in research. As a matter of facts, the debate on the efficacy of homeopathy is still very hot, as shown by a series of reviews<sup>(2-5)</sup> and chiefly by the controversial meta-analysis published by The Lancet<sup>(12,37)</sup> and by the significant expert reactions to the latter<sup>(103-105)</sup>.

Even though the number of papers published in peer-reviewed papers in increasing, the results of many clinical studies on the effectiveness of homeopathy are characterized by low standards of methodology<sup>(1,4,106)</sup>. 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 the publication bias (the tendency to publish more positive than negative trials, a problem that is also present in conventional medicine) and the lack of independent replications of most conducted studies. As a matter of facts, even if the same criticisms are applicable to conventional medicine<sup>(12)</sup>, the positive findings of most studies have not been unequivocally and generally accepted as valid.

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 the large majority of the available literature in this field, although some omission can not be excluded. Clearly, the few dozens of papers reported are highly heterogeneous in terms of the disease conditions, of the drugs used, and of experimental designs.

We have collected a total of 64 studies, 35 of which were double-blind randomized clinical trials (type 1a of 1), 7 randomized non-blinded

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equivalence studies (type 1b), 9 non randomized equivalence studies, 8 observational prospective studies, 5 retrospective studies of case-series but only 41 studies are considered here and reported in **Tables 4-6**. In **Table 7** these studies are grouped according to the clinical condition and the type of homeopathic treatment; the clinical evidence of the major groups of treatments was classified according to the criteria that have been reported in **Table 3**. 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.

The best evidences of effectiveness appear in the top two rows of **Table 7** and are *Galphimia glauca* (low potencies) in allergic oculorhinitis, classical individualized homeopathy for otitis and for fibromyalgia. In grade C (unclear or conflicting evidence) we found most of studies, because promising results reported by some authors were not replicated by others. The number of homogeneous trials is too small to attempt pooling and meta-analysis.

It would also be appropriate to compare the efficiency of different forms of homeopathy for the same condition, but the small sizes of the studied populations and the differences between them still prevent any reliable quantitative evaluation.

In synthesis, there are many promising studies supporting the clinically demonstrable activity of homeopathic medicines, but the database of high-quality homeopathic research in various fields is very small, the "hard" proofs of efficacy, particularly in the high-dilution realm, are still fragmentary and their methodological quality is often poor. Quite surprisingly, it has been shown in a comparative study<sup>(12)</sup> that the

mean quality of a representative random sample of allopathic medicine clinical trials is lower than the global quality of homeopathic trials! In any case and in the final analysis, the proofs so far collected are insufficient to allow a claim that highly diluted homeopathic medicines are more efficacious than placebos in treating highly prevalent inflammatory or immune diseases.

### Placebo and Effectiveness, Different Questions

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<sup>(108-110)</sup>. Thus, homeopathy seems to be safe, but there is no accepted theory for the action of medicines diluted beyond the Avogadro limit<sup>(111)</sup>.

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 the therapeutic approach is clinically effective. The evidence of specific activity of a drug over placebo is usually achieved in experimental research where the active substance (verum) is blindly tested against an identical placebo in two homogeneous groups of patients (randomized clinical trial, RCT). 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 ther-

apy. The need of more pragmatic studies aimed to "improving" instead of "proving" homeopathy have been suggested<sup>(2,82,112)</sup>.

The uncertainty regarding the efficacy and mechanisms of homeopathy may be due also to the publication bias, according to which the available literature may not reflect the number of trials done, since clinical trials are more likely to be published when they are positive than when they are negative. This is true both of homeopathic and allopathic therapies, but the situation is complicated by the fact that probably a "negative" publication bias against homeopathy exists in mainstream journals of conventional medicine. For example, a study<sup>(113)</sup> showed that among 46 randomized trials published in a total of 23 different journals (26 in CAM journals and 20 in conventional journals), 69% of those in conventional journals (n=20), reported negative findings compared to only 30% of those in CAM journals (n=26).

