

Lecture Series

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

The evidence-based research of the effectiveness of homeopathic medicines in common immunologic disorders is reviewed. In part 1, we introduce methodological issues of clinical research in homeopathy, and criteria utilized to evaluate the literature. Then 24 studies (12 randomized and 12 non-randomized) on common upper respiratory tract infections and otorhinolaryngologic complaints are described. In part 2, the focus will be on allergic diseases and the effectiveness of homeopathy will be globally evaluated and discussed using the criteria of evidence-based medicine.

Keywords: evidence-based homeopathy – homeopathy – homeopathic medications – immunology – otitis – sinusitis – stomatitis – upper respiratory tract infections

Introduction

Homeopathic research has developed over the past 20 years with the increasingly greater use of modern medical methods (clinical trials, observational studies, statistical evaluations, computerized storage programs and instrumental or laboratory testing). Over 200 clinical trials designed to verify the efficacy of homeopathic treatments have been published, many (but not all) of which have led to positive results. As in other medical disciplines, statistically significant results could be reached by pooling all of the methodologically reliable studies in a given area, but with homeopathy this occurred very rarely, because few series have been conducted for single conditions and because the experimental approaches or the medicines used are too heterogeneous to be able to conclude that any one protocol is efficacious. Some of these series document clinically useful effects and differences against placebo (1–5) and some series do not (6), or their evidence is ‘promising’ but insufficient for drawing conclusions (7,8).

Recent controversies on the question of whether homeopathy is a placebo response (9–13) have shown that an approved answer to this dilemma is at present not possible, because evaluation of the evidence and the inclusion or exclusion of papers from meta-analyses vary according to pre-selected

criteria, that differ in different reviews, a sort of ‘bias’ of the observer (14,15). Moreover, there is a noteworthy confusion concerning what type of ‘homeopathy’ is evaluated (e.g. use of low or high potencies) and when homeopathy is accused for its lack of ‘plausibility’ (9,16,17), the different modalities are not suitably distinguished.

The aim of this lecture series is not to provide a meta-analysis of homeopathic literature, neither to focus on the placebo question, themes that have been addressed with variable results by others (1,9,16,18–26), but to provide an overview of the best of available homeopathic literature in the fields of immunoallergology and common inflammatory diseases. As we have seen in the introductory lecture (27), immunoallergology represents a bridge between homeopathy and modern medicine insofar as it is a field in which it is easier to apply concepts such as the effect of substances administered on the basis of the logic of the ‘similar’ and the great sensitivity of living systems to modulations induced by ultramicrodoses of natural or endogenous substances. In this field, there is a body of pre-clinical research suggesting that homeopathic remedies may regulate the immune system at cellular and/or systemic levels (28–30). There are also preliminary *ex vivo* observations of significant changes of immune cells (CD4 lymphocytes) in people treated with high potencies of homeopathic medicines (31) and, broadly speaking, it has been suggested that T cells can be the target of

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immunoregulation by a range of complementary and alternative medicines (32).

Patients with diseases of the immune system like allergies and asthma, or with enhanced susceptibility to recurrent infections, or with rheumatological diseases often have recourse to homeopathy as 'alternative' medicine (33,33–41). Unfortunately, there is paucity of evidence-based recommendations using homeopathic remedies in these conditions.

Evidence-based medicine will have increasing impact also in the field of complementary and alternative medicine, but the systematic evaluation of research evidence in homeopathy is an expectation that requires suitable methods of evaluation (42,43). In this new and controversial field, stringency of tools utilized to systematically evaluate the scientific literature should always be accompanied by a consensus concerning clinical protocols that significantly reflect modalities of cure, types of follow-up and relevance of outcomes, which can be different from those of conventional medicine. Otherwise the results, instead of helping the judicious use of evidence in making clinical decisions, become only the source of new controversy, especially when disseminated by the media, as was in the recent *Lancet's* meta-analysis that was inappropriately boosted by the editorial title 'The end of homeopathy'(44).

