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ORIGINAL ARTICLE

Homeopathy for Allergic Rhinitis: A Systematic Review

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Abstract

Objective: The aim of this study was to evaluate the efficacy and effectiveness of homeopathic intervention in the treatment of seasonal or perennial allergic rhinitis (AR).

Method: Randomized controlled trials evaluating all forms of homeopathic treatment for AR were included in a systematic review (SR) of studies published up to and including December 2015. Two authors independently screened potential studies, extracted data, and assessed risk of bias. Primary outcomes included symptom improvement and total quality-of-life score. Treatment effect size was quantified as mean difference (continuous data), or by risk ratio (RR) and odds ratio (dichotomous data), with 95% confidence intervals (CI). Meta-analysis was performed after assessing heterogeneity and risk of bias.

Results: Eleven studies were eligible for SR. All trials were placebo-controlled except one. Six trials used the treatment approach known as isopathy, but they were unsuitable for meta-analysis due to problems of heterogeneity and data extraction. The overall standard of methods and reporting was poor: 8/11 trials were assessed as ''high risk of bias''; only one trial, on isopathy for seasonal AR, possessed reliable evidence. Three trials of variable quality (all using *Galphimia glauca* for seasonal AR) were included in the meta-analysis: nasal symptom relief at 2 and 4 weeks (RR = 1.48 [95% CI 1.24–1.77] and 1.27 [95% CI 1.10–1.46], respectively) favored homeopathy compared with placebo; ocular symptom relief at 2 and 4 weeks also favored homeopathy (RR = 1.55 [95% CI 1.33–1.80] and 1.37 [95% CI 1.21–1.56], respectively). The single trial with reliable evidence had a small positive treatment effect without statistical significance. A homeopathic and a conventional nasal spray produced equivalent improvements in nasal and ocular symptoms.

Conclusions: The low or uncertain overall quality of the evidence warrants caution in drawing firm conclusions about intervention effects. Use of either *Galphimia glauca* or a homeopathic nasal spray may have small beneficial effects on the nasal and ocular symptoms of AR. The efficacy of isopathic treatment of AR is unclear.

Keywords: homeopathy, homeopathic, allergic, allergy, rhinitis, hay fever, pollinosis, rhinorrhea, hypersensitivity

Introduction

Homeopathy

HOMEOPATHY IS DEFINED as ''a therapeutic method using preparations of substances whose effects, when administered to healthy subjects, correspond to the manifestations of the disorder (symptoms, clinical signs, pathological states) in the individual patient.''[1] There are three fundamental principles of homeopathy: (1) like treats like, (2) use of the minimal dose, and (3) individualization.[2] Hahnemann described the process of identifying the therapeutic effects of a substance by administering dilutions of it to healthy volunteers (''provers''). These symptom lists served as the indications for prescribing homeopathic medicines to patients with the corresponding pathological symptoms. For example, if a substance caused a fever in a healthy person, then it might

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be used homeopathically with the aim of curing a patient suffering from fever of a similar nature. The therapeutic repertoire of such medicines is called the homeopathic *materia medica*.

There remains considerable debate about the plausibility of homeopathic therapeutic effectiveness, particularly due to the concept of potentization, where repeated serial dilution and succussion of medicinal substances is expected to enhance their therapeutic power. The most contentious of this concept is that dilutions are often beyond Avogadro's constant (6.022×10^{23}/mol),[3] where the likelihood of a single molecule of the original substance being present in the remedy approaches zero. The ''12C'' potency of a homeopathic medicine is approximately equivalent to Avogadro's constant, which means it is likely that there are no ''active'' molecules in the higher dilutions.[1] (''C'' stands for ''centesimal'' system of potentization: ''1C'' is prepared by diluting one part of the homeopathic drug with 99 parts of the solvent.) As a result, the therapeutic effect is considered by some to be the placebo effect of the lengthy and empathetic consultation process.[4,5] It has been hypothesized, however, that the Avogadro limit is unable to account for the floating silica fragments and, possibly, original particulate matter in the water that arise during the process of making homeopathic medicines.[6] Several lines of laboratory evidence are now emerging to suggest that homeopathic high dilutions could have biological effects. Three major models for how this happens are currently being investigated: water clusters or clathrates; coherent domains postulated by quantum electrodynamics; and the formation of nanoparticles from the original solute.[7] None of the potential explanations is widely accepted by scientists.

Types of homeopathy

The different types of homeopathy being practiced have been broadly classified by Linde et al. and Shang et al.[8,9] into individualized, clinical and complex homeopathy, and isopathy:

- *Individualized (classical) homeopathy*: When a single homeopathic remedy is selected based on the total symptom picture of a patient.
- *Clinical homeopathy*: When one or several single remedies are administered for standard clinical situations or conventional diagnoses.
- *Complex homeopathy*: When multiple remedies are mixed into a standard formula to treat a person's multiple symptoms and diagnoses.
- *Isopathy*: When serial agitated dilutions are made from the causative agent in an infectious or toxicological condition.

Allergic rhinitis

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated immunological response of the nasal mucosa to airborne allergens such as pollens, dust, or animal dander. Inhalation of allergens in individuals with a sensitized immune system produces degranulation of mast cells with the release of chemical mediators. These mediators are responsible for the symptoms of AR. AR is clinically defined by the presence of rhinorrhea, nasal obstruction, nasal itching, and sneezing, which are reversible spontaneously or with treatment.[10] Rhinitis affects quality of life, performance, and attendance at school[11] and at work.[12] It has significant impact on healthcare costs.[13] Allergies are responsible for an estimated annual expenditure of £1 billion in the National Health Service in the United Kingdom.[14] Conventional treatment includes oral or topical antihistamines, intranasal or systemic corticosteroids, and allergen immunotherapy.[15]

AR is also a global health problem, affecting 500 million patients worldwide.[15] AR can be broadly classified into seasonal and perennial. AR has been found to cause significant impairment of psychological well-being and is perceived to impair cognitive functioning.[16] The prevalence of AR was found to be 23% in Western Europe, with a low rate of diagnosis.[17] AR prevalence is also high in developing nations: rhino-conjunctivitis was 15.3% among 11- to 15-year-old schoolchildren in northern Africa.[10] In addition, there is evidence to support a link between AR and asthma,[18] and these two conditions often coexist in patients.[12,19]

AR and homeopathy

The 2010 Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines[15] recommend the use of antihistamines, intranasal or sublingual allergen-specific immunotherapy, and similar interventions in adults and children with AR, with or without concomitant asthma. The guidelines also recommend that AR patients should not be given homeopathic treatment. Antihistamines are able to cross the blood–brain barrier and adversely impact working memory and vigilance, causing sedation.[20] Sublingual immunotherapeutic agents frequently (in approximately 30% of cases) cause local adverse effects.[15]

However, complementary and alternative medicines (CAM) is being used extensively in the treatment of AR.[21] Some of the reasons for patients turning toward CAM include the distrust of conventional medicine, lack of a satisfactory interaction between patient and physician, and the belief that CAM is devoid of adverse effects.[22]

Evidence for recommending homeopathy for AR appears to be lacking. This systematic review and meta-analysis attempted to examine the veracity of this clinical intervention. The recurrent nature of this condition and consequent frustration for the patient may have contributed to homeopathy (and other CAM) manufacturers marketing large numbers of products with claims of symptom reduction and prevention of recurrence. These are often preparations containing a mixture of common homeopathic remedies indicated for symptoms of AR in the homeopathic *materia medica*. The efficacy of these homeopathic medicines, individually or in combination, has rarely undergone any form of objective testing. Non-pharmaceutical CAM interventions have also gained in popularity, with little or no evidence base.

Several trials have evaluated the effectiveness of homeopathy for AR. Results from these trials are mixed. Collectively, the results of these trials have been noted to be positive.[23] Two systematic reviews involving a single homeopathic remedy (*Galphimia glauca*) for treating AR have been published.[24,25] Findings of both reviews suggest efficacy. Wiesenauer[25] found that the overall rate of improved eye symptoms was 1.25 times (95% confidence interval [CI]

1.09–1.43) higher in the intervention group, and the intervention success rate was 79.3% (95% CI 74.1–85.0%). Some of the drawbacks of Wiesenauer[25] were that the analysis included retrospective studies and that one of the authors was also an author in four of the primary studies. In Ernst,[24] three out of four included studies reported significant results in favor of the intervention. However, it also included the same sole homeopathic medicine, *Galphimia glauca*. Two important drawbacks identified in this review are that, of the included trials, neither used validated outcome measures or intention-to-treat analyses. Passalacqua et al.[26] conducted a systematic review on CAM for rhinitis and asthma, concluding that the evidence for a specific effect of homeopathy is weak. Bellavite et al.[27] conducted a descriptive review of clinical research on advances in homeopathy and immunology. They included AR but did not perform any meta-analysis. That review identified several studies where the intervention group showed better clinical improvement than the placebo group did. No systematic review evaluating all researched homeopathic treatments for AR has been published.