It has been suggested that in homeopathic studies of chronic illness, it might be better to compare patients receiving homeopathy to those receiving standard conventional therapy<sup>(114)</sup>. Subject would be randomized to one of two groups (to eliminate bias in treatment selection) and followed for a period of time. This study design does not answer the question of whether or not homeopathic medicines are placebo, but may give important pragmatic indications: if the system as a whole can be shown more effective than conventional treatment or equally effective at lower side effects, this would be sufficient to make homeopathic treatment worthwhile to many people.

### To Blind or not to Blind

Related to this problem is the blinding procedure that often is utilized in clinical research. This procedure has

been so widely employed in the evidence-based research on conventional drugs that there is the tendency to consider it as the gold standard for any clinical research. However, it has been shown that randomized trials have important limitations in interventions that require particular skills<sup>(115)</sup> and finding the correct homeopathic *simillimum* depends on in-depth anamnesis and atmosphere of trust, which is disrupted by randomization<sup>(18)</sup>. In homeopathy, the parameters of evaluation follow specific rules, that imply the 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 the response by the clinician, and often change of the medicine, particularly in chronic cases. To successfully discriminate between the 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<sup>(14)</sup>.

There is mounting evidence that the placebo effect is related to the expectation of clinical benefit, and several lines of evidence - including the activation of the limbic circuitry, the activation of opioid and serotonin pathways, and the release of dopamine - indicates a link between the placebo effect and reward mechanisms<sup>(116,117)</sup>. Therefore, if we consider these putative mechanisms, we see that the placebo "effect" is definitely not due to the "activity" of the - by the definition - inert substance but mainly to the intrinsic healing capacities and response of the treated subject. This response is also the one that is expected to be triggered by the homeopathic remedy, either acting through the neuroendocrine pathways or through an immunological mechanism that is connected with the central response to stress system.

We have to consider the great importance that is given by classic homeopathy to the interactions such as those between patient-doctor-medicine and environment-body-mind. It has been suggested that according to the theory of "entanglement" the remedy would act in the context of a tripartite relationship with the patient and the practitioner<sup>(118-121)</sup>. 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<sup>(122)</sup>.

It is essential to raise the right questions and to utilize the right methods. In homeopathy, the traditional double-blind RCT is the gold standard to investigate the mechanism of action of a remedy, i.e. to distinguish its specific effects from other unspecific factors, in rigorous experimental settings (high internal validity). This may be done assuming that the blinding procedure does not affect the therapeutic setting, as would be the case of short-lasting conditions where the goal is cure one or few common symptoms of the disease (a sort of "allopathized" homeopathy). When the difference of effects between a homeopathic potency and placebo has been assessed by double-blind RCTs, e.g. for dilutions of pollen in allergy or for many complex remedies, the large majority of trials give positive results in favor of a real, direct (but admittedly small) effect. We have also seen that, in a well conducted isopathic trial<sup>(72,83)</sup>, the final outcome was clinically insignificant, but the kinetics of response to homeopathic medicine were markedly and significantly different from those of placebo.

In this scenery, a way to accumulate evidence in favor or against the clinical usefulness of homeopathy is that of controlled equivalence studies, comparing homeopathy (or specific homeopathic medicines and formulations) with conventional treatment. Finding that the two approaches are equieffective is particularly important in those fields that have been considered in the present review, where a definite and satisfying therapy is often lacking. For example, it is still under discussion whether antiinflammatory drugs and antibiotics are effective in the treatment of URTI, also because they are known to have considerable side-effects. In contrast, homeopathy is reported to have little side-effects and, according many reports, a comparable efficiency.

### Observational Research

Observational research into uncontrolled homeopathic practice documents consistently strong therapeutic effects and sustained satisfaction in patients<sup>(5)</sup>. An observational study showed that a substantial proportion (70.7%) of patients attending a homeopathic hospital outpatient unit recorded positive changes in a wide range of chronic diseases<sup>(123)</sup>. Superimposable to this finding is the report showing that seven out of ten patients visiting a Norwegian homeopath reported a meaningful improvement in their main complaint six months after the initial consultation<sup>(124)</sup>. Similar or even higher percentages of patients declaring their satisfaction with homeopathic cure were reported by others<sup>(125-129)</sup>. 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

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the choice of homeopathic therapy vs. conventional therapy, even if the clinical results are perceived as equivalent<sup>(59)</sup>.

