

Advances in homeopathy and immunology: a review of clinical research

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1. ABSTRACT

The present paper reviews the clinical research carried out over the past three decades to evaluate the effectiveness of homeopathy for the treatment of respiratory allergies, common upper respiratory tract infections, otorhinolaryngologic complaints, and rheumatic diseases. We include in the analysis both randomised and non-randomised trials, assigning them different weightings in the final balance of evidence, on the basis of semi-quantitative criteria. Overall, the literature concerning a total of 83 original studies suggests that homeopathy may have significant effects in some conditions, e.g. *Galphimia glauca* (low homeopathic dilutions/dynamizations) in allergic oculorhinitis, *Anas barbariae* (high homeopathic dilution/dynamization) in influenza-like syndromes, classical individualised homeopathy in otitis, in allergic complaints and in fibromyalgia, and a few low-potency homeopathic complexes in sinusitis, rhinoconjunctivitis, arthritis. The evidence for individualised homeopathic therapy in the field of upper respiratory tract infections and for homeopathic immunotherapy in respiratory allergies is more conflicting. Pragmatic equivalence trials suggest that, in primary care, homeopathic treatment is not inferior to conventional treatment. A larger number of observational studies and of clinical trials -- conducted in a methodologically correct manner without altering the treatment setting-- are needed before sure conclusions concerning the application of homeopathy for specific diseases can be drawn.

2. INTRODUCTION

The use of complementary therapies is widespread and expanding in both the United States and Europe. Patients suffering from immune-system disorders such as allergies and asthma, enhanced susceptibility to recurrent infections, or chronic inflammatory diseases of the musculoskeletal system often turn to homeopathy as an “alternative” medicine, in the hope of resolving ailments not successfully cured by conventional drugs, or as a “complementary” treatment to reduce their consumption of anti-inflammatory drugs or steroids that may have adverse effects, to relieve certain symptoms and improve their quality of life (1-8). There is accordingly a need for clinical trials demonstrating the safety and effectiveness of homeopathic remedies in the treatment of inflammatory and infectious diseases, which often originate from abnormalities (excess, deficiency, disorders) of the immune system.

Homeopathic medicine and immunology are historically as well as conceptually linked. Both disciplines originated at the end of the eighteenth century: at the same time as Jenner was administering the first smallpox vaccinations, the German physician Samuel Hahnemann was performing his first homeopathic *provings*. Homeopathic remedies are substances prescribed in extremely low doses (or high dilutions/dynamizations, also known as “potencies”) to treat the same specific syndromes they are known to cause in overdose, by mimicking and

augmenting the patient's immune response and natural defences (9, 10). One important pioneer of immunology, who also had an open mind towards the new homeopathic theories of his day, was Emil Von Behring, who in 1912 wrote "*Hahnemann's principle, according to our present way of thinking, was not bad at all*" and "*The concept that the sick person reacts differently to medications than the healthy one, which had to be established empirically by therapeutic trials, also played a role in Hahnemann's thinking*" (11). Though western immunology went on to develop as part of modern biomedicine, while homeopathy was always regarded as an "alternative" medicine, in the past few decades there has been a rapprochement between the two disciplines. In essence, the profound analogies between homeopathic thought and immunology stem from the fact that all homeopathic theory is fundamentally based on the principle of regulating endogenous healing mechanisms, the best known of which is certainly the immune system and its neuroendocrine associations. "Conventional" immunology, on its part, has been increasingly endorsing a more "systemic" approach, encompassing nutrition, lifestyle, and stress control, the judicious use of extremely low doses of powerful endogenous substances such as cytokines and their antagonists, specific desensitisation with low doses of the same substances that cause the allergy, the concept of "hormesis" (stimulation or cure using low doses of toxic substances) (12). These osmotic exchanges between the two disciplines have been further aided by the fact that homeopathy has in recent decades started using the methods of modern medical science, so that a significant number of experimental studies--at the molecular, cellular and clinical levels--are now available (13-21). In the past twenty years, homeopathic clinical research has increasingly adopted the methods of conventional medicine, namely clinical trials, observational studies, statistical evaluations, computerised storage programs and instrumental or laboratory testing. Over two hundred clinical trials designed to verify the efficacy homeopathic treatments have been published, of which many (but not all) have yielded positive results.

Clinical research in homeopathy was initially focused on the question of the placebo effect. The first significant randomised clinical trial published in a leading medical journal came out in 1986, with the title "*Is homeopathy a placebo response?*" (22). In similar vein, a 2005 meta-analysis on homeopathy had the title "*Are the clinical effects of homeopathy placebo effects?*" (23). Clearly, then, there is a lack of consensus on this point, though one reason for it might be that the placebo question is not correctly addressed, or is confused with clinical efficacy. The authors of the afore-mentioned meta-analysis of homeopathic clinical trials (23) write that the evidence for a specific effect of homeopathic remedies is weak, and that this finding is compatible with the notion that the clinical effects of homeopathy are due to placebo. However, this meta-analysis draws its main conclusion from a subset of 8 larger trials, selected out of a total of 110 trials considered, and its negative outcome has been shown to be chiefly ascribable to a single trial on preventing muscle soreness, and to the marked heterogeneity of the

studies (24, 25). In consequence, the controversy as to whether homeopathy is a placebo response cannot be resolved until many more papers are published and analysed in a suitable and correct way. For this reason, the present work does not attempt any meta-analysis, but instead makes a systematic review of the clinical research carried out over the past three decades to evaluate the effectiveness of homeopathy in conditions characterised by inflammatory and immunological disorders, namely respiratory allergy, common upper respiratory tract infections, otorhinolaryngologic complaints, stomatitis, osteoarthritis and rheumatic diseases.

The clinical evidence has been grouped into three sections, based on the rationale for homeopathic treatment. The first group comprises pathologies of anomalous susceptibility to infection that are at least partly attributable to the inability of the immune system to reject the extraneous aggressor; this includes also various otorhinolaryngologic ailments. The second group comprises disorders arising from hypersensitivity of the immune system, the most common of which is immediate hypersensitivity, or allergy, and its major manifestations as oculorhinitis and asthma. This hypersensitivity typically results from an overproduction of IgE and degranulation of basophils and mast cells, when specific antigens combine with the antibody at the local site. The third group comprises chronic conditions relating to rheumatic diseases, osteoarthritis, or autoimmune pathologies, in which there is over-reactivity and/or a specific immune response directed against auto-antigens, causing self-maintained lesions inside internal organs, skin, muscles and joints.

This review covers all the available literature on human subjects in the aforementioned fields, from 1978 to 2010. The principal information sources drawn from are: current reading of major complementary and alternative medicine journals, screening of the Hominform Information Service databases (British Homeopathic Library, <http://hominform.soutron.com/>), literature searches using Medline, the Cochrane Database of Systematic Reviews, and cross-referencing between published papers. We also consulted previously published systematic reviews and meta-analyses that have covered trials of immuno-allergy. Our analysis includes controlled clinical trials (with and without randomisation), observational studies and case series, but excludes single case reports. All forms of homeopathic therapy have been included, and namely: a) classical individualised homeopathy, b) ailment-specific remedies and complexes, c) isotherapy where indicated. After presenting the overall body of evidence with some technical details in tables, and discussing the most relevant published papers, we will attempt to summarise the positive and negative findings, weighting them according to semi-quantitative criteria.

3. INFECTIONS OF THE UPPER AIRWAYS AND OTORHINOLARYNGOLOGIC DISEASES

Homeopathic research into this diverse range of ailments has included studies of acute and chronic rhinitis,

otitis media, sinusitis, tonsillitis, stomatitis, and influenza-like syndromes. Table 1 provides a summary of these studies in chronological order. The protocols and principal results of the different homeopathic strategies are outlined in the following sections.

3.1 Individualized homeopathy

De Lange and coworkers (38) carried out a double-blind, randomised study in 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 through diaries kept by the parents and attending physicians. The results showed that the homeopathic therapy was slightly but not significantly better than the placebo: the mean number of infective episodes was 7.9/year in the treated group versus 8.4/year in the control group. The children in the active group experienced episodes that were generally shorter and less severe; the percentage of children not requiring antibiotics was 62% for homeopathy against 49% for conventional therapy. The authors conclude that the differences between the two treatments are interesting but slight. One reason for the lack of statistical significance might be that both groups showed considerable improvement during the year of observation, which may have masked any small specific effects of the homeopathic treatment. The study in question has also been criticised (62) because it did not directly compare homeopathy to conventional therapy; since antibiotic use was allowed in both groups, homeopathy had to demonstrate additional benefits above and beyond those of conventional therapy.

Friese and coworkers (39, 63) report an open study comparing the results obtained in treating otitis media in children using two different medical approaches: a) classical homeopathic remedies (e.g. *Aconitum*, *Apis*, *Belladonna*, *Lachesis*, *Pulsatilla*, *Silicea*, *Lycopodium*, *Chamomilla* and *Capsicum*) prescribed after an individual homeopathic case analysis (repertorisation), b) conventional therapy based on antibiotics, mucolytics and antipyretics. The mean 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 was statistically significant ($p < 0.01$). In a similar open, prospective, multicentre study, Kruse (40) 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 such as *Aconitum*, *Apis*, *Belladonna*, *Capsicum*, *Chamomilla*, *Lachesis*, while the reference group was treated with antibiotics, secretolytics, antipyretics and nasal sprays. In the homeopathic group, 70.7% of the children who completed the study did not experience any recurrence, while 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 and four days (n.s.). Thus, the results of this study

also suggest a similar effectiveness of homeopathic and conventional treatments.

An observational study was carried out (44) to ascertain how many children with acute otitis media are relieved of pain with individualised homeopathic treatment. A group of children with this condition received a first individualised homeopathic remedy in the paediatrician's office. If pain-reduction was not sufficient after 6 h, a second (different) homeopathic remedy was given. After a further 6 h, children who had not achieved pain control were started on antibiotics. The six most frequently prescribed remedies were *Pulsatilla*, *Belladonna*, *Sulphur*, *Phosphorus*, *Calcium carbonicum*, *Lycopodium*. Pain control was achieved in 39% of the patients after 6 h, and in another 33% after 12 h. Comparing these findings with the data in the literature, the authors state that the resolution rate is 2.4 times faster than in untreated cases.

An interesting multicentre, prospective, observational study in a real-world medical setting compared the effectiveness of homeopathy with that of conventional medicine (45). 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 conditions: upper respiratory tract complaints including allergies; lower respiratory tract complaints including allergies; or ear complaints. 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 rate of adverse events in the conventional therapy group was 22.3%, versus 7.8% for the homeopathy group. Since the trial was not randomised, no statistical comparisons could be made between groups. In any case, the authors suggest that homeopathy appeared to be at least as effective as conventional medical care in the treatment of patients with these three conditions. A replication of this study was carried out as an international, multi-centre, comparative cohort study of non-randomised design (56). Therapeutic outcomes were measured in terms of the response rate, defined as the proportion of patients experiencing 'complete recovery' or 'major improvement' in each treatment group. The full analysis evaluated data for 1,577 patients, out of which 857 received homeopathic (H) and 720 conventional (C) treatment. The majority of patients in both groups reported their outcomes, after 14 days of treatment, as either complete recovery or major improvement ($p = 0.0003$ for non-inferiority testing). The response rates after 7 and 28 days also showed no significant differences between the two treatment groups. However, onset of improvement within the first 7 days after treatment was significantly faster for the homeopathic treatment in both children ($p = 0.0488$) and adults ($p = 0.0001$). Adverse drug reactions occurred more frequently among adults in the conventional group than in the homeopathic group (C: 7.6%; H: 3.1%, $p = 0.0032$), whereas in children the occurrence of adverse drug reactions was not significantly different. Although the study was non-randomised, it strongly suggests that, in primary care, homeopathic treatment for acute respiratory and ear complaints is not inferior to conventional treatment.