Objective of the review

The primary objective of this systematic review was to determine efficacy and effectiveness of relevant homeopathic products in the treatment of AR. The secondary aim was to compare the effectiveness of different forms of homeopathy on AR. The review therefore includes studies that compared a homeopathic intervention with a placebo, compared homeopathic treatment with conventional treatment for AR, and examined the effectiveness of different homeopathic medicines (at same or different dilutions). Studies that compared one form of homeopathy to another were also eligible for the review.

Methods

The methods have been clearly stated in the previously published protocol.[28] A prospective protocol was first published in PROSPERO (CRD42013006741).

Criteria for considering studies for this review

A detailed description of the criteria for considering studies for this review has been published in the protocol.[28] Some details are provided below.

Types of studies. Randomized and controlled trials comparing homeopathy (individualized, clinical, isopathic, or complex) with placebo, conventional treatment, or other homeopathy for the treatment of seasonal or perennial AR in patients of any age were included.

Types of participants. All age groups (newborn to adult) suffering from any form of AR were included. These included participants with acute or chronic comorbidities but without immunodeficiency. Participants included those on conventional treatment for other health issues. Trials in which conventional medicines were used as rescue medication were eligible for inclusion. Symptoms of AR include rhinorrhea, nasal obstruction, nasal itching, and sneezing, which are reversible spontaneously or with treatment.[12] A detailed list of the symptoms considered for a diagnosis of AR was based on the Guideline Summary of Management of Allergic and Non Allergic Rhinitis[29] and is included in the published protocol.[28]

There is no specific duration of symptoms required for diagnosis. However, a very short or non-repetitive history of symptoms generally excludes a diagnosis of AR. The presence of any one of the nasal symptoms is essential for a diagnosis of AR, except when nasal blockage is the only symptom. Nasal blockage on its own rarely indicates allergy.[12] Since it has not been defined for a diagnosis of AR, duration of symptoms is not an inclusion criterion for this review.

Investigations

Investigations are not always required to confirm a diagnosis of AR. However, a confirmation of AR diagnosis sometimes involves a skin-prick test and/or specific and serum total IgE tests.[18] The use of investigations for confirming diagnosis was not considered as an inclusion criterion. Trials allowing the administration of conventional treatment as a rescue medication were included.

Types of interventions. Trials involving experimental homeopathic treatments delivered orally, by inhalation, or applied on the body were included. Therefore, globules for oral ingestion, nasal sprays, ointments, and other applications prepared with homeopathic medicines were included in this review. In these trials, the homeopathic preparations contained either a single medicine or more than one medicine as in complex homeopathy. The homeopathic interventions may be administered as one single preparation or more than one preparation. The comparators in the included trials were placebos and/or other homeopathic medicines or conventional treatment; the latter may include antihistamines, immunotherapy, or decongestants, for example. Concerns regarding pooling different forms of homeopathy in meta-analysis and its limitations were understood. The published protocol outlined the intention to perform subgroup analysis to address this.

A detailed discussion on the differences between the different forms of homeopathy is included in the published protocol.[28]

Types of outcome measures

Primary outcomes. The primary outcomes of this review are: the improvement of global symptoms recorded in validated daily or weekly diaries and any scores from validated visual analogue scales (VAS); the total quality-of-life score (such as the Juniper Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]); individual symptom scores, which include any appropriate measures of nasal obstruction, runny nose, sneezing, itching, and eye symptoms; and the number of days requiring medication. In the case of child participants, AR symptoms rated by parents was considered an acceptable outcome measure.

Secondary outcomes. The secondary outcomes of this review are: IgE levels, individual ocular symptoms assessment (considered separately from symptom scores, which include other symptoms), any adverse event, hospitalization

Table 1. Search Strategy Segmentation

	Segment	*Detail*
A	Intervention	Homeopathy and homeopathic with all synonyms
B	MeSH and medical terms (population)	Rhinitis with its various types
C	Free text and layman terms (population)	Hay fever, sneezing, etc.
D	Combination	A + B and A + C

MeSH, Medical Subject Heading.

due to an adverse event, and use of conventional medication (frequency and quantity).

Sources of information

Electronic search. The search to locate randomized trials was based on the Cochrane Highly Sensitive Search Strategy.[30]

Medline (1946 to December 2014 inclusive) on Ovid, CENTRAL, The Cochrane Ear Nose and Throat Disorder Group Trials Register, CINAHL, EMBASE (1974 to December 2014) on Ovid, Allied and Complementary Medicine Database (AMED; 1985 to December 2014) on Ovid, CAM-Quest, and Google Scholar were each searched. A search update was performed up to the end of December 2015.

The search did not have any language filters. The reference lists of identified studies were searched for additional trials. Filters for randomized controlled trials, human trials, and so forth were not applied.

Other sources. A manual search of the citation results supplemented the electronic search. The gray literature was searched for papers that met the inclusion criteria in the protocol. Google was also used to attempt to locate and access any relevant studies.

Search strategy

A detailed search strategy was developed using (but not limited to) the Cochrane Handbook's guidance and studying the search strategies of reviews conducted in this area for other interventions. The strategy included free text and Medical Subject Heading (MeSH) terms.

Search strategy segmentation

The search strategy was segmented as shown in Table 1. The detailed advanced search strategy for Medline is in Table 2, using the segment color code from Table 1. Point number 10 in the search strategy (see Table 2) consolidated all segments of the search and generated the list of search results in each database used in this review.

The Cochrane Risk of Bias tool[31] was used to assess bias across all seven domains in each study. Studies with a high risk in at least one domain were classified as having an overall high risk of bias. Studies with an unclear risk in at least one domain but with a low risk in all other domains were classified as having an overall uncertain risk of bias. A study with an overall uncertain risk of bias was classified as a source of reliable evidence if the lack of clarity was confined to just one of domains IV, V, or VI.[32]

The previously published protocol[28] provides a detailed description of the planned meta-analysis.

Table 2. Medline Search Strategy, Updated December 2015

Search number	*Search*	*Results*
1	Homeopathy/	4297
2	(homoeopathy or homoeopathic or homeopathic).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2767
3	1 or 2	5188
4	Rhinitis, Allergic, Perennial/ or Rhinitis, Vasomotor/ or Rhinitis/ or Rhinitis, Atrophic/ or Rhinitis, Allergic, Seasonal/	28,236
5	(nasal congestion or rhinorrhea or rhinorrhoea or sneezing or itchy nose).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	8357
6	((allerg* or hypersensitiv*) adj5 (cat* or dander or dust* or mite* or dog* or ragweed* or pollen or grass* or cedar or alder or willow or birch or mugwort or tree* or weed* or perennial* or season* or spring or summer or nose or nasal)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	28,739
7	(rhiniti* or rhinoconjunctivitis or SAR or PAR).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	135,756
8	(hayfever or hay next fever or pollinosis or pollenosis).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2028
9	4 or 5 or 6 or 7 or 8	143,239
10	3 and 9	106

Results

Description of studies

The search found 672 unique records: 18 papers required a full text assessment before 11 studies were found to be eligible for the review (Fig. 1). A search update to December 2015 yielded no new papers of relevance.

The review includes 11 double-blinded, randomized controlled trials (with a total of 1654 participants) that studied the efficacy of different homeopathic interventions to improve symptoms of AR. All trials compared homeopathic medicines to a placebo, except Weiser et al.,[43] which compared a nasal spray containing homeopathic medicines to a nasal spray containing cromolyn sodium (Table 3).

Six studies[33–38] used isopathic interventions. Three studies by Aabel et al. used a homeopathic preparation of *Betula* (birch pollen) 30C as the intervention.[33–35] A homeopathic preparation of grass pollen was used by Reilly et al.[37] Homeopathic preparations of the principal allergen of participants were used by Taylor et al;[38] this was the only trial that studied perennial AR. Kim et al.[36] used a homeopathic preparation of common allergens.