So, we are in the situation that if we adopt the strict criteria of evidence-based medicine, that were initially developed for chemical drugs, the analysis of published literature on homeopathy finds insufficient evidence to support clinical effectiveness of homeopathic therapy in most conditions of care. If we accept observational studies and equivalence studies as valuable tool of investigation, we find many proofs of the effectiveness of homeopathic drugs. Of course, in the case of equivalence studies it is difficult to judge whether the result is positive in favor of homeopathy or uncertain, because this depends on the conventional arm of the trial. In any case this is valuable information on a pragmatic standpoint because enables the decision based on other factors like patient's personal preference, adverse effects, availability, and costs.

There are many reasons why the development of clinical homeopathic research must proceed with a re-evaluation of observational studies as valuable tools to yield data of clinical effectiveness and medical knowledge. The integration of randomized clinical trials, observational prospective studies and pharmaco-economic studies is the future of the 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 docu-

mented usefulness in general practice<sup>(6)</sup>: the therapy is useful when applied in open practice and produces substantial effects, even in patients with chronic diseases<sup>(130,131)</sup>. But, considering only double-blind and randomized studies of highest methodological quality (the latter evaluated using the most rigorous criteria of evidence-based medicine that were developed for traditional drugs), it is hard to convince skeptics that homeopathy is significantly different from placebo<sup>(3,4,12)</sup>.

This paradox leads to two conclusions: 1) additional clinical research, both experimental and observational, including studies using different designs, is necessary for further research development in homeopathy, and 2) it is conceivable that the discrepancies are due to the lack of a consistent theory of the action mechanism of homeopathy<sup>(6)</sup>, so that additional basic research and innovative approaches to this problem are urgently warranted.

Given their current spread, more scientific research into non-conventional therapies is in the interests of medicine as a whole (and not just homeopathy or allopathy). However, it is not possible to ignore the difficulties that this emerging sector of biomedical research has to face: a) the methodological difficulties, above all related to classical homeopathy, that represent a great challenge for clinical epidemiology; b) the fact that homeopathy is still practiced only in private clinics, and there is a lack of large-scale clinics at university level; and c) the fact that classical homeopathic products (unitary remedies) cannot be patented because they are simply dilutions of natural substances. These are all unlikely to encourage industry to invest the large amounts of money necessary to finance clinical studies involving sufficiently large patient populations.

Nevertheless, the growing public interest in homeopathy (probably due more to a "liking" for the 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 sector of medicine will receive greater attention from the competent authorities and the scientific world. 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 the protocols include objective measurements of clinical and laboratory parameters, as well as adequate control groups of untreated subjects or subjects treated with conventional therapies.

Even in the absence of any undisputable demonstration of the clinical effectiveness of the homeopathic method in allergies, what has been discussed above makes it plausible (at least as a working hypothesis) that a careful analysis of clinical signs and symptoms in accordance with the traditional procedure of Hahnemann can help physicians to implement a therapy aimed at the complex and subtle pathophysiological disorders caused by a disease by exploiting the principle of similars that can be re-evaluated as the principle of the inversion of effects, or "paradoxical pharmacology". This concept will be the target of a further lecture of this series.

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**Table 1. Classification of clinical studies in homeopathy**

Level of evidence	Study design
1a	Double-blind randomized clinical trials
1b	Non-blinded randomized clinical trials, including those comparing homeopathy with conventional therapy as control (equivalence studies)
2	Non-randomized controlled clinical trials, including those comparing homeopathy with conventional therapy (equivalence studies)
3	Prospective observational studies, without control group
4	Retrospective studies of case-series

**Table 2. Classification of publications according the type**

Class	Publication type
1a	Mainstream medicine indexed , peer-reviewed, journal
1b	Complementary/alternative medicine indexed, peer-reviewed, journal
2	Non-indexed journal
3	Book or book chapter, conference proceedings

**Table 3. Levels of evidence of therapeutic efficacy according to Natural Standard (see Methods)**

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.
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.
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.
F (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.
<b>Lack of Evidence</b>	Unable to evaluate efficacy due to lack of adequate available data. This is not equivalent to negative evidence.