Table 1. Homeopathic clinical studies in the fields of infections of upper airways and ear-nose-throat ailments

Authors and year	Study type ^a	Publication type ^b	N. of subjects	Conditions (diagnosis)	Treatment(s)	Outcomes	Key results	References
Gassinger <i>et al.</i> 1981	1b	1b	53	Acute rhinitis	<i>Eupatorium perfoliatum</i> 2x vs. aspirin	Symptoms severity score	Equivalence between homeopathy and allopathy	(26)
Lecoq 1985	1a	2	60	Upper respiratory tract infections	Homeopathic complex <i>L52</i> vs. placebo	Symptoms severity score	Patients rated more relief in verum group	(27)
Bordes and Dorfman 1986	1a	2	60	Cough	Low-dilution (3c) homeopathic complex in syrup (<i>Drosera</i>) vs. placebo	Symptoms	Significantly better decrease of symptoms in treated patients	(28)
Maiwald 1988	1b	1b	170	Acute rhinitis	Homeopathic complex <i>Grippheel</i> vs. aspirin	Symptoms severity score	Equivalence between homeopathy and allopathy	(29)
Casanova and Gerard 1988	1a	2	300	Influenza-like syndrome	<i>Oscillocochinum (Anas barbariae</i> 200K) 1 dose in the morning and 1 in the evening for 3-4 days	Temperature, shivering and myalgia	In the verum group: faster temperature reduction, significantly less shivering and less myalgia after 4 days	(30)
Sprenger 1989	3	2	65	Acute and chronic rhinitis	Low-dilution homeopathic complex formulation <i>Euphorbium compositum</i> , nasal spray	Physician's judgment of the therapy	Positive in 83% of cases (uncontrolled)	(31)
Wiesenaue <i>et al.</i> 1989	1a	2	152	Sinusitis	Low-dilution (3x-4x) homeopathic complex <i>Luffa, Cinnabaris, Kalium bichromicum</i> vs. placebo	Symptoms and global evaluation	No effect over placebo	(32)
Ferley <i>et al.</i> 1989	1a	1a	478	Influenza-like syndrome	<i>Oscillocochinum (Anas barbariae</i> 200k) 5 doses, one every 12 h	Healing rate at 48 h after diagnosis based on rectal temperature and two of the following symptoms: headache, stiffness, lumbar pain, articular ache, shivering.	Clinical healing after 48 h and rate of temperature reduction better in the verum group	(33)
Zenner and Metelmann 1990	3	2	594	Pharyngitis and tonsillitis	Low-dilution (3x-4x) homeopathic complex <i>Lymphomyosot</i> drops	Global evaluation, semi-quantitative	Improvement in >90% of cases (uncontrolled)	(34)
Connert and Maiwald 1991	3	2	26	Rhinitis and nasal obstruction	<i>Euphorbium compositum</i>	Symptoms, rhinomanometry	Decrease of symptoms in most patients (uncontrolled)	(35)
Weiser and Clasen 1994	1a	2	155	Chronic sinusitis	<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	(36)
Heilmann 1994	1a	2	102	Common cold and flu	<i>Engystol-N</i> vs. placebo, i.v. injection	Frequency and symptoms	No changes of frequency of attacks; decrease of symptoms and their duration	(37)
de Lange de Klerk <i>et al.</i> 1994	1a	1a	170 children	Pharyngitis and tonsillitis	Individualized vs. placebo	Frequency, duration and severity of rhinitis, pharyngitis episodes	Little, not significant, effect of homeopathy vs. placebo	(38)
Friese <i>et al.</i> 1997 □	2	1a	131 children	Otitis media	Individualized vs. allopathy	Duration of pain and therapy	Homeopathy slightly better than conventional therapy	(39)
Kruse 1998 □	2	3	126	Otitis media in children	Individualized vs. allopathy	Duration of pain and therapy	Equivalent efficacy	(40)

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Wiesenaue 1998□	3	1b	107	Acute tonsillitis	Low-dilution homeopathic complex of <i>Phytolacca americana</i> , <i>Guajacum officinale</i> , <i>Capsicum annuum</i>	Subjective and objective symptoms	Decrease of symptoms in most patients (uncontrolled)	(41)
Papp <i>et al.</i> 1998□	1a	1b	372	Influenza-like syndrome	<i>Oscillococtinum</i> (<i>Anas barbariae</i> 200k) 1 dose for 3 time/day x 3 days	Evaluation of symptoms during time after treatment	Statistically significant reduction of symptoms after 48 h in the verum group	(42)
Adler 1999	3	1a	119	Acute sinusitis	Homeopathic complex <i>Sinusitis PMD</i>	Symptoms	Trend to positive (uncontrolled)	(43)
Frei and Thurneyse 2001	3	1b	230 children	Acute otitis media	Individualized	Pain	Improvement in 39% of patients after 6 h, another 33% after 12 h (uncontrolled)	(44)
Riley, Fischer <i>et al.</i> 2001□	2	1b	456	Respiratory tract complaints or ear complaints	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	(45)
Jacobs, Springer <i>et al.</i> 2001	1a	1a	75 children	Acute otitis media	Individualized vs. placebo	Treatment failure and symptoms score	Less failure in verum group, not significant; little and significant decrease of symptoms in verum group	(46)
Oberbaum, Yaniv <i>et al.</i> 2001	1a	1a	32 children	Chemotherapy-associated stomatitis	Homeopathic complex <i>Traumeel-S</i> vs. placebo (local therapy with mouth rinsing)	Stomatitis development and scores	Less stomatitis in verum group, decrease of symptoms	(47)
Rabe, Weiser <i>et al.</i> 2004	2	1a	485	Mild respiratory upper tract infections	Homeopathic complex <i>Grippheer</i> vs. anti-inflammatory agents	Symptoms	Equivalence between homeopathy and allopathy	(48)
Ammerschlagel, Klein <i>et al.</i> 2005	2	1b	739	Rhinitis and sinusitis	Low-dilution homeopathic complex formulation <i>Euphorbium compositum</i> , nasal spray vs. xylometazoline	Symptoms and tolerability	Equivalent efficacy	(49)
Steinsbekk, Fonnebo <i>et al.</i> 2005□	1b	1b	169 children	Upper respiratory tract infections	Individualized vs. conventional care	Symptoms score	Decrease of days with symptoms in homeopathic group	(50)
Steinsbekk, Bentzen <i>et al.</i> 2005□	1a	1a	251 children	Upper respiratory tract infections	Parents-selected homeopathic medicines vs. placebo	Prevention of new episodes, symptoms scores	No effectiveness of homeopathy over placebo	(51)
Trichard, Chaufferin <i>et al.</i> 2005	4	1b	499 children	Acute rhinopharyngitis	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 (case series, uncontrolled)	(52)
Frass, Dielacher <i>et al.</i> 2005	1a	1a	50	Tracheal secretion (intubated patients)	Potassium dichromate 30c vs. placebo	Tracheal secretions on day 2, time to extubation	Homeopathy significantly better than placebo	(53)
Schmiedel and Klein 2006□	3	1a	397	Acute rhinitis	Homeopathic complex <i>Engystol</i> vs. conventional treatment	General and local symptoms	Homeopathic medicine equivalent to the conventional treatment	(54)
Steinsbekk, Lewith <i>et al.</i> 2007	1a	1a	208 children	Upper respiratory tract infections	Individualized vs. parents-selected medicines	Prevention of new episodes, symptoms scores	No difference between the two methods of prescription	(55)
Haidvogel, Riley <i>et al.</i> 2007	2 multicentr.	1b	1,557	Upper respiratory tract infections	Homeopathic strategy vs. allopathic (e.g. anti-inflammatory drugs, antibiotics).	Healing or major improvement after 14 days of treatment	Homeopathic treatment not inferior to the allopathic and best tolerated	(56)

Zabolotnyi, Kneis <i>et al.</i> 2007 [□]	1a	1a	113	Maxillary sinusitis	Homeopathic complex <i>Sinfrantal</i> vs placebo	Symptoms	Significant improvement over	(57)
Mousavi, Mojaver <i>et al.</i> 2009a	1b	1b	100	Aphthous ulcer	Individualized vs. placebo	Pain and ulcer size	Significant improvement after 4-6 days of treatment	(58)
Mousavi, Sherafati <i>et al.</i> 2009b [□]	1b	1b	30	Oral Lichen planus	<i>Ignatia</i> 30c	Pain and lesion size	Significant improvement after 4 months of treatment	(59)
Witt, Ludtke <i>et al.</i> 2009c	3	1a	134	Chronic sinusitis	Individualized	Symptoms, quality of life	Major improvement persisting at least 2 years (not controlled)	(60)
Ramchandani 2010	3	1b	30 children	Upper respiratory tract infections	Individualized	Number of episodes during 6 months before and after treatment	Decrease of episodes after homeopathic treatment	(61)

^aClinical trial: 1a: double-blind randomized controlled; 1b: non-blinded randomized (open) controlled; 2: non randomized controlled clinical trial; 3: prospective observational study, without control group; 4: retrospective study of case series.

^bPublication: 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.

A randomised double-blind placebo controlled pilot study was carried out (46) on children with otitis media. Subjects presenting middle ear effusion and ear pain and/or fever for no more than 36 h were enrolled in the trial. They received either an individualised homeopathic remedy 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, however these differences were not statistically significant. Diary scores showed a significant decrease in symptoms at 24 and 64 h after treatment in favour of homeopathy ($P < 0.05$).

A pragmatic, randomised, equivalence trial was performed by Steinsbekk and coworkers (50), investigating whether individualised treatment by a homeopath is effective in preventing childhood upper respiratory tract infections. Children recruited via mailed letters, from a group previously diagnosed with upper respiratory tract infections, were randomly assigned to receive either homeopathic care or conventional health care for 12 weeks. There was a significant difference in the median total symptom score in favour of homeopathic care (24 points) compared to the control group (44 points) ($p = 0.026$). The number of days with symptoms was 8 and 13 for the homeopathic and reference groups respectively ($p = 0.006$). Negative results were obtained by the same group in a double-blind placebo controlled randomized trial (51) investigating the effect of self treatment with one of three self selected homeopathic medicines for the prevention of childhood upper respiratory tract infections. A large group of children, recruited by post from those previously diagnosed with upper respiratory tract infections, were randomly assigned to receive either placebo or highly diluted homeopathic medicines, administered twice weekly for 12 weeks. Parents chose the remedy based on simplified constitutional indications. No difference was found between the frequency and scores of infection of the two groups. Of course, the negative outcome of this innovative

protocol may have been due to the inefficacy of the remedies themselves, or to the process by which they were selected and the types of remedies used. To clarify this point, in a further study (55), the same group of researchers compared homeopathic care (individual homeopathic consultations with any homeopathic medicine in any potency being prescribed) with self treatment with one of three self-prescribed homeopathic medicines in 30c dilution, administered twice weekly, for 12 weeks. The results indicated that there were no significant differences in clinical effects between the two types of homeopathic therapy for symptoms scores of upper respiratory tract infections.