Five studies used non-isopathic interventions. Four studies by Wiesenauer et al. used a homeopathic preparation of *Galphimia glauca* as the intervention,[39–42] while one study investigated a homeopathic nasal spray.[43]

Five studies used study diaries as one of the methods of recording outcomes. Four studies asked participants to note a single daily reading on a VAS.[34,35,37,38] Participants of three studies[33,37,38] were asked to score 17, 7, and 6 symptoms, respectively. The RQLQ was used in two studies.[36,43] Taylor et al.[38] also used a twice-daily reading of

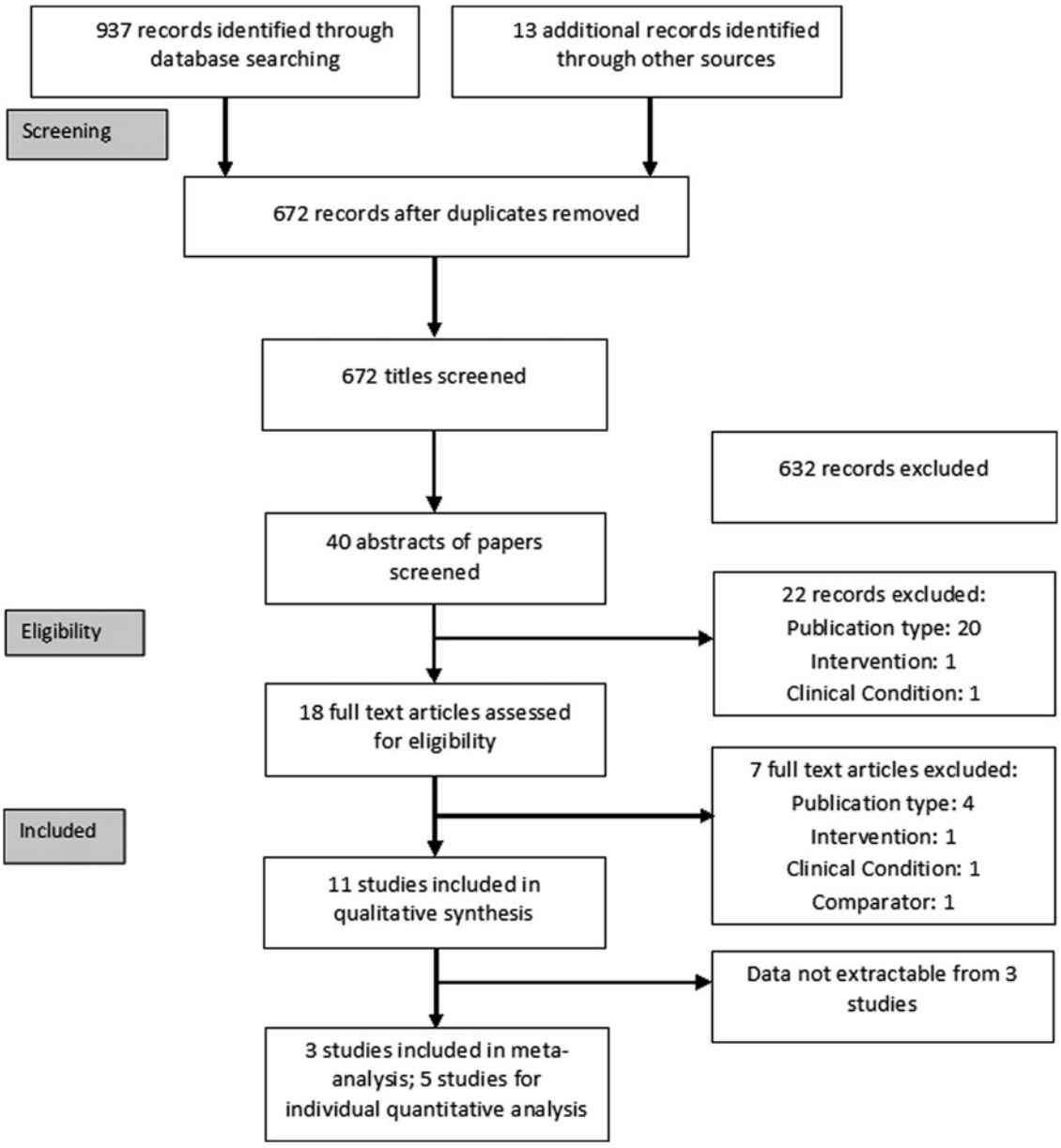

FIG. 1. PRISMA flowchart. Adapted from Moher et al.[49]

Table 3. Description of Included Studies

Study	*Country*	*Participants*	N	*Mean age*	*Male %*	*Intervention*	*Outcome(s)*	*Outcome measure*
Aabel[33]	Norway	Both sexes; aged 7–25 years; clear history of birch pollen allergy, positive skin-prick test for birch	73	12.5	45.2	30C dilution of *Betula*, globules	Symptoms in daily diaries	VAS
Aabel et al.[35]	Norway	Both sexes; aged 18–50 years; clear history of pollen allergy, positive skin-prick test for birch, four nasal symptoms (discharge, stuffiness, itching, and sneezing), and presence of eye symptoms on four-point scales. Combined score needed to be at ≥3.	66	37.5	54.5	30C dilution of *Betula*, globules	Symptoms in daily diaries	Score 0–3
Aabel[34]	Norway	Both sexes; aged 7–50 years; clear history of birch pollen allergy	51	—	—	30C dilution of *Betula*, globules	Symptoms in daily diaries	VAS
Kim et al.[36]	United States	Both sexes, >21 years of age; moderate to severe AR for 2 years	34	45.5	26.4	6× dilution of allergens, sublingual spray	Rhinoconjunctivitis symptoms; quality of life	Seven-point scale for quality of life and symptoms
Reilly et al.[37]	Scotland	Both sexes; 2-year seasonal rhinitis history and eligible current symptoms	108	21	46.2	30C dilution of grass pollen, globules	Symptoms in daily diaries	Score 0–3 and VAS
Taylor et al.[38]	Scotland	Both sexes; >16 years of age, atopic: reactive to inhaled allergens, positive skin test; >1 year history of perennial rhinitis	50	33.5	29.4	30C dilution principal allergen, globules	Symptoms in daily diaries; nasal inspiratory flow	VAS; nasal inspiratory flow readings
Wiesenauer et al.[39]	Germany	Both sexes; any age; clinical diagnosis of AR	86	—	49	6× dilution of *Galphimia glauca*, globules	Symptoms at 2 and 4 weeks	Four-level grading
Wiesenauer and Gaus[40]	Germany	Both sexes; acute allergic hay fever syndrome (pollinosis) caused by flowering plants and grasses, and with ocular and nasal symptoms	74	—	23.1	6× dilution of *Galphimia glauca*, globules	Nasal and ocular symptoms at 2 and 4 weeks	Four-level grading
Wiesenauer et al.[41]	Germany	Both sexes; clinical diagnosis of acute AR; at least 2-year history of symptoms	171	—	38	Dilution of *Galphimia glauca*, globules	Nasal and ocular symptoms at 2 and 4 weeks	Four-level grading
Wiesenauer and Lüdtke[42]	Germany	Both sexes; patients suffering acute allergic hay fever syndrome (pollinosis)	122	—	38.6	4× dilution of *Galphimia glauca*, globules	Nasal and ocular symptoms at 2 and 4 weeks	Four-level grading
Weiser et al.[43]	Germany	Both sexes; aged 18–60 years; seasonal AR diagnosed by RAST (IgE), scratch or skin prick	142	35.75	56.1	*Luffa operculata*, nasal spray	Rhinoconjunctivitis symptoms; quality of life	Seven-point scale for quality of life and symptoms

VAS, visual analogue scale; AR, allergic rhinitis; IgE, immunoglobulin E.

Table 4. Excluded Studies

Study	*Reason for exclusion*
Chirila, 1984	Not a trial
Hardy, 1984	Not a trial
Reilly, 1985	Not a trial
Wiesenauer, 1986	Ineligible comparator
Ruff, 1992	Not a trial
Friese, 2007	Not on AR
Liu, 2013	Not a homeopathic intervention

the nasal inspiratory peak flow as one of their outcome measures. VAS for present quality of life on follow-up visits was used by Weiser et al.[43]; global assessment of therapeutic efficacy, as assessed by patient and doctor, was also recorded by them. Three studies by Wiesenauer et al.[40–42] separately assessed nasal and ocular symptoms at 2 and 4 weeks. The fourth study by Wiesenauer et al.[39] used a composite assessment of symptoms at 2 and 4 weeks of the trial.

Patients were generally recruited from a primary care setting. Details are given in Table 3 and Appendix II. A list of excluded studies along with reasons for exclusion can be found in Table 4.

Methodological quality

The overall standard of trial methods and reporting was poor. Results in the studies by Aabel et al.[33–35] were presented only as graphs of median symptom scores and difference between groups. Aabel[34] only tested the consistency of VAS responses between the earlier studies and a new trial. Reilly et al.[37] and Taylor et al.[38] only presented results as mean change in VAS and as VAS and nasal inspiratory peak flow, respectively. In the study by Taylor et al.,[38] four different principal allergens were used to make the homeopathic intervention. Details of the risk of bias in each domain per study and a risk of bias summary graph are provided in Table 5 and Figure 2.

The method of randomization was not described clearly in four studies.[34,39,41,42] There was limited information regarding allocation concealment in five studies,[33,34,41–43] and it was unclear if personnel were blinded in three studies.[34,36,37] There was clear evidence of high rates of attrition in seven studies.[35–37,39–42] There is a chance for some bias to have been present in the blinding of medication in Weiser et al.[43] This was an equivalence trial. The intervention was a homeopathic nasal spray, and the control was a spray with conventional medicines. It is likely that there would have been a difference in the smell and appearance of the two.