TABLE 4. Homeopathic clinical studies of infections of upper airways and ear-nose-throat diseases

Reference and year	Condition (diagnosis)	Study type	Publ. classif.	Study group	Treatment(s)	Outcomes	Key results
Gassinger 1981 (42)	Acute rhinitis	1b	1b	53	<i>Eupatorium perfoliatum</i> 2x vs. aspirin	Symptom severity score	Equivalence between homeopathy and allopathy
Bordes 1986	Cough	1a	2	60	Low-dilution (3c) homeopathic complex in syrup ( <i>Drosera</i> ) vs. placebo	Symptoms	Decrease of symptoms 20/30 treated patients, as against only 8/30 in the placebo group
Connert 991(55)	Rhinitis and nose obstruction	3	2	26	<i>Euphorbium compositum</i>	Symptoms, rhinomanometry	Decrease of symptoms in most patients (uncontrolled)
Weiser 1994 (56)	Chronic sinusitis	1a	2	155	<i>Euphorbium compositum</i> vs. placebo	Subjective symptoms and functional tests	21.1% improvement in the verum group, 14.4% in the placebo group. No change in tests.
Friese 1997 (43)	Otitis media	2	1a	131 children	Individualized vs. allopathy	Duration of pain and therapy	Homeopathy slightly better than conventional therapy
Kruse 1998 (44)	Otitis media in children	2	3	126	Individualized vs. allopathy	Duration of pain and therapy	Equivalent efficacy
Wiesenaue 1998 (60)	Acute tonsillitis	3	1b	107	Low-dilution homeopathic complex of <i>Phytolacca americana</i> , <i>Guajacum officinale</i> , <i>Capsicum annum</i>	Subjective and objective symptoms	Decrease of symptoms in most patients (uncontrolled)
De Lange 1999 (45)	Pharyngitis, tonsillitis	1a	1a	170 children	Individualized vs. placebo	Frequency, duration and severity of rhinitis, pharyngitis episodes	Little, non significant, effect in favor of homeopathy vs. placebo
Frei 2001 (47)	Acute otitis media	3	1b	230 children	Individualized	Pain	Improvement in 39% of patients after 6h, another 33% after 12h (uncontrolled)
Riley 2001 (48)	Respiratory tract complaints or ear complaints	2	1b	456	Individualized homeopathy vs. allopathy	Healing or a major improvement after 14 days of treatment, adverse effects	Improvement in 82.6% of homeopathic patients, 68% of allopathic

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TABLE 4. (Contd.) Homeopathic clinical studies of infections of upper airways and ear-nose-throat diseases

Reference and year	Condition (diagnosis)	Study type	Publ. classif.	Study group	Treatment(s)	Outcomes	Key results
Jacob 2001 (49)	Acute otitis media	1a	1a	75 children	Individualized vs. placebo	Treatment failures and symptoms scores	Less failures in verum group, not significant; little and significant decrease of symptoms in verum group
Steinsbekk 2005A (50)	Upper respiratory tract infections	1b	1b	169 children	Individualized vs. untreated	Symptoms score	Decrease of days with symptoms in homeopathic group
Steinsbekk 2005B (51)	Upper respiratory tract infections	1a	1a	251 children	Individualized, parents-selected, vs. placebo	Prevention of new episodes	No effectiveness of homeopathy over placebo
Trichard 2005 (52)	Acute rhinopharyngitis	4	1b	499 children	Homeopathic strategy vs. allopathic strategy (e.g. antibiotics).	Number of episodes, quality of life, costs	Various indexes significantly in favor of homeopathic strategy, lower medical costs (uncontrolled)

TABLE 5. Homeopathic clinical studies of allergy and asthma

Reference and year	Condition (diagnosis)	Study type	Publ. classif.	Study group	Treatment(s)	Outcomes	Key results
Hardy 1984 (60)	Allergic oculorhinitis (house dust)	1a	2	70	Homeopathic immunotherapy (H.I.T.) made with house dust potencies	Symptoms	H.I.T. better than placebo
Wiesenauer 1985 (61)	Allergic oculorhinitis	1a	1b	164	<i>Galphimia glauca</i> 6x dynamized vs. placebo and <i>Galphimia glauca</i> 6x non-dynamized	Eye and nose symptoms	Trend to positive, not statistically significant: less symptoms in patients taking dynamized verum medicine than other groups
Mosquera 1990 (63)	Asthma	4	3	120 children	Individualized homeopathy bronchial asthma.	General assessment	Improvement in most cases (uncontrolled)
Castellsagu 1992 (65)	Allergic asthma	4	1b	26 children	Individualized	Global evaluation	Improvement in most patients (uncontrolled)
Eizayaga 1996 (66)	Allergic asthma	4	1b	62	Individualized	Smptoms scores	Significant decrease of symptoms after therapy (uncontrolled)