Another study compared the 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 (52). Data from a large set of patients, clinically observed for 6 months, were analysed and grouped according to the type of drug prescribed and the episodes of acute rhinopharyngitis, complications, and adverse effects. The results showed that the 'homeopathic strategy' yielded significantly better results than the 'antibiotic strategy' in terms of the 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 favour of homeopathy (£88 vs. €99, $p < 0.05$). The authors suggest that homeopathy may be a cost-effective alternative to antibiotics in the treatment of recurrent infantile rhinopharyngitis. Needless to say, these conclusions will have to be confirmed or disproved by randomised studies on homogeneous groups of patients.

In a randomised, single blind, placebo-controlled clinical trial, Mousavi and coworkers (58) investigated the efficacy of individualised homeopathy in the treatment of oral recurrent aphthous ulceration. Patients with minor aphthous ulcers were treated with individualised homeopathic remedies or a placebo and followed up for 6 days. Pain intensity and ulcer size were statistically reduced in the verum group at day 4 and at day 6 ($p < 0.05$). No adverse effects were reported,

suggesting that homeopathic treatment is an effective and safe method for the treatment of this condition.

Witt and coworkers (60) evaluated homeopathic treatment of sinusitis in a large prospective multicentre observational study population. Successive patients presenting for homeopathic treatment were followed up for 2 years, and complaint severity, health-related quality of life, and medication use were regularly recorded. There were significant improvements in complaint severity and in quality of life scores at 3, 12, and 24 months. Due to the observational nature of the study, the authors correctly conclude that the observed effects may be due to life-style regulation and to placebo or context effects associated with the treatment.

An observational study of the individualised homeopathic treatment of recurrent upper respiratory tract infections in children below the age of 5 was carried out at a private Homeopathic Medical College (61). The number of attacks of upper respiratory tract infection during the 6-month period preceding the date of starting homeopathic treatment (Control value), and during the 6-month period following the start of treatment (Treatment value) were compared. The results of the study indicate statistically significant differences ($p < 0.001$) between the two data sets in favour of the homeopathically treated cases.

3.2. Ailment-specific homeopathic remedies and complexes

Although people are best treated with an individualised homeopathic remedy chosen by a professional homeopath, several trials have found certain common homeopathic remedies or combinations of remedies to be at least as effective as conventional medications. One of the earliest of these was the study by Gassinger and coworkers in 1981 (26). In a controlled clinical trial, patients suffering from the common cold were randomly assigned to treatment with acetylsalicylic acid or with the homeopathic remedy *Eupatorium perfoliatum* in a low potency. The efficacy of the drugs was assessed on days 1, 4 and 10 of the infection through symptom check lists and physical examinations. Neither the subjective symptoms, nor body temperature, nor the laboratory data differed significantly between the two groups, leading the authors to conclude that the homeopathic treatment was as effective as the allopathic treatment. Similar results to those of the above study were also obtained by Maiwald and coworkers in 1988 (64). In a simple blind randomised trial on a group of soldiers in the German army suffering from the common cold, and treated with acetylsalicylic acid or with a complex homeopathic preparation called *Grippheel* (made from low potencies of *Aconitum*, *Bryonia*, *Lachesis*, *Eupatorium perfoliatum*, *Phosphorus*). A comparison between changes in clinical status and subjective disorders on days 4 and 10, and between the length of time taken off work for the two groups, revealed no significant differences, leading the researchers to conclude that the two therapeutic approaches are equi-effective. More recently, the same homeopathic complex was evaluated in a prospective, observational cohort study on patients suffering from mild viral infections of the upper respiratory

tract (48), with encouraging results, showing an equivalent effectiveness of homeopathy and conventional medications.

A French study (28) of good methodological quality investigated the treatment of dry or hacking cough with a syrup based on the plant *Drosera* and 9 other substances in low homeopathic dilutions, demonstrating an excellent effectiveness of the treatment compared to a placebo: after one week of therapy, the symptom was significantly reduced or disappeared in 20 out of 30 patients receiving the treatment, compared to only 8/30 patients on the placebo.

A homeopathic remedy, *L52*, a complex formulation containing *Eupatorium perfoliatum* 3x, *Aconitum napellus* 4x, *Bryonia alba* 3x, *Arnica montana* 4x, *Gelsemium sempervirens* 6x, *Cinchona* 4x, *Belladonna* 4x, *Drosera* 3x, *Senega* 3x, showed promising results in a double-blind study compared to a placebo for the relief of symptoms of upper respiratory tract infections (27), but not in the prevention of flu in a large double-blind, placebo-controlled study (65).

Ferley and coworkers (33) used a homeopathic preparation that is very widely used, particularly in France (called "*Oscillocochinum*"), consisting essentially of a high Korsakovian dilution (200k) of *Anas barbariae* (duck) liver and heart extract. The study demonstrated a positive effect of the active drug treatment, in that it significantly increased the number of cures within 48 hours of diagnosis. Even more noteworthy is the fact that the paper was published by an important non-homeopathic journal. Probably, the soundness of the methodology and the large patient sample size made it very hard to contest the authors' findings. This evidence is in agreement with other randomised studies (30, 42), and a Cochrane review has evaluated as statistically significant and positive, though quantitatively small, the overall evidence in favour of the clinical efficacy of this homeopathic remedy in the treatment of influenza-like syndromes (66). The last-mentioned review also includes some reports concerning a putative effect of *Oscillocochinum* as preventive treatment, but the methodological quality of these studies is low and no sound conclusions are as yet possible. As far as the treatment of influenza-like syndromes is concerned, the study by Lewith and coworkers (67) reports an unsuccessful trial based on homeopathic dilutions of the influenza vaccine. The evidence concerning the homeopathic approach to influenza is described and discussed in a book by the author of this review (68).

Sprenger (31) reports an open study of a low-dilution complex homeopathic preparation, *Euphorbium compositum*, used as a nasal spray in patients with acute or chronic rhinitis. The product consisted of a mixture of low homeopathic potencies of *Euphorbium resinifera*, *Pulsatilla pratensis*, *Luffa operculata*, *Mercurius iodatus ruber*, *Mucosa nasalis suis*, *Hepar sulphuris calcareum*, *Argentum nitricum* and *Sinusitis nosode*. The physician's judgment of the therapy was good in 83% of cases, fair in 10.8% and no effect in 6.2%; the patients' evaluations were the same, whereas tolerability was excellent in 55.4% of

cases and good in 44.6%. Though no statistical evaluation of the approach is given, the results appear to be in line with those of more aggressive conventional treatments, and the absence of any substantial toxicity makes the compound quite interesting. Another observational, uncontrolled, study on patients suffering from chronic rhinopathy associated with previous long-term application of medication (abuse of nasal spray) gave positive results in 22 out of 26 patients, with normalisation of rhinomanometry tests (35). Subsequently, Weiser and Clasen (36) studied the clinical effectiveness of the same complex, *Euphorbium compositum*, in a double-blind, randomised, placebo-controlled study, in subjects with chronic sinusitis. The treated group showed a significant improvement in subjective symptoms such as respiratory obstruction, and sensation of internal pressure and pain, however there was no substantial variation in instrumental tests. An overall evaluation found a 21.1% improvement in the verum group compared to 14.4% in the placebo group ($p = 0.016$). The treatment was well tolerated. More recently, another open, multicentre, prospective, active-controlled cohort study was carried out on the homeopathic complex *Euphorbium compositum* (nasal drops), whose effectiveness and tolerability were compared with the reference allopathic drug xylometazoline (49). Clinically relevant reductions in the intensities of disease-specific symptoms were observed in both groups. Non-inferiority of the homeopathic complex remedy to xylometazoline could be shown for all the studied variables. Tolerability was good with both therapies.

The efficacy of three plants used in homeopathy to treat acute tonsillitis was evaluated in an open trial (41). A fixed combination of low dilutions of three plant substances (*Phytolacca americana*, *Guajacum officinale*, *Capsicum annuum*) was used in patients with this condition and no antibiotics were administered. According to the Materia Medica, this homeopathic complex remedy should be characterised by immunomodulatory, analgesic, and anti-inflammatory properties. A decrease in the objective and subjective symptoms of acute tonsillitis symptoms was observed as early as 2.5 days after starting treatment; no serious adverse effects were reported.

Wiesenaue and coworkers (32) demonstrated the inefficacy, in the treatment of sinusitis, of a number of remedies prepared from various combinations of *Luffa operculata*, *Kalium bichromicum*, and *Cinnabaris* (in low homeopathic dilutions). Their conclusion is that, unless other data emerge from a study of individualised homeopathic prescriptions ("repertorisation"), the drugs should not be considered active in acute or chronic sinusitis in the general population; they also point out that similar negative results have been obtained with antibiotics, nasal decongestants and drainage of the nasal cavities.

The efficacy and safety of a fixed-combination homeopathic medication (*Sinusitis PMD*) consisting of *Lobaria pulmonaria*, *Luffa operculata*, and *potassium dichromate* were investigated in an open-label practice-based study of patients with acute sinusitis (43). Most patients received only the test medication and no

antibiotics. After a mean of 4 days of treatment, secretolysis had increased significantly and typical sinusitis symptoms, such as headache, pressure pain at nerve exit points, and irritating cough, were reduced. The average treatment duration was 2 weeks. At the end of the treatment, 81.5% of patients described themselves as symptom free or significantly improved. Adverse drug effects were not reported.

A different complex that has been used in these kinds of respiratory complaints is *Engystol-N* (made of *Vincetoxicum* 6x, 10x and 30x, *Sulfur* 4x and 10x). A randomised, double-blind, placebo-controlled trial assessed the efficacy of this formulation, administered twice weekly as an intravenous injection, for prophylaxis of the common cold and flu (37). The placebo was the same isotonic saline solution used as the verum solvent. The frequency of occurrence of flu or common cold were not changed by the treatments, but the average length of the illness and severity of symptoms were less for the verum group than for the placebo group. No statistical analysis of the data was provided. In a non-randomised, observational study Schmiedel and Klein (54) compared the effects of *Engystol* with those of conventional therapies with antihistamines, antitussives, and nonsteroidal antiinflammatory drugs on upper respiratory symptoms of the common cold, over a treatment period of two weeks. The effects of treatment were evaluated on the variables of fatigue, sensation of illness, chill/tremor, aching joints, overall severity of illness, sum of all clinical variables, temperature, and time to symptomatic improvement. Both treatment regimens provided significant symptomatic relief, and significantly more patients ($p < 0.05$) using *Engystol*-based therapy reported improvement within 3 days (77.1% vs 61.7% for the control group).

An Israeli team (47) assessed a complex preparation (*Traumeel-S*, containing low homeopathic potencies of *Arnica montana* and several other plant extracts and minerals) for its effect in chemotherapy-associated stomatitis, a condition that is a common consequence of chemotherapy, and for which there is little effective treatment. The clinical trial, of randomised, placebo-controlled, double-blind design, was conducted on children and young adults who had undergone stem cell transplantation. The remedy was administered as a mouth rinse, five times daily for a minimum of 14 days, or until at least 2 days after all signs of stomatitis were absent. In the active treatment group, 33% of patients did not develop stomatitis, compared to only 7% in the placebo group. The mean area under the curve of stomatitis scores was 10.4 for the *Traumeel* treatment group and 24.3 for the placebo group ($p < 0.01$). These results suggest that this homeopathic complex may reduce the severity and duration of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation.