Here, we have distinguished publications in two major groups, each of which holds a rationale for deployment of homeopathic remedies. A first group (described in this part of the review) includes pathologies consisting of anomalous susceptibility to infections that may be, at least in part, due to inadequacy of efficiency of the immune system in the rejection of an extraneous aggressor. The second group (described in a subsequent part of the review), includes pathologies due to hypersensitivity of the immune system, the most widespread of which is immediate hypersensitivity, or allergy, and its major manifestations at the level of respiratory system. For each group of pathologies, the different homeopathic methods utilized, namely (i) classical individualized homeopathy, (ii) isotherapy, (iii) specific medicines for each disease or symptom (pluralist or clinical approach) or (iv) complex formulations (used particularly in homotoxicology) are dealt with in separately. A general discussion of the evidence-based homeopathy in these fields will be reported in the second part of the review.

Analyses

This review reports literature on human subjects available to us from 1978 to 2006. Principal information sources were current reading of major CAM journals during the past 15 years, screening of the monthly publication of complementary medicine index (British Library), of the databases of Central Council for research in Homeopathy and of Hom-inform Information Service, literature searching using Medline, CAM on PubMed, Cochrane Database of Systematic Reviews and CAMbase, cross-referencing. We have also checked the existing systematic reviews and meta-analyses

that cover trials of immunoallergology. The analysis includes controlled clinical trials (with and without randomization), observational studies and case series. All forms of homeopathic intervention are included. That a few published papers, still unknown to us, escaped from our screening, is conceivable; in any case, we have not made any pre-selection, based for example on the quality of studies or on their outcomes (positive versus negative) so that the present review is certainly representative of the 'state of the art' of international literature in the considered fields.

When complementary and complex interventions such as acupuncture or homeopathy are considered, there is no consensus on the quality criteria used to classify the clinical data according to the importance of treatment outcomes, the scientific strength and the reliability (11,45,46). Problems arise especially concerning blinding and concealment, follow-up indexes particularly in chronic cases, healing markers, primary and secondary outcomes, and the validity of experimental versus observational studies. Therefore, to allow a semi-quantitative ranking of homeopathic treatment studies, we have adopted the following two criteria.

First, we have classified the publications according to the type of study, using, with slight modifications, the classification system that has been developed by the National Cancer Institute for human studies of complementary and alternative medicine in cancer studies (<http://www.cancer.gov/cancertopics/pdq/levels-evidence-cam/HealthProfessional/page2>). According to this classification, the score in descending order of strength is reported in Table 1. The main modification with respect to the NCI classification is that we have included the randomized (non-blinded) equivalence studies, comparing two modalities of therapy, in level 1b and the non-randomized equivalence studies in level 2. Those types of studies have increasing importance in CAM literature (47).

A second criterion that may help in 'weighing' each paper is the publication type, which we scored according to a classification where the top papers are those published in mainstream medical literature and the last level is provided by publications in books or conference proceedings (Table 2). Communications reporting single cases or expert opinions were excluded. Although this order may be questionable for a

Table 1. Classification of clinical studies in homeopathy

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

Table 2. Classification of publications in homeopathy according to the type

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

number of reasons (especially as concerns the difference between mainstream and complementary/alternative medicine journals), we believe that it may facilitate the reader in judging the grade of evidence provided by each study.

Infections of Upper Airways and Otorhinolaryngologic Diseases

Homeopathic research in otorhinolaryngology includes studies of acute and chronic rhinitis, otitis media, sinusitis and tonsillitis. Here, the diseases of infectious origin are considered, while the allergic diseases are considered later. Several homeopathic researchers have worked on these diseases, which are frequent in the general population, with often positive results. The unnecessary use of antibiotics in the initial treatment of acute otitis media and URI is currently being questioned. Homeopathy has been used historically to treat this illness, and it is interesting to determine if there are methodologically rigorous trials to support its effectiveness.

We also report a relevant study on post-chemotherapy stomatitis, which is caused both by direct mucosal damage and by infections due to immunodeficiency. We have omitted the trials on influenza both because of limited space and existence of recent systematic reviews covering the topic (26,48). A summary in chronological order is reported in Table 3 and a brief outline of each protocol with the main results of different homeopathic strategies is given as follows.