Three studies[38,42,43] were judged to have uncertain risk of bias overall. One of these studies, Taylor et al.,[38] was designated a source of reliable evidence overall (due to its classification of uncertain risk of bias solely in domain VI). Each of the other eight trials[33–37,39–41] was judged to have high risk of bias overall (see Table 5).

Attempts were made to contact study authors where required. One author was unable to provide records for the studies, and another provided rough study notes that could not be used.

Meta-analysis

Due to the high level of heterogeneity across studies in terms of medical condition and outcome measures, and the

Table 5. Absence of Risk of Bias in Included Studies

Study	*I. Sequence generation*	*II. Allocation concealment*	*IIIA. Blinding: personnel*	*IIIB. Blinding: outcome assessors*	*IV. Complete outcome data*	*V. Selective outcome reporting*	*VI. Free of other bias (excluding funding)*	*No. of domains for which criteria fulfilled*			*Risk of bias (excluding vested interest)*	*Reliable evidence*
								Y	*U*	*N*		
Aabel[33]	Y	U	Y	Y	Y	Y	N	5	1	1	High	No
Aabel et al.[35]	Y	Y	Y	U	N	Y	Y	5	1	1	High	No
Aabel[34]	U	U	U	N	N	Y	N	1	3	3	High	No
Kim et al.[36]	Y	Y	U	U	N	Y	Y	4	2	1	High	No
Reilly et al.[37]	Y	Y	U	U	N	Y	U	3	3	1	High	No
Taylor et al.[38]	Y	Y	Y	Y	Y	Y	U	6	1	0	Uncertain	Yes
Weiser et al.[43]	Y	U	Y	Y	Y	Y	U	5	2	0	Uncertain	No
Wiesenauer et al.[39]	U	Y	Y	Y	N	U	U	3	3	1	High	No
Wiesenauer and Gaus[40]	Y	Y	Y	Y	N	Y	Y	6	0	1	High	No
Wiesenauer et al.[41]	U	U	Y	Y	N	U	Y	3	3	1	High	No
Wiesenauer and Lüdtke[42]	U	U	Y	Y	U	Y	U	3	4	0	Uncertain	No

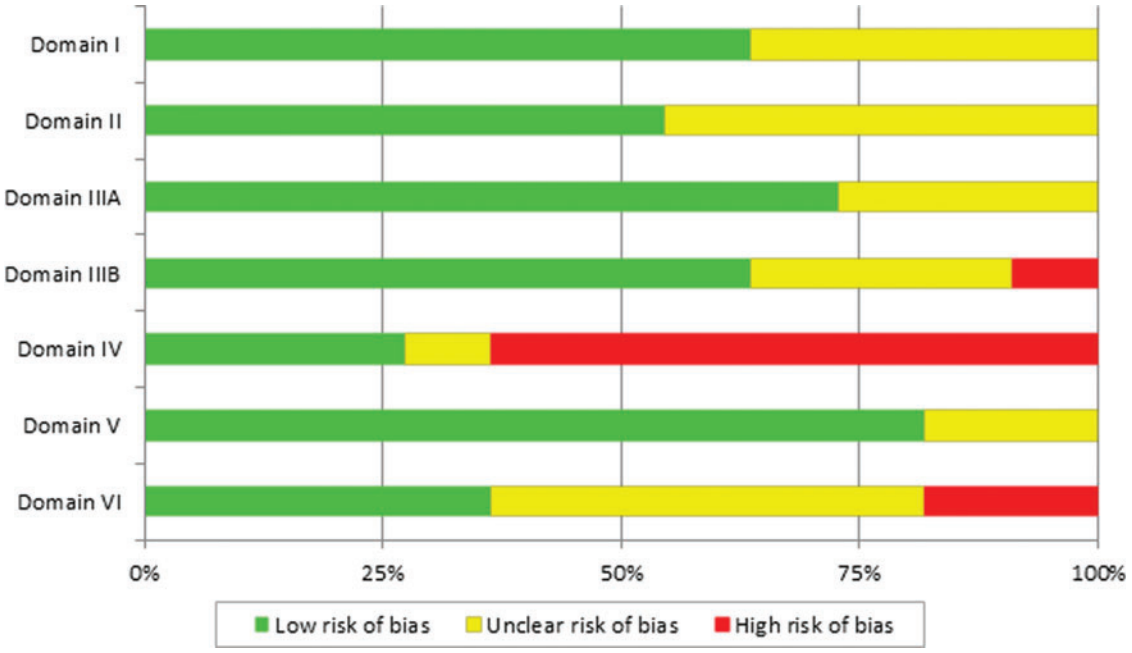

FIG. 2. Risk of bias summary graph. Color images available online at www.liebertpub.com/acm

poor quality of results reporting, only three studies[40–42] could be used for meta-analysis. Thus, pooling of data was not possible for studies of seasonal AR and perennial AR, or for studies with dichotomous and continuous outcome measures. Data were non-extractable from the three studies by Aabel (see above). All three studies are by the same author group (Wiesenauer et al.), and all are trials with *Galphimia glauca* as the intervention. The principal summary measure was risk ratio (RR). Prior to meta-analysis, the outcome measures in the Wiesenauer studies were converted into dichotomous outcomes: ''symptom relief'' was defined to comprise those participants who were symptom-free as well as those who showed obvious relief. The RR of nasal symptom relief at 2 weeks (RR = 1.48 [95% CI 1.24–1.77]; Fig. 3) and 4 weeks (RR = 1.27 [95% CI 1.10–1.46]; Fig. 4) favored homeopathy. The RR of ocular symptom relief at 2 weeks (RR = 1 · 55 [95% CI 1.33–1.80]; Fig. 5) and 4 weeks (RR = 1.37 [95% CI 1.21–1.56]; Fig. 6) also favored homeopathy (see Tables 6 and 7).

When two trials assessed as having a high risk of bias overall were excluded from the meta-analysis, a single trial remained from the original three: Wiesenauer and Lüdtke,[42] which was assessed as having an uncertain overall risk of bias. The results of this single trial favored homeopathy for ocular symptoms at both 2 and 4 weeks (RR = 1.64 [95% CI 1.21–2.22] and 1.34 [95% CI 1.07–1.68], respectively) and for nasal symptoms at 2 weeks only (RR = 1.40 [95% CI 1.03–1.90]).

The fourth study by the same author group[39] had to be excluded from meta-analysis because the outcomes were reported as overall treatment success at 2 and 4 weeks, without segregating nasal and ocular symptoms. Overall treatment success at 2 weeks favored homeopathy (RR = 1.78 [95% CI 1.26–2.50]; $p = 0.001$). Overall treatment success at 4 weeks favored homeopathy (RR = 1.18 [95% CI 0.90–1.55]; $p = 0.23$).

Out of the eight studies of seasonal AR excluded from meta-analysis, one[43] was an equivalence trial. Three of the remaining studies by the same author group (Aabel et al.) contained non-extractable data. Five studies[36–39,43] reported a positive therapeutic effect in the intervention group in one or more outcomes. Four[36,37,39,43] of these five reported statistically significant positive effects. The fifth trial, which had reliable evidence,[38] did not have statistically significant

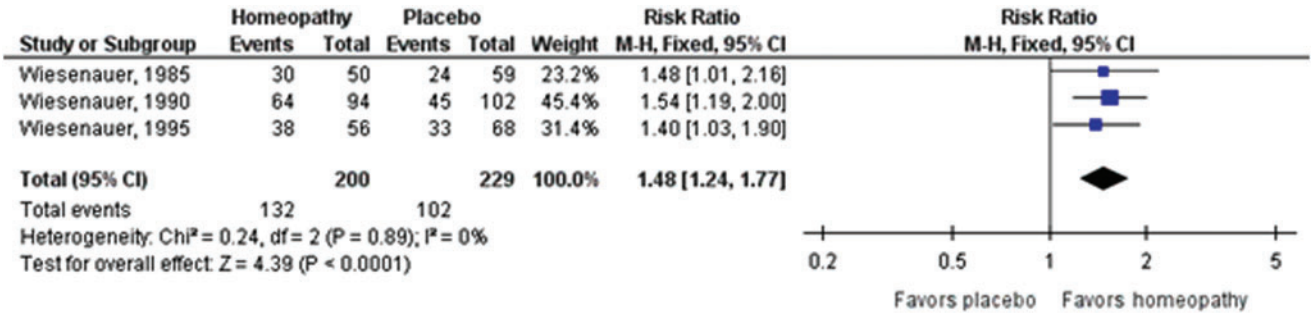

FIG. 3. Nasal symptom relief at 2 weeks. Color images available online at www.liebertpub.com/acm