The group of Frass explored, in a hospital setting, the effectiveness of homeopathic adjunctive care on tracheal secretions in critically ill patients (53). A single

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medicine, namely potassium dichromate (in high homeopathic potency) was tested on tracheal secretions in patients who received controlled mechanical ventilation due to respiratory failure. This randomized, double-blind, placebo-controlled study showed that the amount of tracheal secretions as well as the time for successful extubation were significantly reduced in group receiving the homeopathic medicine ($p < 0.0001$). These data suggest that homeopathic treatment may be an useful additional therapeutic measure in this condition.

A prospective, randomised, double-blind, placebo-controlled trial carried out in the Ukraine (57) investigated the efficacy of a complex homeopathic medication (*Sinfrontal*), compared to a placebo, in patients with maxillary sinusitis. Between day zero and day seven, *Sinfrontal* produced a significant reduction in the total symptom score compared to the placebo ($p < 0.0001$). Eight adverse events were reported, assessed as being of mild or moderate intensity. The authors suggest that this complex homeopathic medication is safe and appears to be an effective treatment for acute maxillary sinusitis.

A group led by Mousavi (59) evaluated the effectiveness of homeopathic *Ignatia* in the management of oral lichen planus in a single blind randomised controlled clinical trial. After 4 months of treatment, mean lesion sizes and mean pain measures were found to differ between the control and treatment groups, in favour of *Ignatia* ($p < 0.05$).

4. ALLERGIC CONDITIONS

Allergies are the most common immunological disorders among the general population, and growing evidence suggests that the incidence of allergic disorders is rising dramatically. A number of surveys indicate that patients seeking homeopathic care for their allergic symptoms do so out of dissatisfaction with the conventional health care system, and that their choice is chiefly driven by the promise of fewer side-effects and by a desire to "try everything" (2, 4, 69-72). There is a substantial body of literature suggesting that homeopathy may provide some benefit in these conditions, particularly when they affect the respiratory system (10, 18). We shall here describe the homeopathic studies that have been carried out in the field of allergology and, more specifically, oculorhinitis (hay fever) and allergic asthma. A summary of these papers, in chronological order, is provided in Table 2.

4.1. Individualised homeopathy

A retrospective study, reported at a homeopathic conference (76), included children who had suffered from allergic bronchial asthma, and who were treated with individualised homeopathy. The results appear to be encouraging, with 44.2% of patients showing a "satisfactory reaction", 36.7% a "manifest improvement", 18.3% a "relative improvement" and only 0.8% "no reaction". The remedies most frequently

prescribed were *Lycopodium clavatum*, *Sulphur*, *Pulsatilla* and *Silicea*. For this same pathology, Castellsagu (79), retrospectively evaluated a series of children who were treated with a single remedy in accordance with the classical homeopathic method. Several different remedies were prescribed--the most frequently used being *Sulphur*, *Calcarea carbonica*, *Lycopodium* and *Pulsatilla*--in a range of potencies. After three years of treatment, the results showed a complete cure in 58% of cases, improvements in 23% and failures in 19%. In short, the results obtained with such a serious chronic disease appear encouraging, however the open and uncontrolled nature of the trial makes it impossible to draw any definite conclusions. Another retrospective study evaluated patients suffering from bronchial asthma (both children and adults), who had received individualised homeopathic treatment for more than three years (85). A statistically significant decrease in the frequency and severity of attacks before and after treatment was reported. There was also a marked reduction in the use of conventional medication. The most frequently prescribed remedies were *Arsenicum album*, *Nux vomica*, *Sulphur*, *Pulsatilla*, and *Silica*.

A communication given at a conference of the "Liga" international homeopathic medical society described a trial on the effectiveness of classical individualised treatment of asthmatic patients allergic to dermatophagoides (86). Symptoms and immunological parameters were evaluated before and after an eight-month treatment period. A significant reduction in the number of exacerbations, and improved spirometry test results and immunological markers, were observed in the active homeopathic group. However a full report would be needed for a detailed evaluation of this trial. A study investigating individualised homeopathic therapy in asthma was published in a Mexican homeopathic journal (88). The trial was of double blind design and placebo-controlled, however the randomisation was not specified. The main result was a reduction in asthma attacks after 4 months of treatment, with a significant difference in favour of homeopathy.

The effects of individualised homeopathic remedies as an adjunct to conventional treatment were compared against a placebo in children with mild to moderate asthma (96). There were no clinically relevant or statistically significant changes in active quality of life scores. Symptom severity scores showed relative improvements, but the magnitudes of the effects were small. The authors conclude that adjunctive homeopathic therapy is not superior to a placebo in improving the quality of life of children with mild to moderate asthma. Although this study received high media coverage as proof of the inefficacy of homeopathy, various authors have questioned whether the parameters used were sensitive enough to differentiate between children who have no asthma and those who have only mild asthma (102, 103). In fact, some of the patients enrolled had very mild or absent symptoms, which could scarcely have been ameliorated. Therefore, this study should be interpreted with caution.

Table 2. Homeopathic clinical studies in the field of respiratory allergies

Authors and year	Study type ^a	Publication type ^b	N. of subjects	Conditions (diagnosis)	Treatment(s)	Outcomes	Key results	References
Hardy 1984	1a	2	70	Allergic oculorhinitis (house dust)	Homeopathic immunotherapy (H.I.T.) made with house dust potencies	Symptoms	H.I.T. better than placebo	(73)
Wiesenaue and Gaus 1985	1a	1b	164	Allergic oculorhinitis	<i>Galphimia glauca</i> 6x dynamized vs. placebo e <i>Galphimia glauca</i> 6x non-dynamized	Eye and nose symptoms	Trend to better improvement in the homeopathic group, not statistically significant; less symptoms in patients taking dynamized verum medicine than other groups	(74)
Reilly, Taylor <i>et al.</i> 1986	1a	1a	144	Allergic oculorhinitis (hay fever)	<i>Pollens</i> 30c (H.I.T.) vs. placebo	Symptoms (VAS)	H.I.T. better than placebo	(22)
Wiesenaue and Ludtke 1987	1a	3	132	Allergic oculorhinitis	<i>Galphimia</i> 2c vs. placebo	Eye and nose symptoms	Significantly less eye symptoms in verum group	(75)
Mosquera Pardo 1990	4	3	120 children	Allergic asthma	Individualized homeopathy	General assessment	Improvement in most patients (uncontrolled)	(76)
Campbell <i>et al.</i> 1990; Reilly <i>et al.</i> 1994	1a	1a	28	Allergic asthma	Allopathy + Allergen 30c (H.I.T.) vs. allopathy+ placebo	Symptoms (VAS) and respiratory tests	Less symptoms in the verum group than placebo, no differences in tests	(77, 78)
Castellsagu 1992 □	4	1b	26 children	Allergic asthma	Individualized	General assessment	Improvement in most patients (uncontrolled)	(79)
Nolleveaux 1992 □	3	3	108	Allergic oculorhinitis	<i>Pollen</i> 30c, <i>Apis</i> 15c, <i>Lung histamine</i> 15c	Symptoms	Improvement in most patients (uncontrolled)	(80)
Wiesenaue and Ludtke 1995	1a	2	115	Allergic oculorhinitis	<i>Galphimia</i> 4x vs. placebo	Eye and nose symptoms	Significant relief in verum group	(81)
Matusiewicz 1995-1997	1a	2	40	Allergic asthma	Homeopathic complex <i>Engystol-N</i> vs. placebo	Respiratory tests	Clinical improvement only in verum group	(82-84)
Eizayaga and Eizayaga 1996	4	1b	62	Allergic asthma	Individualized	Symptoms scores	Significant decrease of symptoms after therapy (uncontrolled)	(85)
Lara-Marquez, Pocino <i>et al.</i> 1997	1a	4	19	Allergic asthma	Individualized vs. placebo	Symptoms, spirometry parameters and immunological markers	Verum better than placebo, significant changes of laboratory markers	(86)
Micciché, Trapani <i>et al.</i> 1998	2	2	70 children	Allergic oculorhinitis	Homeopathic protocol based on three low-dilution drugs vs. conventional therapy	General assessment	Trend to better improvement in the homeopathic group	(87)
Riveron-Garrote, Fernandez <i>et al.</i> 1998	1a	2	80	Allergic asthma	Individualized vs. placebo	General symptoms and attack intensity	Higher reduction of asthma attacks in verum group	(88)
Matusiewicz, Wasniewski <i>et al.</i> 1999	1a	2	84	Allergic asthma	Homeopathic complex <i>Asthma H Inj. Pifugerplex</i> (subcutaneously)	Use of allopathic drugs, laboratory and spirometric tests	Slight decrease of conventional medication and infections; no change in spirometric tests	(89)
Weiser, Gegenheimer <i>et al.</i> 1999	1b	1b	146	Allergic rhinitis	Low-dilution homeopathic complex formulation <i>Luffa compositum</i> vs. chromolyn sodium	Symptoms and quality-of-life questionnaires	Equivalence of homeopathy and allopathy	(90)
Taylor, Reilly <i>et al.</i> 2000	1a	1a	50	Allergic rhinitis	Individual allergen 30c vs. placebo (H.I.T.)	Symptoms (VAS) and nasal air flux tests	Slightly better outcomes in verum group	(91)
Aabel, Laerum <i>et al.</i> 2000	1a	1b	66	Allergic rhinitis	Homeopathic birch pollen <i>Betula</i> 30c vs. placebo	Symptoms scores	Slightly less symptoms during 10 days; aggravation after taking verum	(92)
Aabel 2000	1a	1b	73 children	Allergic rhinitis	Homeopathic birch pollen <i>Betula</i> 30c vs. placebo	Symptoms (VAS)	Verum significantly worst than placebo	(93)
Aabel 2001	1a	1b	51	Allergic rhinitis	Homeopathic birch pollen <i>Betula</i> 30c vs. placebo	Symptoms (VAS)	Similar improvement in verum and placebo	(94)

Lewith, Watkins <i>et al.</i> 2002	1a	1a	242	Allergic asthma	Allergen (dust mite) 30c vs. placebo (H.I.T.)	Symptoms (VAS) and expiration flux (FEV)	No final therapeutic effect, initial aggravation	(95)
Frenkel and Hermoni 2002	4	1b	48	Allergic asthma and other allergies	Homeopathic care (various)	Conventional medication consumption	The homeopathic intervention led to reduction in the use of medications (uncontrolled)	(71)
White, Slade <i>et al.</i> 2003	1a	1a	96 children	Asthma (mild to moderate)	Individualized vs. placebo	Quality-of-life questionnaires, symptoms and tests	No changes in quality of life, small not significant improvement of symptoms in verum group	(96)
Li, Bush <i>et al.</i> 2003	3	1a	12 children	Allergic asthma	H.I.T. prepared from individual allergen vs. placebo	Spirometric tests	No improvement after treatment (uncontrolled)	(97)
Kim, Riedlinger <i>et al.</i> 2005	1a	1a	40	Allergic rhinitis	H.I.T. prepared from individual allergen vs. placebo	Symptoms, quality-of-life questionnaires	Better clinical changes in verum group as compared with placebo	(98)
Witt, Keil <i>et al.</i> 2005	2	1b	178	Allergic diseases including rhinitis and asthma	Classic homeopathy vs. conventional care	Symptoms, and quality-of-life questionnaires, costs	Better outcomes in homeopathic group	(99)
Colin 2006	4	1b	147	Respiratory allergies	Classic homeopathy	Symptoms	Clinical improvement in >90% in cases (uncontrolled)	(100)
Goossens, Laekeman <i>et al.</i> 2009	3, multicentr.	1b	46	Allergic rhinitis	Classic homeopathy	Quality-of-life questionnaires	Major improvement of quality of life after 3 and 4 weeks	(101)

^aClinical trial: 1a: double-blind randomized controlled; 1b: non-blinded randomized (open) controlled; 2: non randomized controlled clinical trial; 3: prospective observational study, without control group; 4: retrospective study of case series.