Classical Individualized Homeopathy

The first report of classical homeopathy is relatively recent, dating in 1997 when Friese *et al.* (59) reported an open study comparing the results obtained treating otitis media in children, treated using two different medical approaches. They compared classical unitary homeopathic remedies (*Aconitum*, *Apis mel.*, *Belladonna*, *Lachesis*, *Pulsatilla*, *Silicea*, *Lycopodium*, *Chamomilla* and *Capsicum*) prescribed after an individual homeopathic case analysis, with conventional therapy based on antibiotics, mucolytics and antipyretics. The duration of pain was 2 days in the homeopathic group and 3 days in the conventional therapy group and the duration of therapy was 4 and 10 days, respectively. The latter difference was statistically significant, but it should be noted that the duration of antibiotic therapy for these conditions cannot be shorter than a week, so this comparison may not reflect the clinical

outcomes. In brief, this pragmatic study comparing homeopathic with conventional therapy showed that results were similar, but with a trend in favor of homeopathy.

In an open, prospective, multicenter study, Kruse (60) evaluated a group of children with otitis media for 6 weeks, controlling results against conventional therapy. The homeopathy group was treated with single remedies like *Aconitum* 30×, *Apis* 6×, *Belladonna* 30×, *Capsicum* 6×, *Chamomilla* 3×, *Lachesis* 12× and other remedies; the reference group was treated with antibiotics, secretolytics, antipyretics and sympathomimetics such as nasal sprays. In the two groups the number of children remaining relapse-free and the average duration of pain were similar.

A Negative Trial and Subsequent Arguments

De Lange de Klerk (62) performed a double-blind, randomized study that 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 treating acute phases. The year-long therapy was continuously adjusted on an individual basis, and data were collected by means of diaries kept by parents and attending physicians. Results showed that homeopathic therapy was slightly but not significantly better than placebo. The paper was criticized by homeopathic expert clinicians (73) and methodologists (15) maintaining that homeopathy in that study required beneficial proof in addition to conventional therapy. If homeopathy was effective, control children would require more antibiotics and tonsillectomy, and this was the case; such surplus of conventional therapies could have created false negative results.

Observations of Benefit

The purpose of the observational study of Frei and Thurneysen (64) was to determine how many children with acute otitis media are relieved of pain with individualized homeopathic treatment. Children with this condition received a first individualized homeopathic medicine in the pediatric office. If pain reduction was not sufficient after 6 h, a second (different) homeopathic medicine was given. After a further 6 h, children who had not reached pain control were started on antibiotics. Pain control was achieved in 39% of the patients after 6 h, another 33% after 12 h. Compared with literature's data, the authors stated that the resolution rate is 2.4 times faster than in untreated cases. The six more frequently prescribed remedies were *Pulsatilla*, *Belladonna*, *sulphur*, *phosphorus*, *calcium carbonicum*, *Lycopodium*.

An interesting multicenter, prospective, observational study in a real world medical setting compared the effectiveness of homeopathy with conventional medicine (65). Thirty investigators with conventional medical licenses at six clinical sites in four countries enrolled a series of patients with at least one of the following three complaints: upper respiratory tract complaints including allergies; lower respiratory tract complaints including allergies; or ear complaints. Four

Table 3. Homeopathic clinical studies on infections of upper airways and ear–nose–throat diseases