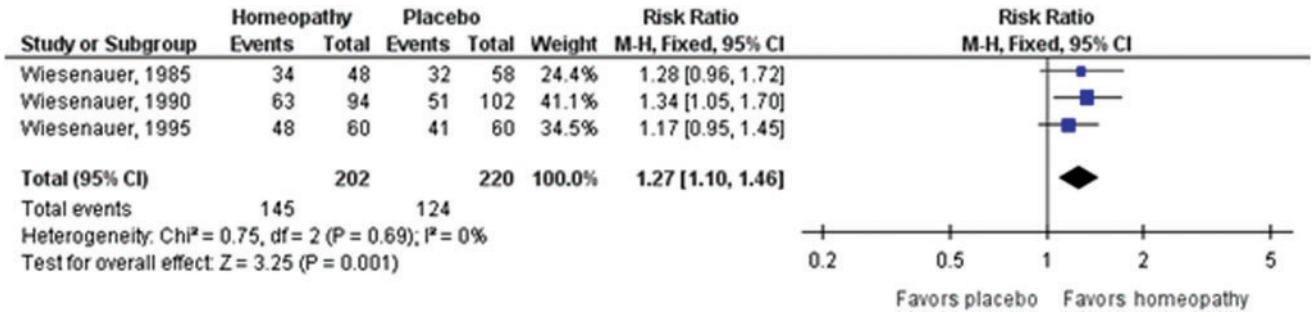

FIG. 4. Nasal symptom relief at 4 weeks. Color images available online at www.liebertpub.com/acm

findings. The equivalence trial (Weiser et al.[43]) concluded that the therapeutic effects of the homeopathic nasal spray were comparable to a conventional nasal spray.

Out of the six studies using isopathy, three were the studies[33–35] that contained non-extractable data. The three other studies[36–38] using isopathy each reported a positive effect. That effect was not statistically significant in the case of the trial with reliable evidence, as above.[38]

VAS

Reilly et al.[37] and Taylor et al.[38] reported a mean change in symptom score on VAS. In Reilly et al., the mean change in the homeopathy group was −17.2 (standard deviation [*SD*] = 28.8) and −2.6 (*SD* = 33.6) in the placebo group. The mean difference between the homeopathy and control groups was −14.60 (95% CI −26.44 to −2.76; $p = 0.02$; see Table 8).

The study by Taylor et al.,[38] which investigated perennial AR, reported a mean change of −5.0 (*SD* = 15.83) in the homeopathy group and −4.0 (*SD* = 14.55) in the comparator. The mean difference between the homeopathy and control groups was −1.00 (95% CI −9.48 to 7.48; $p = 0.82$).

Two studies by Aabel et al.[33,34] also used VAS scores in two different formats. The authors concluded that there was no improvement in the intervention group. Detailed data were not extractable from the published studies for this meta-analysis.

VAS for present quality of life was used by Weiser et al.[43] on visits 1–5. The homeopathy group showed a 24% increase in VAS scores compared with a 29% increase in the cromolyn sodium group. Statistical equivalence between the two treatment approaches was the main conclusion of this trial. This also suggests a clinically significant improvement in patients equivalent to the improvement achieved after use of cromolyn sodium nasal spray.

RQLQ

In Kim et al.[36], the mean overall RQLQ score for the homeopathy group was 1.85 (*SD* = 1.15) and 2.25 (*SD* = 0.93) in the placebo group. The mean difference between the homeopathy and control group for overall RQLQ score was −0.40 [95% CI −1.10 to 0.30]; $p = 0.26$).

The study by Weiser et al.[43] was an equivalence trial comparing a nasal spray containing a preparation of homeopathic medicines with a cromolyn sodium nasal spray. In this study, the mean RQLQ score for nasal and ocular symptoms in the homeopathy group was 1.86 (*SD* = 1.42) and 1.26 (*SD* = 1.34), respectively. Corresponding RQLQ scores in the comparator group were 1.74 (*SD* = 1.34) and 1.10 (*SD* = 0.98), respectively.

The mean overall RQLQ scores were also calculated on the last follow-up by interpolating data from a graph in the published study by Weiser et al.[43] The mean score in the homeopathy group was 1.57 ($n = 71$; *SD* = 1.163]; the mean score in the comparator group was 1.33 ($n = 71$; *SD* = 1.028).

Symptom scores

Reilly et al.[37] used a six-symptom list with scores ranging from 0 to 3. The RR of patients with symptom improvement at 4 weeks was 1.17 (95% CI 0.84–1.64; $p = 0.36$), favoring homeopathy. Aabel et al.[35] used a 17-symptom list. No statistically significant difference was found between the two groups.

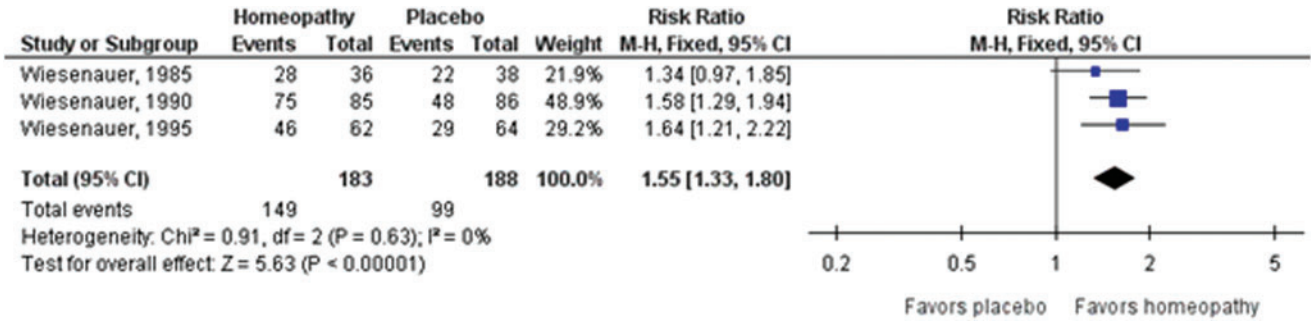

FIG. 5. Ocular symptom relief at 2 weeks. Color images available online at www.liebertpub.com/acm

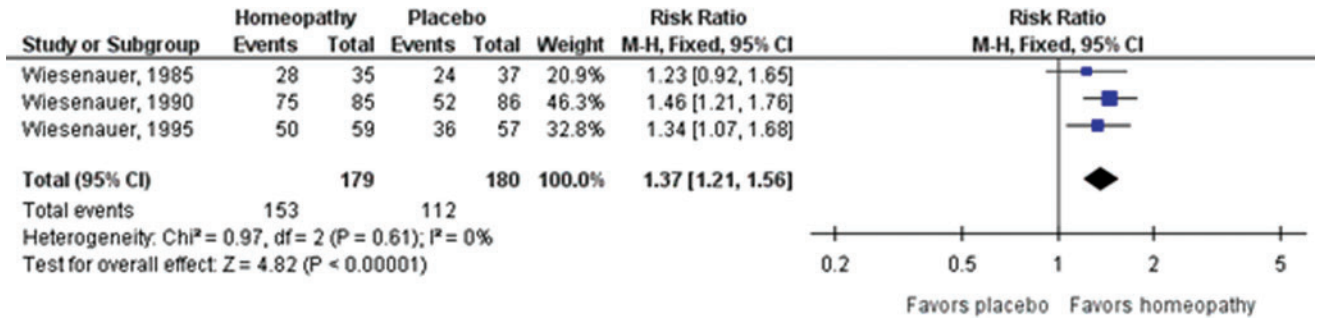

FIG. 6. Ocular symptom relief at 4 weeks. Color images available online at www.liebertpub.com/acm

Use of conventional medication

In Reilly et al.,[37] the number of participants using rescue medication was similar in both arms of the trial. However, the consumption was significantly less in the homeopathy group. The difference between the means of total number of rescue medication tablets taken in each group was reported as 7.5 (95% CI 1–16; $df = 70$; $p = 0.03$).

A higher consumption of rescue medication was reported in the homeopathy group, although this was not statistically significant, in Aabel.[33]

Five participants in Aabel et al.[35] suffered a serious asthmatic reaction and required frequent anti-asthmatics. The consumption of every other kind of rescue medication (nasal sprays, eye drops, and antihistamines) was less in the homeopathy group. Statistical significance was not reported for this finding by the authors.

No rescue medication was allowed in Kim et al.[36] Wiesenauer and Lüdtke[42] excluded from analysis those participants who used rescue medication.