^bPublication: 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.

An observational study comparing the outcomes and costs of homeopathic therapy against those of conventional treatment in routine care has been published (99). 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 for this subset of patients may be of interest for this review. Allergic children were treated either with a classic homeopathic approach or with conventional therapies provided by doctors selected from an address list of general practitioners. The two groups were not randomised, but their disease grades at baseline were similar. After 12 months of treatment, symptom severity scores decreased more significantly in the homeopathic group than in the conventional group. There was also a tendency toward more improved quality of life within the homeopathic group, but this did not prove statistically significant after diagnosis-specific adjustment. Similar findings were reported by the same group in an observational study of children with atopic eczema (104).

A series of cases of respiratory allergy treated with individualised and constitutional homeopathy in a private homeopathic practice have been reported (100). The author estimates 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, and no patients deteriorated. For pulmonary allergies, two instances of worsening and three of no improvement were observed out of a total of 42 cases. A prospective observational study was conducted to investigate the quality of life in

patients with rhino-conjunctivitis (101). Patients aged between 14 and 68 completed a questionnaire specific to their condition at baseline, and after individualised homeopathic treatment. The mean score at baseline was 3.40 (+/- .98). After three and four weeks of homeopathic treatment it had fallen to 1.9 (p = 0.0001) and 1.6 (p = 0.0001) respectively. These results suggest that homeopathic treatment may be effective in allergic rhinitis, however they would need to be confirmed in a formal randomised trial.

A pharmacoeconomic study (not included in Table 2 because it does not concern effectiveness) assessed the impact of homeopathic treatment of allergic diseases within a health maintenance organisation (71). The computerised medication charts of each patient were evaluated for conventional medication consumption three months before and three months after the homeopathic therapy, with each patient serving as his or her own control. The results showed that 56% of patients reduced their use of conventional medication following the homeopathic intervention. The most significant reduction was in antihistamine use, followed by decreases in the use of bronchodilators and steroids, resulting in average savings of \$24 per patient during the 3-month period following the homeopathic intervention.

4.2. Ailment-specific homeopathic remedies and complexes

A group led by Wiesenauer has for many years been investigating treatments using low homeopathic potencies extracted from the plant *Galphimia glauca*. In a

double-blind, randomised study of patients with seasonal allergic rhinitis, *Galphimia glauca* in the 6th decimal dilution/dynamization was tested in patients affected by allergic rhinoconjunctivitis (74). After one 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 remedy prepared by dilution alone, without dynamization. Though these data appear promising, there was no clear-cut statistical difference. Two years later, Wiesenauer and Ludtke (75) published the results of another double-blind, randomised, placebo-controlled study of the effects of *Galphimia glauca* in allergic rhinitis. After one month of treatment, the experimental group showed clear improvements in terms of eye symptoms and nasal symptoms. The authors suggest that this remedy should be used only after homeopathic identification of sensitive individuals, in order to minimise the number of non-responders. Wiesenauer subsequently continued this line of research, and his group has published a number of papers on the efficacy of *Galphimia glauca*, the most effective potency being the 4x (81, 105). A meta-analysis of 7 randomised clinical trials to assess the efficacy of homeopathic preparations of *Galphimia glauca* in the treatment of allergic rhinitis was published by Ludtke and Wiesenauer (106). The data consistently indicate a statistically significant effect of the low-dose homeopathic medicine versus a placebo, particularly for the relief of eye symptoms. The estimated success rate is reported to be about 80%. The validity of these experimental studies has also been confirmed by independent reviews (107, 108).

A group of investigators have tested the effectiveness of two homeopathic complexes in bronchial asthma. A first clinical trial tested the complex *Engystol-N* (tablets) (82-84). Patients were randomly assigned to verum or placebo groups, in blind conditions. During the observation period, those treated with the homeopathic complex showed greater improvement of respiratory function. In another paper (89), the same authors describe a double-blind, randomised, placebo-controlled study of patients with allergic bronchial asthma already under treatment with steroids, bronchodilators and other drugs. One vial of the complex *Asthma H Inj. Pflugerplex* (a mixture of low dilutions of various homeopathic plants and minerals) was administered subcutaneously every week for nine months. Administration of *Triamcinolone* was found to decrease in the treated group and increase in the 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 the spirometric parameters, possibly because patients were advised to take the lowest cortisone dose compatible with the absence of cough and resting dyspnea.

Micciché and coworkers (87) carried out an open study on children with allergic oculorhinitis, comparing conventional anti-histaminic and cortisone

treatment with a homeopathic protocol based on three remedies (*Doliosobios* No.15, an organotherapeutic, *Mn-Cu Oligodrop* and *Histaminum*) initiated after the start of pollen season in order to evaluate their acute phase efficacy. After two months of treatment, 30/35 children in the homeopathic group were cured, two obtained only slight benefit, and three had to be switched to conventional treatment due to relapses. In the conventional treatment group, 21/35 children were cured, seven showed slight improvement, and seven had to discontinue treatment because of toxic effects. As in other reports of equivalence studies, homeopathy clearly shows a similar effectiveness when it is compared with conventional therapies. However, the validity of the results is limited by the fact that this was not a randomised study.

Weiser and coworkers (90) report a study of seasonal allergic rhinitis, using a homeopathic complex (*Luffa compositum*) in nasal spray formulation, consisting of a fixed combination of *Luffa operculata*, *Galphimia glauca*, *Histamine* and *Sulfur* (in three increasing homeopathic potencies). A reference group of patients was not given homeopathic therapy and treated only by standard intranasal therapy based on *Cromolyn sodium*. The results of the study demonstrate a quick and lasting effect of the homeopathic treatment, which produced a nearly complete remission of hay fever symptoms. Adverse systemic effects did not occur. Local adverse events appeared in 3 patients out a total of 146. In conclusion, the authors suggest that, for the treatment of hay fever, the homeopathic nasal spray is as efficient and well tolerated as the conventional therapy.

4.3. Homeopathic immunotherapy

One of the most extensive lines of research in homeopathy is that investigating the use of high dilutions of known allergenic substances to prevent or cure those same allergies. This is an application of the ancient isopathic principle (9), which has also been termed "homeopathic immunotherapy" (HIT) (77).

To introduce the description of these results, it is worth citing an early report published in 1984 by Hardy in a non-indexed journal (73). This author obtained relief of oculorhinitis symptoms in patients allergic to house dust using homeopathic potencies of house dust. A similar approach was investigated in depth over a long time horizon by a group led by Reilly: a double-blind study, published as preliminary report in 1985 (109) and as a full paper in 1986 (22), compared the effects of a placebo and of a homeopathic preparation made from highly diluted/dynamized allergens (30th centesimal dilution) designated *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 the anti-histamine rescue treatments than did the 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 (77). Patients received a placebo for four

weeks and were then randomly divided into two groups, one of which continued the placebo, while patients in the other group were treated with a homeopathic preparation of the main allergen to which each individual was sensitive. The outcome was a statistically significant difference in favour of the active treatment. These trials, enriched by further statistical analyses and a meta-analysis of all patients, were published in 1994 (78) and showed an extremely high probability ($p = 0.0004$) that the homeopathic effect was not due to placebo. Reilly's group subsequently organised a multicentre study on patients affected by allergic rhinitis (91). The study involved administering a high homeopathic 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 compared with those receiving placebo ($p = 0.0001$). It is interesting to note that the group treated with the homeopathic allergen preparations more frequently reported an initial worsening--a phenomenon commonly known to occur in homeopathy. This study offers further proof that high homeopathic dilutions cannot be considered equivalent to a simple placebo. However, as the authors themselves underline, this does not mean that their proposed HIT as a routine homeopathic therapy for chronic rhinitis (also because classic homeopathy requires individualised treatment).

A trial of the homeopathic medication *Lung histamine* (5c potency) used prophylactically in children with asthma, also yielded promising results in reducing the frequency of though due to the design of the study the evidence is not persuasive (111). An uncontrolled study conducted in Belgium observed the effect of *Pollen* (30c potency) prepared from a mixture of 12 grass pollens, combined with *Apis mellifica* and *Lung histamine* (both at 15c), in allergic oculorhinitis (80). The regimen was one tablet per day, and progress was monitored for six months by recording nasal and ocular symptoms as well as by a doctor's assessment. Between 69% and 86% of patients--depending on the parameter evaluated--showed clinical improvements.

A further study of HIT was published in 2002 by an independent group led by Lewith (95). Patients with asthma and positive skin prick tests for house dust mite were enrolled in the trial. After a 4-week baseline assessment, participants were randomised to receive either oral HIT made with their specific allergen or a placebo, and then assessed over 16 weeks by means of three doctor's visits and diary assessments every other week. Though there was no difference in most final outcomes between homeopathic immunotherapy and the placebo, the two treatments did show different patterns of change during the course of the trial, with respect to diary assessments of morning peak expiratory flow, visual analogue scale and mood. Essentially, the homeopathic remedy produced a slight but statistically significant worsening during the early phases of treatment compared to the placebo, while at the end of the experimental period the effectiveness of therapy was

not obtained. So, we have the paradox of a trial disproving both the null hypothesis of homeopathy = placebo and the hypothesis of therapeutic efficacy of the HIT. This study sparked considerable discussion in the same journal (112). In a subsequent paper, some of the authors of the previous negative trial of homeopathic immunotherapy discussed their data for that trial using complexity theory (113). There is evidence for different fluctuations in outcome (both physiological and subjective) for 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 may require a different trial methodology from that currently in use.

A series of double-blind, randomised, placebo-controlled trials on the preventive and therapeutic effectiveness of *Betula* pollen (HIT), was carried out by a Norwegian group. The first study (92) investigated the effect of the homeopathic remedy *Betula* 30c vs. placebo on adult patients with birch pollen allergy. No statistically significant difference between groups was found, except for a brief period when those receiving verum showed fewer and less serious symptoms. For some days, these differences were statistically significant. The verum group also reported some aggravation after medication--more so than the placebo group--a result in agreement with those of previously mentioned trials. The second study (93) involved children and yielded inconclusive results, possibly--according to the authors--because the pollen count was very low during the treatment period, and was only high enough to provoke allergic symptoms on three days. This time the verum treated patients fared worse than placebo group; they used more rescue medications and had higher symptom scores during the three days of higher pollen count. The authors suggest that, though the findings may represent a putative "aggravation response", they certainly do not support the usefulness of the tested homeopathic prophylaxis for this condition. A third trial (94) adopting similar protocol to the above, with the addition of a cross-over of treatments, found a substantial response in both the verum and placebo groups, with no significant clinical advantage for HIT.