TABLE 5. (Contd.) Homeopathic clinical studies of allergy and asthma

Reference and year	Condition (diagnosis)	Study type	Publ. classif.	Study group	Treatment(s)	Outcomes	Key results
Lara-Marquez 1997 (67)	Allergic asthma	1a	4	19	Individualized vs. placebo	Symptoms, spirometry parameters and immunological markers	Verum better than placebo, significant changes of laboratory markers
Micciché 1998 (98)	Allergic oculorhinitis	2	2	70 children	Homeopathic protocol based on three low-dilution drugs vs. conventional therapy	Global evaluation	Trend to better improvement in the homeopathic group
Riveron-Garrote 1998 (68)	Allergic asthma	1a	2	80	Individualized vs. placebo.	General symptoms and attack intensity	Higher reduction of asthma attacks in verum group
Taylor-Reilly 2000 (8)	Allergic rhinitis	1a	1a	50	Individual allergen 30c vs. placebo (H.I.T.)	Symptoms (VAS) and nasal air flux tests	Slightly better tests in verum group
Aabel 2000 (69)	Allergic rhinitis	1a	1b	66	Homeopathic birch pollen Betula 30c vs. placebo	Symptoms score	Slightly less symptoms during 10 days. Aggravation after taking verum
Aabel 2000 (70)	Allergic rhinitis	1a	1b	73	Homeopathic birch pollen Betula 30c vs. placebo	Symptoms (VAS)	Verum worse than placebo
Aabel 2001 (71)	Allergic rhinitis	1a	1b	51	Homeopathic birch pollen Betula 30c vs. placebo	Symptoms (VAS)	Similar improvement in verum and placebo
Lewith 2002 (72)	Allergic asthma	1a	1a	242	Allergen (dust mite) 30c vs. placebo (H.I.T.)	Symptoms (VAS) and expiration flux (FEV)	No final therapeutic effect, initial aggravation
White 2003 (73)	Asthma (mild to moderate)	1a	1a	96 children	Individualized vs. placebo	Quality of life, symptoms and tests	No changes of QOL, small not significant improvement of symptoms in verum group
Li 2003 (74)	Allergic asthma	3	1a	12 children	H.I.T. prepared from individual allergens vs. placebo	Spirometric tests	No improvement after treatment (uncontrolled)
Kim 2005 (75)	Allergic rhinitis	1a	1a	40	H.I.T. prepared from common allergens vs. placebo	Symptoms, quality-of-life questionnaires	Better clinical changes in verum group as compared with placebo
Witt 2005 (76)	Allergic diseases including rhinitis and asthma	2	1b	178	Classic homeopathy vs. conventional care	Symptoms, quality-of-life questionnaires, costs	Better outcomes in homeopathic group

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TABLE 6. Homeopathic clinical studies of arthrorheumatic diseases