Adverse events/aggravations

Homeopathic aggravation is a temporary worsening of existing symptoms following the administration of a correct

Table 6. Effect Sizes: Dichotomous Data

Study/outcome[a]	*Trial category*	*Condition*	*Homeopathy*		*Placebo*		*OR (95% CI) (OR > 1 favors homeopathy)*	p	*RR (95% CI) (RR > 1 favors homeopathy)*	p
			Events	N	*Events*	N				
Reilly et al.[37] Outcome 1[b]	Placebo	SAR								
Outcome 2			34	56	27	52	1.43 (0.67–3.07)	0.36	1.17 (0.84–1.64)	0.36
Wiesenauer et al.[39]	Placebo	SAR								
Outcome 1			34	41	21	45	**5.55 (2.04–15.13)**	**<0.001**	**1.78 (1.26–2.50)**	**0.001**
Outcome 2			30	37	24	35	1.96 (0.66–5.84)	0.22	1.18 (0.90–1.55)	0.23
Outcome 3			**63**	**94**	**51**	**102**	**5.94 (2.71–13.02)**	**<0.001**	**1.34 (1.05–1.70)**	**0.02**
Outcome 4			**75**	**85**	**52**	**86**	**4.90 (2.23–10.79)**	**<0.001**	**1.46 (1.21–1.76)**	**<0.001**
Wiesenauer and Gaus[40]	Placebo	SAR								
Outcome 1			30	50	24	59	1.97 (0.88–4.43)	0.10	**1.48 (1.01–2.16)**	**0.05**
Outcome 2			28	36	22	38	2.17 (0.74–6.31)	0.16	1.34 (0.97–1.85)	0.07
Outcome 3			**34**	**48**	**32**	**58**	**2.19 (1.01–4.72)**	**0.05**	**1.28 (0.96–1.72)**	**0.10**
Outcome 4			**28**	**35**	**24**	**37**	**2.55 (0.92–7.03)**	**0.07**	**1.23 (0.92–1.65)**	**0.16**
Wiesenauer et al.[41]	Placebo	SAR								
Outcome 1			**64**	**94**	**45**	**102**	**2.70 (1.51–4.84)**	**<0.001**	**1.54 (1.19–2.00)**	**0.001**
Outcome 2			**75**	**85**	**48**	**86**	**2.03 (1.14–3.63)**	**0.02**	**1.58 (1.29–1.94)**	**<0.001**
Outcome 3			**63**	**94**	**51**	**102**	**5.94 (2.71–13.02)**	**<0.001**	**1.34 (1.05–1.70)**	**0.02**
Outcome 4			**75**	**85**	**52**	**86**	**4.90 (2.23–10.79)**	**<0.001**	**1.46 (1.21–1.76)**	**<0.001**
Wiesenauer and Lüdtke[42]	Placebo	SAR								
Outcome 1			**38**	**56**	**33**	**68**	**3.47 (1.64–7.36)**	**0.001**	**1.40 (1.03–1.90)**	**0.03**
Outcome 2			**48**	**60**	**41**	**60**	**3.24 (1.33–7.90)**	**0.01**	1.17 (0.95–1.45)	0.15
Outcome 3			**46**	**62**	**29**	**64**	**2.24 (1.07–4.67)**	**0.03**	**1.64 (1.21–2.22)**	**0.002**
Outcome 4			50	59	36	57	1.85 (0.80–4.27)	0.15	**1.34 (1.07–1.68)**	**0.01**

Statistically significant values are shown in bold.
[a]Refer to Table 7.
[b]Refer to Table 8.
CI, confidence interval; OR, odds ratio; RR, risk ratio; SAR, seasonal allergic rhinitis.

Table 7. Outcome Key

Trial	*Outcome number*	*Outcome*
Wiesenauer and Gaus[40]	1	Nasal symptom relief—2 weeks
Wiesenauer et al.[41]	2	Nasal symptom relief—4 weeks
Wiesenauer and Lüdtke[42]	3	Ocular symptom relief—2 weeks
	4	Ocular symptom relief—4 weeks
Wiesenauer et al.[39]	1	Overall treatment success—2 weeks
	2	Overall treatment success—4 weeks
Aabel[33]	1	Symptom score (VAS)—28 days
Aabel et al.[35]	1	Symptom score (VAS)—after 10 days onset
Aabel[34]	1	Symptom score (VAS)—10 days
Reilly et al.[37]	1	Mean change in symptom score (VAS)—4 weeks
	2	Patients with symptom improvement—4 weeks
Kim et al.[36]	1	Change in mean overall RQLQ score—4 weeks
	2	Mean RQLQ score (nasal)—4 weeks
	3	Mean RQLQ score (ocular)—4 weeks
Taylor et al.[38]	1	Mean change in symptom score (VAS)—4 weeks
Weiser et al.[43]	1	Mean overall RQLQ score—6 weeks (visit 5)
	2	Mean RQLQ score (nasal)—6 weeks (visit 5)
	3	Mean RQLQ score (ocular)—6 weeks (visit 5)

RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

homeopathic prescription.[44] Homeopathic aggravation was reported in Reilly et al.[37] More of the patients with aggravation were in the homeopathy group ($\chi^2 = 3.92$; $p < 0.05$).

Initial aggravation was also reported in the homeopathy group in Taylor et al.[38] A statistically nonsignificant higher number of rhinitis-related aggravations was seen in the homeopathy group ($\chi^2 = 3.28$; $p = 0.07$).

Aggravation of symptoms was seen in the homeopathy group in Aabel et al.[35] After the pollen season but before unblinding, an unplanned, supplementary questionnaire was sent to participants. They were required to answer if any aggravation of symptoms had been experienced immediately after consumption of the pills. There were more participants in the homeopathy group who reported an aggravation ($p = 0.03$).

A higher dilution of *Betula* was used in Aabel[33] to attempt to limit the possibility of aggravation noted in the previous study.[35] However, higher symptom scores were reported in the homeopathy group. One participant complained of nausea in the report by Wiesenauer and Lüdtke.[42]

Table 8. Effect Sizes: Continuous Data

Study/outcome[a]	*Trial category*	*Condition*	*Homeopathy*			*Placebo*			*Mean diff. (95% CI) (–ve favors homeopathy)*	p
			Mean	SD	N	*Mean*	SD	N		
Aabel[33]	Placebo	SAR								
Outcome 1							Data not extractable			
Aabel et al.[35]	Placebo	SAR								
Outcome 1							Data not extractable			
Aabel[34]	Placebo	SAR								
Outcome 1							Data not extractable			
Kim et al.[36]	Placebo	SAR								
Outcome 1			1.85	1.15	18	2.25	0.93	16	–0.40 (–1.10 to 0.30)	0.26
Outcome 2			2.95	2.65	18	2.86	2.21	16	0.09 (–1.54 to 1.72)	0.91
Outcome 3			1.66	1.31	18	2.82	1.80	16	**−1.16 (−2.23 to −0.09)**	**0.03**
Reilly et al.[37]	Placebo	SAR								
Outcome 1			–17.2	28.8	56	–2.6	33.6	52	**−14.60 (−26.44 to 2.76)**	**0.02**
Outcome 2[b]										
Taylor et al.[38]	Placebo	PAR								
Outcome 1			–5.0	15.83	23	–4.0	14.55	27	–1.00 (–9.48 to 7.48)	0.82
Weiser et al.[43]	Equivalence	SAR								
Outcome 1			1.57	1.163	71	1.33	1.028	71	0.24 (–0.12 to 0.60)	0.19
Outcome 2			1.86	1.42	71	1.70	1.34	71	0.16 (–0.29 to 0.61)	0.49
Outcome 3			1.26	1.34	71	1.10	0.98	71	0.16 (–0.23 to 0.55)	0.42

The findings in bold indicate those that are statistically significant (p-value less than 0.05).
[a]Refer to Table 7.
[b]Refer to Table 6.

Funding

Five of the trials[33–36,40] were conducted with homeopathic medicines sponsored by the manufacturer. One study[43] was funded by the manufacturer. Four studies[36–38,41] were funded in part by nonprofit organizations supporting homeopathic research and education.

Discussion

Summary of main results

The limited quality of the included studies does not warrant drawing any definite inferences about the effects of homeopathy for AR. The central estimate of effect size statistically favored homeopathy in the meta-analysis of the three eligible trials (all of which studied *Galphimia glauca*). Out of these three, a formal sensitivity analysis, excluding trials assessed as having a high risk of bias, left one trial[42] assessed as having an uncertain risk of bias and whose results favored homeopathy for ocular symptoms at 2 and 4 weeks and, marginally, for nasal symptoms at 2 weeks only. The treatment effect size of this trial, based on the RR and on the originally reported odds ratios, can be regarded as moderate.[45]

For seasonal AR, and limiting interpretation of the evidence solely to trials without overtly high risk of bias, *Galphimia glauca* may improve ocular symptoms; improvement of nasal symptoms may be shorter in duration. From the six trials in this review, the efficacy of isopathy is unclear due to insufficient good-quality evidence, including problems with data extraction. For perennial AR, the single relevant study provided inconclusive evidence for the efficacy of isopathy.