| Reference and year | Condition (diagnosis) | Study type | Classification of publication | Study group | Treatment(s) | Outcomes | Key results |
|-------------------------------------|------------------------------------|------------|-------------------------------|--------------|---|--|--|
| Gassinger <i>et al.</i> (1981) (49) | Acute rhinitis | 1b | 1b | 53 | <i>Eupatorium perfoliatum</i> 2× versus aspirin | Symptom severity score | Equivalence between homeopathy and allopathy |
| Lecoq (1985) (50) | Upper respiratory tract infections | 1a | 2 | 60 | Homeopathic complex L52 versus placebo | Symptoms severity score | Patients rated more relief in verum group |
| Bordes and Dorfman (1986) (51) | Cough | 1a | 2 | 60 | Low-dilution (3c) homeopathic complex in syrup (<i>Drosera</i>) versus placebo | Symptoms | Decrease of symptoms 20 out of 30 treated patients, as against only 8 out of 30 in the placebo group |
| Maiwald <i>et al.</i> (1988) (52) | Acute rhinitis | 1b | 1b | 170 | Homeopathic complex <i>Grippheerl</i> versus aspirin | Symptom severity score | Equivalence between homeopathy and allopathy |
| Sprenger (1989) (53) | Acute and chronic rhinitis | 3 | 2 | 65 | Low-dilution homeopathic complex formulation <i>Euphorbium compositum</i> , nasal spray | The physician's judgment of the therapy | Positive in 83% of cases (uncontrolled) |
| Wiesnauer <i>et al.</i> (1989) (54) | Sinusitis | 1a | 2 | 152 | Low-dilution (3×–4×) homeopathic complex <i>Luffa</i> , <i>Cinnabaris</i> , <i>Kalium bichromicum</i> versus placebo | Symptoms and global evaluation | No effect over placebo |
| Zenner and Metelmann (1990) (55) | Pharyngitis and tonsillitis | 3 | 2 | 594 | Low-dilution (3×–4×) homeopathic complex <i>Lymphomyosot</i> drops | Global evaluation, semi-quantitative | Improvement in >90% of cases (uncontrolled) |
| Connert and Maiwald (1991) (56) | Rhinitis and nose obstruction | 3 | 2 | 26 | <i>Euphorbium compositum</i> | Symptoms, rhinomanometry | Decrease of symptoms in most patients (uncontrolled) |
| Weiser and Clasen (1994) (57) | Chronic sinusitis | 1a | 2 | 155 | <i>Euphorbium compositum</i> versus placebo | Subjective symptoms and functional tests | 21.1% improvement in the verum group, 14.4% in the placebo group. No change in tests |
| Heilmann (1994) (58) | Common cold and flu | 1a | 2 | 102 | <i>Engystol-N</i> versus placebo, i.v. injection | Frequency and symptoms | No change of frequency of attacks, decrease of symptoms and their duration |
| Frise <i>et al.</i> (1997) (59) | Otitis media | 2 | 1a | 131 children | Individualized versus allopathy | Duration of pain and therapy | Homeopathy slightly better than conventional therapy |
| Kruse (1998) (60) | Otitis media in children | 2 | 3 | 126 | Individualized versus allopathy | Duration of pain and therapy | Equivalent efficacy |
| Wiesnauer (1998) (61) | Acute tonsillitis | 3 | 1b | 107 | 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) |

| | | | | | | | |
|----------------------------------|--|----|----|--------------|---|--|---|
| De Lange de Klerk (1999) (62) | Pharyngitis, tonsillitis | 1a | 1a | 170 children | Individualized versus placebo | Frequency, duration and severity of rhinitis, pharyngitis episodes | Little, non significant, effect in favor of homeopathy versus placebo |
| Adler (1999) (63) | Acute sinusitis | 3 | 1a | 119 | Homeopathic complex | Symptoms | Trend to positive (uncontrolled) |
| Frei and Thurneysen (2001) (64) | Acute otitis media | 3 | 1b | 230 children | Individualized | Pain | Improvement in 39% of patients after 6 h, another 33% after 12 h (uncontrolled) |
| Riley et al. (2001) (65) | Respiratory tract complaints or ear complaints | 2 | 1b | 456 | Individualized homeopathy versus allopathy | Healing or a major improvement after 14 days of treatment, adverse effects | Improvement in 82.6% of homeopathic patients, 68% of allopathic |
| Jacobs (2001) (66) | Acute otitis media | 1a | 1a | 75 children | Individualized versus placebo | Treatment failures and symptoms scores | Less failures in verum group, not significant; little and significant decrease of symptoms in verum group |
| Oberbaum et al. (2001) (67) | Chemotherapy-associated stomatitis | 1a | 1a | 32 children | Homeopathic complex <i>Traumeel-S</i> versus placebo. | Stomatitis development and scores | Less stomatitis in verum group |
| Rabe et al. (2004) (68) | Mild upper respiratory tract infections | 2 | 1a | 485 | Homeopathic complex <i>Grippheerl</i> versus NSAIDS | Symptoms | Equivalence between homeopathy and allopathy |
| Ammerschlagel et al. (2005) (69) | Rhinitis and sinusitis | 2 | 1b | 739 | Low-dilution homeopathic complex formulation <i>Euphorbium compositum</i> , nasal spray versus xylometazoline | Symptoms and tolerability | Equivalent efficacy |
| Steinsbekk et al. (2005) (70) | Upper respiratory tract infections | 1b | 1b | 169 children | Individualized versus untreated | Symptoms score | Decrease of days with symptoms in homeopathic group |
| Steinsbekk et al. (2005) (71) | Upper respiratory tract infections | 1a | 1a | 251 children | Individualized, parents-selected, versus placebo | Prevention of new episodes | No effectiveness of homeopathy over placebo |
| Trichard et al. (2005) (72) | Acute rhinopharyngitis | 4 | 1b | 499 children | Homeopathic strategy versus allopathic strategy (e.g. antibiotics) | Number of episodes, quality of life, costs | Various indexes significantly in favor of homeopathic strategy, lower medical costs (uncontrolled) |