Other authors, in a letter communication (97), report obtaining negative results in an open study in which they assessed the effects of homeopathic immunotherapy in children with stable asthma. This might be ascribable to the small sample size ($n = 12$), or to an effective lack of efficacy of the remedy.

A more recent double-blind trial found significantly positive effects of homeopathic immunotherapy on seasonal allergic rhinitis (98). The remedy was prepared from common allergens (tree, grass, weed species) specific to the Southwest region of the US, and compared to a placebo. Study outcomes included allergy-specific symptoms using the rhinoconjunctivitis quality-of-life questionnaire. The

subjects reported no adverse effects during the 4-week intervention period.

5. ARTHRO-RHEUMATIC DISEASES

Despite growing interest in uncovering the underlying mechanisms of arthritis and rheumatic diseases, medical treatment for these conditions remains symptomatic. Current medical therapies 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—along with acupuncture—being one of the most common among these (114). Judged on the basis patients' self-reported efficacy, homeopathy achieved higher scores for osteoarthritis, while satisfaction was lower for rheumatoid arthritis and connective tissue diseases (115). Retrospective studies and case histories suggest that recovery or clinical improvement may be achieved with homeopathic treatments for conditions such as osteoarthritis, ankylosing spondylitis and rheumatoid arthritis (116). A systematic review of the clinical evidence for and against the effectiveness of homeopathic remedies in the treatment of patients with osteoarthritis has been published (117). Its authors conclude that, although the small number of randomised clinical trials conducted thus far tend to favour homeopathic treatment, they do not provide any conclusive evidence as to the effectiveness of homeopathic remedies in the treatment of osteoarthritis patients. Another research review concludes that the body of evidence suggests that homeopathic remedies, either individually prescribed or used in a homeopathic formula, can provide relief for people with rheumatic disease (108). The literature of experimental and observational trials in this field is summarised in Table 3.

5.1. Individualised homeopathy

In 1978 a Scottish group led by Gibson published a study on the homeopathic treatment of rheumatoid arthritis conducted at the Glasgow Homeopathic Hospital (118). In this pilot study, a group of patients with rheumatoid arthritis was treated with classic homeopathy, and another group was treated with high doses of salicylate. Both groups were compared with a third group of patients who received a placebo. The patients treated with homeopathy did better than those who received salicylate. However the design of the trial was neither randomised nor double blind, so that it is not possible to distinguish the effects due to the physicians from those due to the treatments; what is more, there was an exceedingly high drop-out rate. In a subsequent study, the same group evaluated individualised homeopathic therapy against a placebo (119) in double-blind conditions. Each patient in the verum group received his or her own prescribed remedy, while the others were treated with a placebo. The results, after three months of therapy, showed an improvement in symptoms (mainly spontaneous pain, stiffness in the joint, prenil strength) for 83% of the

treated patients, compared to only 22% of those receiving the placebo. On the other hand, no differences between the verum and placebo groups were observed with regard to laboratory variables.

In a double-blind randomised trial, carried out on patients with active rheumatoid arthritis (123), subjects were treated for a period of six months. All patients were interviewed monthly by an expert homeopathic physician, and the selected homeopathic remedy was continued or changed based on to the patient's response. The patients were also assessed every month by a blinded evaluator. Those treated with homeopathy showed a significant intra-group improvement between the trial outset and the end of treatment, for 3 out of the 5 observed variables, and namely 15-meter walking time, articular index and functional class. With the placebo, only one variable, the articular index, improved significantly. Both groups showed a significant decrease in the daily dose requirement of prednisone. The overall assessment by physicians confirmed an improvement in both groups (59% and 44% of patients for verum and placebo respectively), but there was no statistically significant difference. Reported adverse effects were few, and comparable for both groups.

Another published study reached a negative conclusion as to the effectiveness of homeopathy (individualised prescriptions) in rheumatoid arthritis (129). This was a 6-month randomised, 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 individualised homeopathic treatment or identical matching placebos. The main outcome measures were visual analogue scale pain scores, objective indexes of stiffness and laboratory erythrocyte sedimentation rate. There were a number of drop-outs from the trial. The placebo and active homeopathy had different effects on pain scores; mean pain scores were significantly lower after 3 months of placebo therapy than after 3 months of active therapy ($p = 0.032$). Articular index, sedimentation rate and morning stiffness were similar for active homeopathy and the placebo. In conclusion, this trial found no evidence that active homeopathy improves the symptoms of rheumatoid arthritis in patients attending a routine clinic who are stabilised on conventional anti-inflammatory treatment.

An Italian group of homeopathic physicians assessed the results of homeopathic therapy in association with traditional therapies, in patients suffering from osteoarthritis and nontraumatic back pain pathologies (131). This was a non-randomised, prospective observational study, that also included a parallel group under conventional therapy. All the patients were under treatment at the Hospital outpatient clinic, where the examinations (conventional and homeopathic), diagnostic

Table 3. Homeopathic clinical studies in the field of arthrorheumatic diseases and osteoarthritis

Authors and year	Study type ^a	Publication type ^b	N. of subjects	Conditions (diagnosis)	Treatment(s)	Outcomes	Key results	References
Gibson, Gibson <i>et al.</i> 1978	2	1a	195	Rheumatoid arthritis	Individualized prescription vs. salicylate and placebo, 12 months	Medical assessment	Better relief in the homeopathic group compared to the allopathic and placebo. High incidence of drop-out.	(118)
Gibson, Gibson <i>et al.</i> 1980	1a	1a	46	Rheumatoid arthritis	Individualized prescription contro placebo, 3 mesi	Pain and articular index	Better relief in the homeopathic group vs. placebo	(119)
Shipley, Berry <i>et al.</i> 1983 □	1a	1a	36	Hip and knee osteoarthritis	<i>Rhus toxicodendron</i> 6x vs. placebo and fenoprofen	Symptoms	No effect of homeopathy vs. placebo; fenoprofen better than homeopathy vs. placebo	(120)
Fisher 1986	1a	1b	24	Fibromyalgia	<i>Arnica</i> , <i>Rhus tox</i> , <i>Bryonia</i> 6c vs. placebo	Pain symptoms	Trend to better improvement in the homeopathic group, not statistically significant	(121)
Fisher, Greenwood <i>et al.</i> 1989	1a	1a	30	Fibromyalgia	<i>Rhus tox</i> (individualized) vs. placebo	Pain symptoms	Slightly positive therapeutic effect in most patients in the verum group vs. placebo	(122)
Andrade, Ferraz <i>et al.</i> 1991	1a	1a	44	Rheumatoid arthritis	Individualized prescription vs. placebo, 6 months	Clinical mesurement and general medical assessment	Slight but not significant differences of the verum group over the placebo	(123)
Wiesenaue and Gaus 1991	1a	1b	111	Chronic polyarthritis	Homeopathic preparation “ <i>Rheumaselect</i> ” or placebo, 12 weeks	Inflammation markers, functional indexes, allopathic drugs consumption, general assessment	Slightly better outcomes in the verum group	(124)
Nahler, Metelmann <i>et al.</i> 1996	1b	2	114	Knee osteoarthritis	<i>Zeel compositum-N</i> vs. hyaluronic acid, intrarticular injection	Pain during motion (subjective scores), tolerability	Equivalence of the homeopathic complex and hyaluronic acid	(125)
Shealy, Thomlison <i>et al.</i> 1998 □	1b	2	65	Knee osteoarthritis	Homeopathic complex formulation <i>Rhus toxicodendron</i> , <i>Cauticum</i> , and <i>Lac vaccinum</i> vs. acetaminofen	Motion tenderness (VAS)	Equivalence of homeopathic and allopathic medicines	(126)
Schirmer, Fritz <i>et al.</i> 2000	1a	1a	104	Anklosing spondylitis	<i>Formica rufa</i> 6x and re-injection of patient own blood vs. placebo	Questionnaire on arthritis and general assessment	No difference with the placebo	(127)
van Haselen and Fisher 2000	1b	1a	172	Knee osteoarthritis	Local application of a homeopathic gel vs. piroxicam gel	Pain and arthritis index	Equivalence of homeopathic and allopathic gel	(128)
Fisher and Scott 2001	1a	1a	112	Rheumatoid arthritis	NSAIDS individualized prescription vs. NSAIDS+ placebo	Pain and articular index	No effect of homeopathy over the placebo	(129)
Birnesser, Klein <i>et al.</i> 2003	2	2	592	Knee osteoarthritis	<i>Zeel compositum-N</i> vs. COX-2 inhibitors	Symptoms scores	Equivalence of homeopathic and allopathic medicines	(130)
Pomposelli, Codecà <i>et al.</i> 2003	3	2	55	Osteoarthritis, back pain	Individualized prescription	Pain/motion tenderness quality of life	Improvements after the therapy, higher in the homeopathic group vs. the conventional group (non randomized)	(131)
Bell, Lewis <i>et al.</i> 2004a	1a	1a	62	Fibromyalgia	Individualized prescription vs. placebo	Pain, motion tenderness, quality of life	Significantly better outomes of the homeopathy group vs. the placebo	(132)
Relton, Smith <i>et al.</i> 2009	1b	1b	47	Fibromyalgia	Individualized prescription vs. conventional treatment	Fibromyalgia Impact Questionnaire	Better reduction of symptoms in patients treated with homeopathy vs. control; no adverse effects	(133)

^aClinical trial:1a: double-blind randomized controlled; 1b: non-blinded randomized (open) controlled; 2: non randomized controlled clinical trial; 3: prospective observational study, without control group; 4: retrospective study of case series.

^bPublication: 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.

investigation and administration of the quality-of-life SF-36 questionnaires were carried out. The study was divided into three phases of observation lasting a total of 12 months.

Self-selection on the part of patients led to the formation of groups that were fairly homogeneous with respect to sex and age, but differed with respect to clinical situation and

quality of life. The group treated with homeopathy comprised patients with more painful, non-traumatic pathologies of the spinal column and worse scores for quality of life, an observation borne out by the higher consumption of medicines among this group at the start of the therapy. Quality of life (along the dimensions of “Physical pain”, “Energy and vitality”, “Social function” and “General health”) improved noticeably and significantly only in patients receiving homeopathic therapy, while remaining substantially unchanged for those in conventional therapy. The most prescribed remedies were *Ignatia amara*, *Calcarea carbonica*, *Silicea*, *Staphisagria*, *Gelsemium*, *Sulphur*, and *Causticum*. On the whole, this study suggests that homeopathic therapy (associated with physiotherapy and if necessary with pharmacological therapies) might give better results than conventional therapy alone, and points to the need for a randomised trial comparing homogeneous groups of patients.