There was conflicting evidence on aggravation of symptoms following homeopathic treatment. Four studies reported an aggravation in symptoms in the homeopathy group.[33,35,37,38] It is unclear whether the high risk of bias present in three of these studies had any impact on the reporting of such events. Rhinitis-related aggravation was statistically nonsignificant in Taylor et al.,[38] a trial assessed as comprising reliable evidence. Based on the studies included in this review, it is therefore difficult to confirm the presence of symptom aggravation during the homeopathic treatment of AR.

The large majority of trials used homeopathic medicines sponsored by the manufacturer or included funding by nonprofit organizations supporting homeopathic research and education. It is not possible to ascertain what impact, if any, this level of involvement by the homeopathic drug manufacturer or nonprofit organization might have had on the data management or reporting by the original researchers.

Comparison with existing evidence

A number of reviews examining homeopathic treatment for AR have been published.[24–27] The significant limitations regarding some of them have been discussed earlier. Moreover, no previous review has evaluated *all* homeopathic treatments for AR. It is acknowledged that due to the stringent standards for risk-of-bias assessment in this review, some studies may have been judged to be of different quality from that in previous reviews. Notably, Kleinjen et al.[46] and Linde et al.[8] judged Reilly et al.[37] to be of high quality, despite its high dropout rate, due to which it was judged in the present review to have high risk of bias. This is the first systematic review that has attempted to examine the effect of all kinds of homeopathic treatment that have been used for AR specifically. The weak evidence that has been identified to support a positive therapeutic effect of homeopathic treatment in AR harmonizes with the findings of these previous reviews.

Strengths and limitations

The strength of this review is its methodological rigor. All methods for this review, including those for meta-analysis, were clearly described in a protocol, which was first published in PROSPERO and, after peer review, in an open-access journal.[28] The PRISMA Statement[47] checklist was consulted, and all relevant items were included in the review (see Appendix I); no deviations were made from the protocol. A comprehensive search strategy was designed, and clear inclusion criteria were set for potentially eligible studies; the authors are confident that the entire relevant literature was identified, though it is recognized that it is possible that some studies were missed. The extent of missing data from unpublished studies is unknown. The number of studies in the meta-analysis was too low to justify use of a funnel plot to detect evidence of publication bias. The detailed search strategy did not yield any trials that examined individualized homeopathy.

The risk of bias was high in all but three of the studies included in the review as a whole. This prevented conclusions from being drawn about clinical significance from the results. Moreover, the outcome measures were heterogeneous, limiting the number of studies that could be included in meta-analysis. Loss to follow-up in the included studies was not adequately explained, and only four studies[37,38,42,43] made a statement regarding adherence to the intention-to-treat principle.

Conclusions

This review provides an accurate, complete, and fair representation of the current evidence in the treatment of AR using homeopathic interventions. The limited quality of the evidence makes it difficult to make definitive inferences about effects. Data from three trials included within this review suggest that *Galphimia glauca* may usefully improve ocular symptoms and that a commercially available homeopathic nasal spray may be effective in improving symptoms of AR. The efficacy of isopathy for any type of AR is unclear. Whether symptom aggravation may occur is also unclear. Future trials of homeopathy for AR, including those using the as-yet untested individualized (''classical'') approach for this condition, need to take the results of this review into account and be of higher methodological quality. Specifically, researchers of prospective trials should ensure that they have a sample size appropriate to the chosen outcome measure and the inter-group difference they expect to observe; loss to follow-up is fully accounted for in their data analysis and interpretation; the selected outcome measures are suitably validated; and checklists such as the one in the CONSORT statement[48] are used to ensure high quality of trials and their reporting.

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Author Disclosure Statement

All authors declare that there are no conflicts of interest. None of the authors has any competing interests.

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(*Appendix follows* →)

Appendix I: PRISMA Checklist

Section/topic	*#*	*Checklist item*	*Reported on page #*
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary, including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4–5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information, including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5–6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6–7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data-collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	—
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, table 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	—
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 5

(*continued*)

Appendix I. (Continued)

Section/topic	#	*Checklist item*	*Reported on page #*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	8, table 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; see item 16).	—
Discussion			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

Appendix II: Details of Included Studies

Aabel, 2000

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	U
II	Allocation concealment	U
IIIA	Blinding: personnel	U
IIIB	Blinding: outcome assessors	N
IV	Complete outcome data	N
V	Selective outcome reporting	Y
VI	Free from other sources of bias	N

Participants: 140 patients with a clear history of birch pollen allergy were recruited; 80 were randomized. Inclusion criteria: 7–25 years of age and a positive skin-prick test. Exclusion criteria: diseases of any other kind (asthmatic and patients with eczema excluded), conditions causing nasal obstruction (nasal polyps, septum deviation, chronic edema from perennial rhinitis, etc.),use of medication, including oral contraceptives; women planning pregnancy, pregnant, lactating mothers, and those not willing to stop drinking coca cola or coffee or both during treatment period. Average age intervention/placebo: 12.8:11.7; male:female intervention/placebo: 18:15/19:21.

Intervention: Globules of homeopathically prepared *Betula* in 30C potency, one tablet once a week for 4 weeks without symptoms. One tablet during allergy symptoms. Maybe repeated every 12 h. Up to three tablets a day during high pollen counts for 10 days from the appearance of symptoms.

Outcomes: VAS with allergy symptoms in daily study diaries. Single daily reading. Rescue medication noted.

Notes: The definition of ''high pollen count'' unclear; author's blinding not explicitly mentioned; graphs do not have table of values; external validity affected by exclusion criteria.

Aabel et al., 2000

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	Y
II	Allocation concealment	U
IIIA	Blinding: personnel	Y
IIIB	Blinding: outcome assessors	Y
IV	Complete outcome data	Y
V	Selective outcome reporting	Y
VI	Free from other sources of bias	N

Participants: 70 patients with clear history of birch pollen allergy were randomized. Inclusion criteria: 18–50 years age, positive skin-prick test, four nasal symptoms (discharge, stuffiness, itching, and sneezing), and the presence of eye symptoms on four-point scales. Combined score needed to be at least 3. Exclusion criteria: diseases of any other kind other than the allergy under study, conditions causing nasal blockage, using medication, contraceptives, pregnant, planning pregnancy, not willing to stop drinking coca cola or coffee for treatment period. Average age intervention/placebo: 39/36; male:female intervention/placebo: 17:15/19:15.

Intervention: 3-day run-in period—one tablet daily. Thereafter, one tablet daily until allergy gets better. Resumed if symptoms returned. Up to three tablets a day during high levels of pollen.

Outcomes: Study diaries for 28 days, scoring 17 symptoms from 0 to 3. Rescue medication noted.

Notes: Allergy symptoms could have arisen from alder and hazel pollen—20 participants; high pollen count not defined; graphs do not have table of values. External validity affected by exclusion criteria.

Aabel, 2001

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	Y
II	Allocation concealment	Y
IIIA	Blinding: personnel	Y
IIIB	Blinding: outcome assessors	U
IV	Complete outcome data	N
V	Selective outcome reporting	Y
VI	Free from other sources of bias	Y

Participants: 51 participants of previous trials in 1995 and 1996. Inclusion criteria: aged 7–50 years, clear history of birch pollen allergy confirmed with skin-prick test. Exclusion criteria: diseases of any kind other than allergy (eczema and asthma excluded), nasal blockage (polyps, DNS, chronic edema due to perennial rhinitis), on medication, pregnant or likely to get pregnant, lactating mothers, unwilling to stop drinking coca cola or coffee during treatment. No characteristics of participants given.

Intervention: Globules of *Betula* homeopathically diluted to 30C. One tablet a week for 4 weeks until symptoms start. One tablet when symptoms appear, with an interval of 12 h before repeating. May take up to three tablets in 24 h during high pollen counts.

Outcomes: Daily study diary with single VAS score.

Notes: 1995 participants had 17-point sum score. Scores converted to VAS values using *z*-scores. No individual values of participants. No characteristics of participants provided. Only outcome values provided are symptom score comparison of the subgroups. Randomization into four groups not clearly explained. Statistician was aware of code of 1996 participants and responsible for 1997 study's randomization.

Reilly, et al., 1986

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	Y
II	Allocation concealment	Y
IIIA	Blinding: personnel	U
IIIB	Blinding: outcome assessors	U
IV	Complete outcome data	N
V	Selective outcome reporting	Y
VI	Free from other sources of bias	U

Participants: 162 patients recruited from two hospital clinics in Glasgow and London and 26 national health general practices, with symptoms and a history of seasonal allergic rhinitis. Inclusion criteria: 2-year seasonal rhinitis history and eligible current symptoms. Exclusion criteria: only eye involvement, evidence of acute asthma or infection, pregnancy, lactation, risk of pregnancy, serious illness other than allergy, or use of drugs other than trial medication. Average age male:female intervention/placebo: 21:25/21:28; male:female intervention/placebo: 38:41/35:44.