Reference and year	Condition (diagnosis)	Study type	Publ. classif.	Study group	Treatment(s)	Outcomes	Key results
Gibson 1978 (90)	Rheumatoid arthritis	2	1a	195	Individualized prescription vs. salicylates and placebo, 12 months	Physician evaluation	Better relief in homeopathic group than allopathic and placebo. High drop outs.
Gibson 1980 (91)	Rheumatoid arthritis	1a	1a	46	Individualized prescription vs. placebo, 3 months	Pain and articular indexes	Better relief in homeopathic group than placebo
Shiplely 1983 (92)	Osteoarthritis of hip and knee	1a	1a	36	<i>Rhus toxicodendron</i> 6x vs. Placebo and fenoprofen	Symptoms	No effect of homeopathy over placebo, fenoprofen superior to both
Fisher 1986 (93)	Fibrositis (fibromyalgia)	1a	1b	24	<i>Arnica</i> , <i>Rhus tox</i> , <i>Bryonia</i> 6c vs. placebo	Pain symptoms	Trend to positive in favor of homeopathy, but not significant differences
Fisher 1989 (94)	Fibrositis (fibromyalgia)	1a	1a	30	<i>Rhus tox</i> (individualized) vs. placebo	Pain symptoms	Slightly positive: therapeutic success in more patients taking verum vs. placebo
Andrade 1991 (95)	Rheumatoid arthritis	1a	1a	44	Individualized vs. Placebo, 6 months	Clinical measurements and global evaluation by physician	Small but not significant differences in favor of verum over placebo
Van Haselen 2000 (136).	Osteoarthritis of the knee	1b	1a	172	Local application of a homeopathic gel vs. piroxicam gel	Pain and arthritic indexes	Equivalence of homeopathic and allopathic gels
Fisher 2001 (96)	Rheumatoid arthritis	1a	1a	112	NSAIDS + Individualized prescription vs. NSAIDS + placebo	Pain and articular indexes	No effect of homeopathy over placebo
Bell 2004 (97)	Primary fibromyalgia	1a	1a	62	Individualized prescription vs. placebo	Pain symptomsQOL	Homeopathy significantly better than placebo in all outcomes

**Table 7.** Summary of the levels of evidence of clinical homeopathic studies. The characters of references numbers indicate the type of study and of publication: **bold= randomized controlled trial or meta-analysis covering the topic**; *italics=non randomized controlled trial*; normal case= uncontrolled, observational and retrospective studies; underlined>=indexed journals.

Level of Evidence	Infections of upper airways and ear-nose-throat diseases	Allergy and asthma	Arthrorheumatic diseases
A (Strong Scientific Evidence)		<i>Galphimia glauca</i> (low potencies) in allergic oculorhinitis: (61), (62), (92), (7), (6), (2)	
B (Good Scientific Evidence)	Classical individualized homeopathy for otitis (43),(44), (47), (48), (49)		Classical individualized homeopathy in fibromyalgia: (94), (97)
C (Unclear or conflicting scientific evidence)	Classical individualized homeopathy for URTI: In favor: (48), (50); against: (45), (51), (52).	Homeopathic immunotherapy (isotherapy): In favor: (60), (38), (20) (8), (69), (75); In against: (71), (70), (72), (74). Classical individualized homeopathy: In favor: (63), (65), (66), (67), (68), (76); against: (73).	Classical individualized homeopathy for rheumatoid arthritis: In favor: (90), (91), against: (95), (107)
D (Fair Negative Scientific Evidence)			<i>Arnica</i> , <i>Rhus tox</i> , <i>Bryonia 6c</i> for fibromyalgia (93)
F (Strong Negative Scientific Evidence)			<i>Rhus toxicodendron 6x</i> for osteoarthritis (92)

## Warning Against Use of Streptomycin

We cite below a warning on use of Streptomycin by the World Health Organisation. We are accustomed to many such warnings against many of their favourite preparations which bask in the sunshine of their patronage but only for a short while. Certain drugs were acclaimed as panaceas for all the evils to which human flesh is subject to be told a bit later on, that the drugs so acclaimed have been found out to be worse than the evils they were said to remove.

The WHO has issued a warning against unrestricted distribution and indiscriminate use of streptomycin, in a move to avoid the emergence of streptomycin-resistant strains of tubercle bacilli.

Reasons given in the warning against abuse of streptomycin are that in spite of reduced toxicity of new forms of this drug, it must still be considered as having danger; and that precise knowledge as to its clinical indications, especially in pulmonary tuberculosis, is still lacking.

Despite the great success which streptomycin has had in reducing the mortality from tuberculous meningitis and miliary tuberculosis from 100% to between 50%-60%, there are indications that in many types of tuberculosis now being treated with streptomycin, the bacilli which cause the disease speedily become resistant to the drug.

It is in cases of pulmonary tuberculosis in particular that this resistance to streptomycin is most frequently found. The real danger lies in the fact that if children are infected by the resistant types of bacilli then treatment with streptomycin is of no avail. *Recently this is the case with erythromycin.*