hundred and fifty-six patient visits were compared. In any case, homeopathy appeared to be at least as effective as conventional medical care in the treatment of patients with these three conditions.

A randomized double-blind placebo control pilot study was conducted (66) in children with otitis media. Subjects having middle ear effusion and ear pain and/or fever for no more than 36 h entered into the study. They received either an individualized homeopathic medicine or a placebo administered orally three times daily for 5 days, or until symptoms subsided. There were fewer treatment failures in the group receiving homeopathy, but these differences were not statistically significant. Diary scores showed a significant decrease in symptoms after treatment in favor of homeopathy ($P < 0.05$).

Controversial Findings

An equivalence trial was performed by Steinsbekk *et al.* (70), who investigated whether individualized treatment by homeopaths is effective in preventing childhood upper respiratory tract infections (URTI). Children recruited from a group previously diagnosed with URTI, were randomly assigned to receive either homeopathic care or to conventional health care. There was a significant difference in median total symptom score in favor of homeopathic care compared to the control group. On the other hand, negative results were obtained by the same group (71) in a double-blind placebo-controlled randomized trial. Children with recurrent URTI were randomly assigned to receive either placebo or homeopathic medicines in 30c potency, chosen by parents using a simplified constitutional indications for the three medicines most frequently prescribed by Norwegian homeopaths for this group of patients (74). When necessary, patients of both groups were allowed to take conventional medication. There was no difference in the predefined primary outcome between the two groups. This can be due to the lack of effect of the highly diluted homeopathic medicines, to the interference of conventional treatment, or the process of selection of medicines, that was performed by parents.

Cost-Effectiveness

A study to compare effectiveness and costs of two treatment strategies ('homeopathic strategy' versus 'antibiotic strategy') used in routine medical practice by allopathic and homeopathic GPs in the treatment of recurrent acute rhinopharyngitis in children was recently published (72). Data from a large series of patients were analyzed and grouped according to type of drug prescribed, episodes of acute rhinopharyngitis, complications, adverse effects and medical costs. The results showed that the 'homeopathic strategy' yielded significantly better results than the 'antibiotic strategy' in terms of number of episodes of rhinopharyngitis, number of complications and quality of life with lower direct medical costs in favor of homeopathy. Of course, these findings should be confirmed with randomized studies on homogeneous groups of patients.

Fixed Prescription of Low-Potencies

Although people are best treated with an individualized homeopathic remedy chosen by a professional homeopath (75), several trials have found that some common homeopathic remedies or their combinations may be at least as effective as conventional medications.

An early study on the effect of a low-dilution homeopathic medicine on the common cold was done by Gassinger (49). The authors compared the effect of *Eupatorium perfoliatum* 2 \times with that of acetylsalicylic acid. Neither the subjective symptoms, nor body temperature, nor laboratory data showed any significant differences in the two groups, which led the authors to conclude that the homeopathic treatment was as effective as the allopathic treatment. Of course, this is not a direct evidence of the efficacy of homeopathy, mostly because even the effectiveness of analgesic/antipyretic medications in the common cold is uncertain (76).