In a double-blind, randomised trial to assess the effectiveness of individualised classical homeopathy in the treatment of fibromyalgia (134), patients (mean age 49 yr, 94% women) received either a homeopathic remedy in 1LM (1/50,000) potency or a placebo. Participants receiving active treatment showed significantly greater improvements in tender point count and tender point pain, quality of life, global health and a reduced tendency toward depression compared with those on the placebo. This trial was paralleled by a series of interesting analyses aimed at characterising some factors that may be correlated with the therapeutic outcome (135): homeopaths rated each patient's vital force on a five-point scale, with 1 = very weak to 5 = very strong, and this parameter was found to correlate better with perceived mental function, energy, and positive dimensions of the individual, above and beyond the absence of disease. Moreover, fibromyalgia patients showed evidence of sensitisation of pain pathways and electroencephalographic alterations, with the homeopathic treatment group showing significantly increased global alpha-1 and alpha-2 in a test based on laboratory elicitation by olfactory stimulation, while the placebo group showed a decrease (136, 137). These findings suggest that electroencephalographic changes in specific areas of brain may be biomarkers of the individualised homeopathic remedies.

The homeopathic treatment of fibromyalgia was recently investigated in a pragmatic parallel group design (133). Patients were randomly allocated to either conventional care by itself, or to conventional care plus adjunctive care by a homeopath who prescribed individualised homeopathic remedies. Adjusting for baseline, there was a significantly greater mean reduction in the symptoms score (function) among the homeopathic care group than in the group receiving only conventional care. There were no reported adverse events. Given the acceptability of the treatment and its clinically relevant effects on function, there is a need for a definitive study to assess the clinical and cost effectiveness of adjunctive healthcare by a homeopath for patients with fibromyalgia.

5.2. Ailment-specific homeopathic remedies and complexes

A trial that yielded negative results was conducted on patients with osteoarthritis (120), who were divided into three groups: one received *Rhus toxicodendron* (low homeopathic potency), one *fenoprofen*, and the third a placebo. The results showed that only the group treated with *fenoprofen* showed a significant improvement in symptoms, in comparison with the placebo. The negative outcome of this trial suggests that the tested remedy cannot be effective if prescribed based only upon a diagnosis of disease, but without individualisation of the therapy. These methodological issues were addressed in subsequent trials carried out in Great Britain. For example, in a double-blind trial involving patients suffering from fibrositis (primary fibromyalgia) (121), the physician was given a choice of 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 the placebo. A similar trial involving patients with fibromyalgia was carried out in London (122). The diagnosis was made 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* was indicated were included in the trial (this remedy is one of those most often prescribed for this type of disease). This was a double-blind, placebo-controlled, cross-over study. The results were positive in favour of the homeopathic treatment, which led to a reduction in pain symptoms and general conditions. This experience indicates that the problem of disconnection between “conventional” diagnosis and homeopathic prescription, which has to be individualised, can be solved by including in the trial a sub-group of patients who are, according to classical homeopathic guidelines, susceptible to a single medicine.

A particular modality was tested in a randomised double-blind trial (127) on patients with ankylosing spondylitis. The subjects were intramuscularly treated twice weekly for four weeks with a combination of low homeopathic potencies of *Formica rufa* and the patient's own blood, or with an injection of a placebo (physiological saline). Immediately before and after therapy, as well as 4, 12, and 24 weeks later, the doctor's clinical assessment and the patients' subjective health status were recorded. The authors were not able to detect any statistical difference between the treatment and placebo groups.

The homeopathic preparation *Rheumaselect* (a mixture of low potencies of *Rhus toxicodendron*, *Bryonia*, *Nux vomica*, *Berberis*, *Ledum*) showed better overall efficiency compared to a placebo in a randomised, double blind, controlled trial (124). Though both groups showed a remarkable improvement in symptoms, when consumption of antirheumatic and analgesic drugs and the assessment of pain by the patient were combined into a single outcome variable, the result was a significant efficacy of the homeopathic remedy.

In homeopathy, *Rhus toxicodendron*, *Solanum dulcamara*, and *Sanguinaria canadensis* are traditionally used to relieve the pain and inflammation of rheumatic conditions. These three ingredients are combined with *Arnica montana* and *Sulfur* in the homeopathic complex formulation *Zeel compositum-N*. A multicentre, non blinded, randomised study assessed the therapeutic effectiveness and the tolerability of this remedy, administered by intra-articular injection, in osteoarthritis of the knee (125), compared against the standard conventional therapy based on hyaluronic acid (*Hyalart*). The study lasted 5 weeks and the patients received 2 injections each week of one of the two investigated treatments. The primary outcome variables were subjective sensitivity to pain on leg movements, and the general evaluation of tolerability. The therapeutic effectiveness of the two treatments was found to be equivalent, irrespective of the severity of the disease. Local irritation after injection was noted in 5/57 cases in the *Zeel* group and in 13/57 cases in the *Hyalart* group. Taken together, the data suggest that the homeopathic formulation had similar outcomes and a tendency to be better tolerated. The efficacy of *Zeel compositum* medication (in tablets by oral route) in osteoarthritis of the knee was also tested in an open, prospective, multicentre, reference-controlled cohort study (130). The participating physicians (primarily general practitioners) were separated into two groups, one of which prescribed only *Zeel*, and the other only cyclooxygenase-2 inhibitors *celecoxib* or *rofecoxib*. The groups were initially comparable in terms of severity of symptoms. After four weeks, significant improvement in all symptoms was observed under both treatment regimens. Improvement was somewhat more pronounced in the group receiving cyclooxygenase-2 inhibitors due to the more rapid onset of efficacy of this type of medication. After six weeks of treatment, scores indicated that the homeopathic remedy and the allopathic drugs were equally effective.

Another study investigated the relative efficacy of homeopathic remedies (*Rhus toxicodendron*, *Causticum*, and *Lac vaccinum*) in comparison with acetaminophen for the treatment of pain associated with osteoarthritis (126). The study results indicate better pain relief in the homeopathy group (55% achieved relief with homeopathy, compared to 38% with acetaminophen), but not to a statistically significant extent. The investigators conclude that homeopathic treatment of pain in this condition appears to be safe and at least as effective as acetaminophen, but without its potential adverse effects.

Local application of a homeopathic gel containing low dilutions of the remedies *Symphytum officinale*, *Rhus toxicodendron*, and *Ledum palustre* appears to be useful in the treatment of osteoarthritis of the knee (128). A group of out-patients with radiographically confirmed symptomatic osteoarthritis of the knee were enrolled in a pragmatic, randomised, double-blind controlled trial where the homeopathic remedy was compared to a non-steroidal allopathic (piroxicam) gel. Pain reduction was 16.5 mm on a visual-analogue scale in the homeopathy group and 8.1 mm for the piroxicam group, but the difference was not statistically significant.

There was no significant difference between treatment groups for the stiffness index and adverse events. Since double-blind clinical trials involving patients with osteoarthritis of the knee showed the piroxicam topical gel to be significantly more effective than a placebo (138), this equivalence may be considered an indirect proof of the effectiveness of the tested homeopathic remedy.

6. SUMMARY OF THE EVIDENCE

There are several promising studies tending to support a clinically demonstrable activity of homeopathic remedies in inflammatory and infectious disorders, however the body of high-quality homeopathic research within the various fields is small, and “hard” proofs of efficacy, particularly in the high-dilution realm, remains fragmentary. Few well-designed studies have been reproduced by independent research teams for two main reasons: lack of sufficient funding, and a shortage of well-trained homeopaths who are qualified and interested in research. Though the number of papers published in peer-reviewed papers is increasing, many clinical studies are still characterised by low standards of methodology--a problem which is, however, equally common in the conventional medical literature (23). The major quality problems of most trials concern the description of allocation concealment, imprecise outcomes and the reporting of dropouts and withdrawals.

When considering complementary and complex interventions such as acupuncture or homeopathy, there is no consensus as to the quality criteria for classifying the clinical data on the basis of treatment outcomes, scientific strength and reliability (139, 140). On evaluating the evidence in favour of and against the clinical effectiveness of homeopathy, it should be pointed out that the placebo question is important, but not equivalent to the question of whether the homeopathic approach is clinically effective. In classical, individualised homeopathy, the evaluation parameters are based upon specific rules that involve considering the totality of a patient's symptoms, including the disease symptoms and ongoing follow-ups that often require careful evaluation of the response by the clinician. Patients with the same disease receive different prescriptions, and often the prescription changes during the course of the treatment, especially in chronic cases. This methodological aspect, related to the context of the treatment (e.g.: patient-physician interactions), seriously calls into question the use of double blinding for testing homeopathy, since such a protocol would by definition disrupt the aforesaid interactions and possibly affect the global efficacy of the treatment.

There exists in fact a hierarchy of methods, which produce progressively better and hence more rigorous evidence-based medicine that can inform clinical decisions. At the base of this hierarchy are case studies, and retrospective and prospective case series, followed by cohort studies with historical and concomitant non-randomised controls. At the top we find the randomised clinical trials (where double blinding is still a matter of controversy). It has been shown that the hierarchical model

is valid for limited questions of efficacy, for instance for regulatory purposes and newly developed products and pharmacological preparations, but inadequate for evaluating complex interventions such as physiotherapy, surgery and complementary medicine (141). This has to do with the essential tension between internal validity (rigour and the removal of bias) and external validity (generalisability). A more suitable evaluation method would be to incorporate a multiplicity of approaches, using different trial designs, and counterbalancing their individual strengths and weaknesses to obtain pragmatic but equally rigorous evidence that might significantly benefit clinical and health systems innovation. In such a scenario, one way to accumulate evidence in favour of or against the clinical usefulness of homeopathy would be to employ controlled equivalence studies, comparing homeopathy (or specific homeopathic remedies and formulations) with conventional treatments in the “real world” of care settings. Discovering that the two approaches are equi-effective would be particularly important for the fields considered in the present review, in which definitive and satisfying therapies are often lacking. For example, it is still a subject of debate whether anti-inflammatory drugs and antibiotics are effective in the treatment of upper respiratory tract infections, also because they are known to have considerable side effects. In contrast, homeopathy is reported to have no toxicity and, according to some reports, comparable effectiveness.

Clearly, the few dozen papers reported in this review are so highly heterogeneous, in terms of the investigated disease conditions, the tested drugs, and their experimental designs, that any meta-analysis is precluded (with a few exceptions that have been mentioned). It is only possible to make a semi-quantitative evaluation, where multiple studies on the same homeopathic approach for the same group of conditions are available. As stated by the presentation of the Clinical Evidence systematic reviews (www.clinicalevidence.bmj.com), dividing treatments into categories and fitting interventions into these categories is never easy since categorisation always involves a degree of subjective judgement and is sometimes controversial. This is even more arbitrary when complex interventions as those of homeopathic care are compared (141). However, grouping treatments in a scale of different clinical evidence may be useful when taken as a tentative summary, instead as a definite conclusion or as a recommendation for use. So, here the clinical evidence of the major groups of conditions/treatments was classified in table 4 according to the criteria of study design, type of publication and outcomes, as previously outlined (18), with some updating and modification. Briefly, *Strong positive evidence* (Row A) is obtained from significant evidence of a clear benefit from >2 properly randomized trials, or from one properly conducted meta-analysis on homogeneous trials; *good positive evidence* (Row B) is obtained from statistically significant evidence of benefit from 1-2 properly randomized trials, or evidence of benefit from at least 1 randomized trial plus > 1 observational cohort/case-

control/non-randomized trials; *unclear or conflicting evidence* (Row C) is obtained from conflicting evidence from multiple trials or observational studies without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness; *negative scientific evidence* (Row D) is obtained from statistically significant negative evidence (i.e., lack of evidence of benefit) from 1 or more randomized trials or >1 non-randomized trials. The conditions where a global evaluation of efficacy is impossible due to the presence of single reports or lack of adequate available data are excluded from the summary of Table 4.