Intervention: Globules with mixed grass pollen, homeopathically prepared at a dilution of 30C, twice daily for 5 weeks.

Outcomes: Daily study diaries, six symptoms with scores from 0 to 3, and VAS. Doctors recorded same details at week 0 and monitored patient compliance at weeks 3 and 5. Rescue medication noted.

Notes: Washout period allowed for other drugs after recruitment. Individual symptoms scores or VAS readings unavailable.

Taylor et al., 2000

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	Y
II	Allocation concealment	Y
IIIA	Blinding: personnel	Y
IIIB	Blinding: outcome assessors	Y
IV	Complete outcome data	Y
V	Selective outcome reporting	Y
VI	Free from other sources of bias	U

Participants: 121 patients who volunteered from four general practices in London and ENT OPD in Northwick Park Hospital with perennial allergic rhinitis. Inclusion criteria: aged >16 years, atopic: reactive to inhaled allergens, positive skin test, >1 year history of perennial rhinitis. Exclusion criteria: deterioration during grass pollen season, nasal abnormalities causing obstruction, previous homeopathic immunotherapy, allergen avoidance in past 6 weeks, away from usual environment for >1 week during trial, respiratory infection, severe concomitant disease, pregnancy, breastfeeding, likelihood of pregnancy, oral or parenteral steroids in past 6 months, conventional desensitization in past 3 months. Average age male:female intervention/placebo: 31:36; male:female intervention/placebo: 6:18/9:18.

Intervention: Globules with homeopathic 30C dilution of principal allergen based on skin prick. One pill from three vials taken over 24 h constituted one dose (by splitting). No other medication given.

Outcomes: Nasal inspiratory peak flow—three successive readings—morning and evening. Scoring of symptoms from 0 to 4. Daily overall VAS.

Notes: This study is on perennial allergic rhinitis. Different allergens used for different participants reduce power and external validity. Individual scores and values are unavailable. VAS is similar to Reilly 1986 but diagnosis is different.

Weiser et al., 1999

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	Y
II	Allocation concealment	U
IIIA	Blinding: personnel	Y
IIIB	Blinding: outcome assessors	Y
IV	Complete outcome data	Y
V	Selective outcome reporting	Y
VI	Free from other sources of bias	U

Participants: 146 patients recruited from outpatient clinics. Inclusion criteria: aged 18–60 years, seasonal AR diagnosed by RAST (IgE), scratch or skin prick. Exclusion criteria: perennial allergic rhinitis or infectious diseases of the upper respiratory tract, known hypersensitivity to medication, treatment with drugs containing cromolyn sodium or corticosteroids within 2 weeks of the study start: treatment with antihistamines or alpha-sympathomimetics within 24 h of the study start, regular use of anti-inflammatory agents and analgesics. No pregnant or nursing women were accepted. History of allergic symptoms leading to emergency treatment during the past 2 years. Co-medication: any compounds used for treatment of hay fever. Average age intervention/placebo: 36.8:34.7; male:female intervention/placebo: 44:28/38:36.

Intervention: Nasal spray comprising of *Luffa operculata*, *Galphimia glauca* in dilutions of 4×, 12×, and 30×. Histamine and sulfur in dilutions of 12×, 30×, and 200×. One spray of about 0.14 mL administered four times daily into each nostril. During acute exacerbation, eight sprays per nostril. Comparator: nasal spray containing 20 mg/mL of cromolyn sodium.

Outcomes: Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). VAS for present quality of life on visits 1–5. Global assessment of therapeutic efficacy at end of treatment was measured by both patient and investigator on four-point scale.

Notes: Equivalence trial. Per-protocol analysis. No individual values found.

Kim et al., 2005

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	Y
II	Allocation concealment	Y
IIIA	Blinding: personnel	U
IIIB	Blinding: outcome assessors	U
IV	Complete outcome data	N
V	Selective outcome reporting	Y
VI	Free from other sources of bias	y

Participants: 40 patients recruited in the Phoenix area in Arizona using newspaper advertisements, flyers, and other modes. Inclusion criteria: men and women aged ≥21 years, diagnosis of moderate to severe allergic rhinitis for the last 2 years based on clinical assessment, three or more active rhinitis symptoms at enrolment (sneezing, burning/itching nose, nasal discharge, watery/irritated eye, congestion, or itching throat), ability to comply with intervention protocols and to complete study questionnaires. Exclusion criteria: non-allergic rhinitis, sporadic symptoms or perennial allergic rhinitis, pregnancy or lactation, smoking, medical conditions that prohibit full participation (asthma, pulmonary disorders, immunocompromised conditions, alcohol or drug addiction, acute upper respiratory tract infection), concurrent use of therapies for allergic rhinitis such as drugs, botanicals, dietary supplements, acupuncture, or other alternative modalities, new allergic rhinitis treatment in the last 3 months, past immunotherapy/desensitization, or previous history of using homeopathy.

Average age intervention/placebo: 47:44; male:female intervention/placebo: 5:13/4:12.

Intervention: sublingual spray made with allergens common to the region. To be used three times per day for 4 weeks.

Outcomes: RQLQ, Work Productivity and Activity Impairment (WPAI), and Medical Outcomes Study Short Form 36 (MOS SF 36). These were measured at baseline and at 4 weeks.

Notes: Missing data for 15% participants introduces a high source of bias.

Wiesenauer and Gaus, 1985

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	Y
II	Allocation concealment	Y
IIIA	Blinding: personnel	Y
IIIB	Blinding: outcome assessors	Y
IV	Complete outcome data	N
V	Selective outcome reporting	Y
VI	Free from other sources of bias	Y

Participants: 70 participants. Physicians, mainly general practitioners throughout Germany. Inclusion criteria: every patient suffering from acute allergic hay fever syndrome (pollinosis) caused by blooming plants and grass with swollen and inflamed conjunctiva, combined with watering and burning eyes (''ocular symptoms''), tingling and scratching sensations in the nose and the throat, and frequent sneezing and nasal discharge (''nasal symptoms''). Exclusion criteria: patients being treated for other diseases with corticosteroids and/or antihistaminic drugs. Male:female intervention/dilution/placebo: 18:32/23:32/19:36.

Intervention: D6 potentization of *Galphimia glauca* administered orally for 5–6 weeks.

Outcomes: Divided into ocular and nasal symptoms with following subgroups: symptom free, obvious relief, slight improvement, no improvement. Assessed at 2 and 4 weeks.

Notes: No information on details of dosage as decided by the practitioner.

Wiesenauer et al., 1990

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	U
II	Allocation concealment	U
IIIA	Blinding: personnel	Y
IIIB	Blinding: outcome assessors	Y
IV	Complete outcome data	N
V	Selective outcome reporting	U
VI	Free from other sources of bias	Y

Participants: 243 participants recruited. Clinical diagnosis of acute AR in male and female subjects with at least a 2-year history of AR. Male percentage: 38%.

Intervention: *Galphimia glauca*. Administered as drops in C2 potency.

Outcomes: Divided into ocular and nasal symptoms with following subgroups: symptom free, obvious relief, slight improvement, no improvement. Assessed at 2 and 4 weeks.

Wiesenauer et al., 1983

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	Y
II	Allocation concealment	Y
IIIA	Blinding: personnel	Y
IIIB	Blinding: outcome assessors	Y
IV	Complete outcome data	N
V	Selective outcome reporting	Y
VI	Free from other sources of bias	Y

Participants: 86 participants with clinical diagnosis of both sexes and any age. Male percentage: 49%.

Intervention: *Galphimia glauca* 4× dilution in drops.

Outcomes: Divided into ocular and nasal symptoms with following subgroups: symptom free, obvious relief, slight improvement, no improvement. Assessed at 2 and 4 weeks.

Wiesenauer and Lüdtke, 1995

Domain	*Title*	*Absence of risk of bias*
I	Sequence generation	U
II	Allocation concealment	U
IIIA	Blinding: personnel	Y
IIIB	Blinding: outcome assessors	Y
IV	Complete outcome data	U
V	Selective outcome reporting	Y
VI	Free from other sources of bias	U

Participants: 164 patients recruited from 27 general practices from spring to autumn 1987. Inclusion criteria: acute allergic hay fever syndrome (pollinosis). Exclusion criteria: treated for other diseases with corticosteroids or antihistaminic drugs. Male:female intervention/placebo: 26:38/25:43.

Intervention: D4 potentization of *Galphimia glauca*. Recommended dosage was one tablet four times a day.

Outcomes: Divided into ocular and nasal symptoms with following subgroups: symptom free, obvious relief, slight improvement, no improvement. Assessed at 2 and 4 weeks.