Wiesener *et al.* (54) compared the effects of three different homeopathic treatments and placebo in patients with acute and chronic sinusitis. In this randomized, double-blind study the patients were divided into four groups: group A: *Luffa operculata* 4 \times + *Kalium bichromicum* 4 \times + *Cinnabaris* 3 \times ; group B: *K. bichromicum* 4 \times + *Cinnabaris* 3 \times ; group C: *Cinnabaris* 3 \times ; and group D: placebo. The study did not reveal any difference in therapeutic effects in the four groups. Their conclusion was that, unless other data emerge from a study of individual homeopathic prescriptions ('repertorization'), the drugs should not be considered active in acute or chronic sinusitis in the general population; they also pointed out that similar negative results have been obtained with antibiotics, nasal decongestants and drainage of the nasal cavities.

Complex Formulations

To cure one or few symptoms, particularly in short-lasting and acute conditions, complex formulations or mixtures of homeopathic remedies are often used. The complex homeopathy was born a little after the original discovery of Hahnemann and it is not fully comparable with homotoxicology which is a specific methodological way to prescribe complex homeopathic drugs. The latter procedure, also called 'Biological medicine', was developed in the second half of twentieth century (77,78), starting from Germany. Although homotoxicology is characterized by methods of diagnosis and prescription very different from Hahnemann's original homeopathy, most of the formulations have their roots in the materia medica of single components and have the recognition of 'homeopathic medicines' by EU drug legislation.

Trials assessing the effectiveness of complex medicines in relieving specific symptoms are easier to be conducted as compared with those that require individualized treatment and continuous adjustment of therapy. Moreover, there is much higher commercial interest to such formulations than to single remedies, which cannot be patented. These reasons explain why there are relatively more studies of complex formulations than of single homeopathic remedies.

The primary objective of treating of inflammatory diseases of upper respiratory tract (rhinitis, uncomplicated sinusitis) is to relieve obstruction and to improve associated symptoms. In this respect, a homeopathic remedy may be seen much like a local decongestant helping restoration of unrestricted respiration and drainage of nasal sinuses, factors that reduce the risk of further complications and of chronicity. However, many homeopathic formulations contain remedies that are expected to act as immunostimulators and/or according to isopathic principles of cure.

A homeopathic remedy, *L52*, a complex formulation containing *E. perfoliatum* 3×, *Aconitum napellus* 4×, *Bryonia alba* 3×, *Arnica montana* 4×, *Gelsemium sempervirens* 6×, *Cinchona* 4×, *Belladonna* 4×, *Drosera* 3×, *Senega* 3× showed promising results, in a double-blind study against placebo, for relief of symptoms of URTI (50), but not in prevention of flu in a large double-blind, placebo-controlled study (~1200 participants) (79).

In a single-blind randomized trial, army soldiers suffering from common cold were treated with aspirin or with a complex homeopathic preparation called *Grippheel* (*Aconitum* 4×, *Bryonia* 4×, *Lachesis* 12×, *E. perfoliatum* 3×, *phosphorus* 5×) (52). Comparison between the changes in clinical status and in subjective disorders on days 4 and 10 and between the duration of the periods off work in two groups revealed no significant differences, leading to the conclusion that the two drugs are equieffective. More recently, the same medicine has been evaluated in a prospective, observational cohort study in patients affected by mild viral infections of upper respiratory tract (68) with encouraging results, consisting of an equivalent effectiveness of homeopathy and conventional medications.

In the field of respiratory diseases, mention must be made of a study by some French researchers (51) who treated dry cough with a syrup based on the plant *Drosera* and another nine substances in 3c dilution, and found that it was much better than placebo: after 1 week of therapy, the symptom had become less severe or had disappeared in 20 out of 30 treated patients, as against only 8 out of 30 in placebo group.

Euphorbium

Sprenger (53) conducted 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 *Euphorbium resinifera* 4×, *Pulsatilla pratensis* 2×, *L. operculata* 2×, *Mercurius iodatus ruber* 6×, *Mucosa nasalis suis* 6×, *Hepar sulphuris calcareum* 10×, *Argentum nitricum* 10× and *Sinusitis nosode* 13×, and was administered at a dose of 1–2 puffs per nostril 3–5 times a day. The physician's judgment of the therapy was good in 83% of cases, whereas tolerability was excellent in 55.4% of cases and good in 44.6%. Another observational, uncontrolled study on patients suffering from chronic rhinopathy associated with a previous long-term application of medication (abuse of nasal spray) showed positive results in 22 out of 26 patients, with normalization of rhinomanometric tests (56).