The best evidence of effectiveness appears in the top two rows of table 4 and is related to *Galphimia glauca* in allergic oculorhinitis, classical individualized homeopathy in otitis, allergic complaints, and fibromyalgia, *Anas barbariae* (*Oscillococcinum*) for influenza-like syndromes, *Euphorbium compositum* in rhinitis-sinusitis, *Zeel compositum-n* in osteoarthritis. The positive conclusion regarding *Galphimia glauca* is mitigated by the fact that all the studies are from the same group and independent replications should be helpful. *Anas barbariae* is included in “good” instead of “strong” evidence because it presents three randomized trials showing a statistically significant effect, but according to the Cochrane meta-analysis (66) the effect was quantitatively small. Meanwhile, individualized homeopathy in allergic rhinitis and asthma is classified as having a “good” evidence of effectiveness, because there are several papers in favour and only one against, but if we consider that two randomized trials were published in non-peer reviewed literature, the overall balance of evidence should be considered more uncertain. Regarding the treatment of fibromyalgia, although most trials showed positive evidence in favour of homeopathy, some caveat are necessary, as suggested by recent reviews which judged the evidence as partially positive (142) or still insufficient, because the small number of positive studies lack replication (143). In grade C (*unclear or conflicting evidence*) we find other homeopathic therapies of several different conditions, where promising results reported by some authors were not replicated by others. This is particularly evident for homeopathic immunotherapy. The evidence for individualized homeopathy for upper respiratory tract infections is defined as conflicting but if we exclude from consideration the trials of de Lange and coworkers (38) (trend to positive effect, but not statistically significant) and of Steinsbekk (51) (where the self-treatment was investigated), a “good” positive evidence in favour of homeopathy can be suggested in these conditions.

7. PROSPECTS

Though complementary medicine and homeopathy are playing an increasingly prominent role in health care practices, there is a scarcity of controlled studies investigating their effectiveness. More and larger studies are thus urgently needed to properly assess the role of homeopathy in managing immunological disorders and abnormal susceptibility to infections. Yet experts (141,

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Table 4. Levels of evidence in the homeopathic studies. In **bold** the references published in peer-reviewed, indexed, scientific medical journals are reported. For the used criteria of evidence and further considerations see the text.

Level of evidence	Infections of upper respiratory tract and otorhinolaryngologic ailments	Allergy and asthma	Osteoarthritis and arthrorheumatic diseases
A <i>Strong positive evidence</i>		<i>GALPHIMIA GLAUCA</i> (LOW HOMEOPATHIC DILUTIONS) IN ALLERGIC OCULORHINITIS <u>Positive evidence:</u> Wiesenauer and Gaus 1985*** (74) Wiesenauer and Ludtke 1987*** (75) Wiesenauer and Ludtke 1995*** (81) Wiesenauer and Ludtke 1996*** (105) Ludtke and Wiesenauer 1997,*** (106) Linde, Clausius et al. 1997*** (107)	
B <i>Good positive evidence</i>	INDIVIDUALIZED HOMEOPATHY IN OTITIS <u>Positive evidence:</u> Friese, Kruse et al. 1996** (39, 63) Kruse 1998* (40) Frei and Thurneysen 2001* (44) Riley, Fischer et al. 2001** (45) Jacobs, Springer et al. 2001*** (46) Haidvogel, Riley et al. 2007** (56) <i>ANAS BARBARIAE</i> 200K IN THERAPY OF INFLUENZA LIKE-SYNDROMES <u>Positive evidence:</u> Casanova and Gerard 1988*** (30) Papp, Schuback et al. 1998*** (42) Ferley, Zmirou et al. 1989*** (33) <u>Little effect:</u> Vickers and Smith 2009 (review)*** (66) <i>EUPHORBIVM COMPOSITUM</i> IN RHINITIS-SYNUISITIS <u>Positive evidence:</u> Sprenger 1989* (31) Connert and Maiwald 1991* (35) Weiser and Clasen 1994*** (36) Ammerschlagel, Klein et al. 2005** (49)	INDIVIDUALIZED HOMEOPATHY IN ALLERGIC RHINITIS AND ASTHMA: <u>Positive evidence:</u> Mosquera Pardo 1990* (76) Castellsagu 1992* (79) Eizayaga and Eizayaga 1996* (85) Lara-Marquez, Pocino et al. 1997*** (86) Riveron-Garrote et al. 1998*** (88) Witt, Keil et al. 2005** (various allergies) (99) Colin 2006* (100) Goossens, Laekeman et al. 2009** (101) <u>No evidence:</u> White, Slade et al. 2003 (adjunctive care)*** (96)	INDIVIDUALIZED HOMEOPATHY IN FIBROMYALGIA <u>Positive evidence:</u> Fisher, Greenwood et al. 1989*** (122) Bell, Lewis et al. 2004*** (132) Relton, Smith et al. 2009** (adjunctive care) (133) Baranowsky et al. 2009** (review) (142) <u>Positive but insufficient evidence:</u> Perry et al. 2010*** (review) (143) <i>ZEEL COMPOSITUM-N</i> IN OSTEOARTHRITIS <u>Positive evidence:</u> Nahler, Metelmann et al. 1996*** (125) Birnesser, Klein et al. 2003** (130) Birnesser and Stolt 2007** (review) (144)
C <i>Unclear or conflicting evidence</i>	INDIVIDUALIZED HOMEOPATHY IN UPPER RESPIRATORY TRACT INFECTIONS <u>Positive evidence:</u> Riley, Fischer et al. 2001** (45) Steinsbekk, Fonnebo et al. 2005*** (50) Trichard, Chaufferin et al. 2005** (52) Haidvogel, Riley et al. 2007** (56) Witt, Ludtke et al. 2009c* (60) Ramchandani 2010* (61) <u>Little evidence:</u> de Lange de Klerk 1994*** (Adjunctive care) <u>No evidence:</u> Steinsbekk, Bentzen et al. 2005*** (self-treatment) (51, 55) <i>ENGYSTOL-N</i> IN COMMON COLD AND FLU <u>Positive evidence:</u> Heilmann 1994*** (no statistical evidence) (37) Schmiedel and Klein 2006* (54)	HOMEOPATHIC IMMUNOTHERAPY OF ALLERGIC RHINITIS AND ASTHMA <u>Positive evidence:</u> Hardy 1984*** (73) Reilly, Taylor et al. 1986*** (22) Nolleveaux 1992* Reilly, Taylor et al. 1994*** (78) Taylor, Reilly et al. 2000*** (91) Aabel, Laerum et al. 2000*** (minor evidence) (92) Kim, Riedlinger et al. 2005*** (98) <u>No evidence:</u> Aabel 2000*** (93) Aabel 2001*** (94) Hyland and Lewith 2002*** (oscillatory kinetics of symptoms in verum group) (95, 113) Li, Bush et al. 2003* (97)	INDIVIDUALIZED HOMEOPATHY IN RHEUMATOID ARTHRITIS <u>Positive evidence:</u> Gibson, Gibson et al. 1978** (118) Gibson, Gibson et al. 1980*** (119) <u>No evidence:</u> Andrade, Ferraz et al. 1991*** (123) Fisher and Scott 2001*** (129)
D <i>Negative scientific evidence</i>	HOMEOPATHIC COMPLEX <i>LUFFA+CINNABARIS+KALIUM BICHROMICUM</i> <u>No evidence:</u> Wiesenauer, Gaus et al. 1989*** (32)		<i>ARNICA, RHUS TOX, BRYONIA 6C</i> IN FIBROMYALGIA <u>No evidence:</u> Fisher 1986*** (121) <i>RHUS TOXICODENDRON 6X</i> IN OSTEOARTHRITIS <u>No evidence:</u> Shipley, Berry et al. 1983*** (120) <i>FORMICA RUFA 6X</i> IN ANKYLOSING SPONDYLITIS <u>No evidence:</u> Schirmer, Fritz et al. 2000*** (127)

* Non-randomised, non-controlled studies; ** non-randomised, controlled studies; *** randomised, controlled studies.

145, 146) suggest that, alongside randomised trials, there is also a need for observational data documenting the different methods of homeopathic prescribing and how patients respond. Further studies could assess how well individuals respond to a "package of care" (i.e. the effects of medication coupled with a consultation, which is considered a vital part of individualised homeopathic practice) rather than just to the homeopathic medicine versus a placebo.

What emerges from this overview is an efficacy/effectiveness paradox (similar to that found in several other areas of complementary medicine research), with weak evidence in favour of homeopathy when studies are done in randomised and double-blind conditions, yet documented effectiveness in equivalence studies comparing homeopathy and conventional medicine, and documented usefulness in general practice through observational studies: the therapy is useful when applied in open practice and produces substantive effects, even in patients with chronic diseases. Most of the studies reviewed here suggest that homeopathic remedies in high dilutions, prescribed by trained professionals, are safe and unlikely to provoke severe adverse reactions. This leads us to conclude that, even though most decisions about treatments still rest on the individual judgements of clinicians and patients, additional clinical research, both experimental and observational, including studies using different designs, is necessary for further developing the base of evidence for homeopathy. It would also be interesting to compare the effectiveness of different forms of homeopathy for the same condition, however the small sizes of the studied populations, and the differences between them, have thus far not permitted any reliable quantitative evaluation.

There is sharp controversy concerning the "plausibility" of homeopathy (23, 147-153). Though we do not have space here to discuss the purported mechanisms of homeopathic effects, it is worth mentioning that also basic *in vitro* experimental studies provide evidence that the effects of homeopathy differ from placebo. Some homeopathic medicines showed direct effects on the immune system cells (18), or exerted antiviral action (154-156), and homeopathic doses of cytokines have been able to resolve conditions of bronchial hyper-responsiveness in mice, establishing normal cytokine levels (157). A large body of laboratory evidence demonstrates that highly diluted/dynamized histamine – a substance mediator of inflammatory processes – has significant inhibitory effects *in vitro* on basophil granulocytes of the blood (158-161), which are key regulatory cells of inflammation and immunity (162, 163).

As also suggested in the presentation of the Clinical Evidence reviews (www.clinicalevidence.bmj.com), after collecting the evidence from a particular field of medicine, to make recommendations is never appropriate because it is difficult or impossible to give advice that is right and proper in every situation. Another challenge is that much of the evidence most relevant to clinical decisions relates to

comparisons between different interventions rather than to comparison with placebo or no intervention. Differences in individual patients' risks and preferences, and in the local availability of interventions, implies that evidence should be individually interpreted, rather than applied across the board. That said, since the homeopathic remedies are safe and in the light of the clinical findings, their use could be regarded as a possible option in the fields reviewed in this work – particularly in the infections of upper airways, otitis, allergic rhinitis and asthma, and some osteo-rheumatologic complaints – provided that the homeopathic methodology of diagnosis and prescription is correct and is integrated with other possible effective treatments, in the care of the whole person. The homeopathic community has a large task ahead.

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Abbreviations: HIT: homeopathic immunotherapy, c: centesimal homeopathic dilution/dynamization (e.g.: 30c), x: decimal homeopathic dilution/dynamization (e.g. 4x), LM: 1:50,000 homeopathic dilution/dynamization.

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