Subsequently, Weiser and Clasen (57) studied the clinical effectiveness of the same complex *E. compositum* in a double-blind, randomized, placebo-controlled study in subjects with chronic sinusitis. The treated group showed a significant improvement in terms of subjective symptoms such as respiratory obstruction, sensation of internal pressure and pain, but there was no substantial variation in instrumental tests. An overall evaluation showed a better improvement in verum group as in placebo group.

A further open, multicenter, prospective, active-controlled cohort study was carried out more recently on the homeopathic complex *E. compositum* (nasal drops), whose effectiveness and tolerability was compared with the reference allopathic drug xylometazoline (69). Clinically relevant reductions in intensities of disease-specific symptoms were observed with both groups. Non-inferiority of the homeopathic complex remedy to xylometazoline could be shown for all studied variables. Tolerability was good for both therapies. Interestingly, it has been reported that some components of this medicine, e.g. *Euphorbium* and *Pulsatilla*, but not *Luffa*, as plant extract (not homeopathic preparations), have a direct antiviral (respiratory syncytial virus and herpes simplex virus type 1) effect *in vitro* (80).

Other Low-Dilution Complexes

Zenner and Metelmann (55) published the results of an open study of a complex preparation, *Lymphomyosot* drops (*Myosotis arvensis* 3×, *Veronica officinalis* 3×, *Teucrium scorodonia* 3×, *Pinus sylvestris* 4×, and even other 13 plant or mineral components) in treatment of pharyngitis and tonsillitis. In a group of patients with tonsillitis, most of them recorded 'excellent, good or satisfactory' improvements after treatments lasting between 1 and 6 months.

A different complex that has been used in this kind of respiratory complaints is *Engystol-N* (made of *Vincetoxicum* 6×, 10× and 30×, *sulfur* 4× and 10×). A randomized, double-blind, placebo-controlled trial assessed the efficacy of this formulation, administered twice weekly as intravenous injection, for prophylaxis of common cold and flu (58). The frequency of occurrence of flu or common cold was not changed by treatments, but the average length of illness and the severity of symptoms were less for the verum group than for the placebo group. No statistical analysis of data was provided.

The efficacy of three plants used in homeopathy to treat acute tonsillitis was evaluated with an open trial (61). A fixed combination of low dilutions of three plant substances (*Phytolacca americana*, *Guajacum officinale* and *Capsicum annuum*) was used in patients with this condition and no antibiotics were used. According to materia medica, this homeopathic complex remedy should be characterized by immunomodulatory, analgesic and anti-inflammatory properties. A decrease in objective and subjective symptoms of acute tonsillitis symptoms was observed after treatment startup; no serious adverse effects were reported.

The efficacy and safety of a fixed combination homeopathic medication (*Sinusitis PMD*) consisting of *Lobaria pulmonaria*, *L. operculata* and *potassium dichromate* were investigated in an open-label practice-based study of patients with acute sinusitis (63). Most patients received only test medication and no antibiotics. After 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 treatment, most patients described themselves as symptom-free or significantly improved. Adverse drug effects were not reported.

A Remedy for Stomatitis

An Israeli team (67) assessed a complex homeopathic preparation (*Traumeel-S*, containing 4×–12× potencies of *A. montana* and other plant extracts and minerals) for its effect in chemotherapy-associated stomatitis, a common consequence of chemotherapy and a condition for which there is little effective treatment. The study was conducted in children and young adults who had undergone stem cell transplantation, in a randomized, placebo-controlled, double-blind clinical trial. The medicine was administered as a mouth rinse, five times daily. Thirty-three percent of patients in active treatment group did not develop stomatitis, compared with only 7% in placebo group. Stomatitis worsened in 47% of patients in active treatment group compared with 93% in placebo group. The stomatitis scores were better in verum group ($P < 0.01$). It is worth noting that, at variance with respect to most homeopathic medicines, the efficacy and the action mechanisms of *Traumeel* were repeatedly characterized also in pre-clinical studies, as described in previous reviews of this series (28,29).

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