Appendix A – Data extraction and quality assessment forms

The quality assessment form for each study is presented immediately after its data extraction form.

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Alraek T, Lee MS, Choi TY, Cao H, Liu J (2011) Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review. BMC Complement Altern Med 11:87.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: Norwegian Directorate of Health
Conflict of interest: “the authors declare that they have no competing interests”</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 2 RCTs (Level II)</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
NR for all included studies</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy – method unclear (all included studies)</td><td colspan="3">Comparator(s):
Placebo (all included studies)</td></tr>
<tr><td colspan="5">Sample size:
The number of patients enrolled in the RCTs ranged from 61-92/64-103[a]</td></tr>
<tr><td colspan="5">Population characteristics:
• Weatherley-Jones 2004 (RCT): Patients over 18 years of age diagnosed with CFS according to the Oxford criteria.
• Awdry 1996 (RCT): Patients less than 65 years of age diagnosed with CFS according to the Oxford criteria</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: ranged from 6 months to 1 year</td><td colspan="3">Outcome(s) measured:
MFI; FIS; FLP; Daily graphs; Symptoms score</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: Concealment of allocation was adequate in 1 RCT and inadequate in the other RCT</td><td>Comparison of study groups:
Both RCTs focused on homeopathy vs placebo in CFS patients</td><td>Blinding:
All of the included studies were double-blind</td><td>Treatment/ measurement bias: All of the included studies had a low risk of bias in selective outcome reporting (as assessed by Alraek 2011)</td><td>Follow-up (ITT):
1 RCT reported on the number of dropouts and [withdrawals and used ITT analysis. The other RCT provided no details on loss to follow up and used per-protocol analysis</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
The authors assessed the quality of the included studies using the Cochrane tools for assessing risk of bias. A quality grading was given for each of eight domains (e.g. random sequence generation, allocation concealment). An overall quality assessment of the included studies was not formulated</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 7/10 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided but the reporting of patient demographics was weak. Scientific quality of the included studies was assessed using the Cochrane classification and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. The conflict of interest was stated</td></tr>
</table>

RESULTS

Overall:

- "Two RCTs compared homeopathy with placebo. One RCT showed that homeopathy improved fatigue and function. The other RCT reported the beneficial effects of homeopathy on symptom improvement."
- "Compared to placebo, homeopathy also had insufficient evidence of symptom improvement in CFS."

Individual study results

Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Weatherley-Jones (2004) N=103/92[a] *Quality not specified*	Homeopathy for 6 months n=47	Placebo n=46	MFI	No significant difference except general fatigue (P=0.04)
			FIS	No significant difference
			FLP	Significant difference (P=0.04)
Awdry 1996 N=94/61[a] *Quality not specified*	Homeopathy for 1 year n=30	Placebo n=31	Daily graphs	No significant differences reported (no between-group analysis)
			Symptom score	No significant differences reported (no between-grouop analysis)

EXTERNAL VALIDITY

Generalisability: The included RCTs featured patients that were over 18 years of age (1 RCT) and less than 65 years of age (1 RCT). The location of the included studies was not reported

Comments: None

Abbreviations: CFS, Chronic Fatigue Syndrome; FIS, Fatigue Impact Scale; FLP, Functional Limitations Profile; ITT, intention-to-treat; MFI, Multidimensional Fatigue Inventory; NR, not reported; RCT, randomised controlled trial.

[a] Two numbers were recorded for the sample size of each of the included studies. What these numbers are in reference to is not specified in the systematic review

Citation: Alraek T, Lee MS, Choi TY, Cao H, Liu J (2011) Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review. BMC Complement Altern Med 11:87.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**7/10**	

STUDY DETAILS		
Reference: Altunc U, Pittler MH, Ernst E (2007) Homeopathy for childhood and adolescence ailments: Systematic review of randomized clinical trials. Mayo Clin Proc 82(1):69-75.		
Affiliation/source of funds: NR Conflicts of interest: NR		
Study design: Systematic review of 16 RCTs (Level II). The therapeutic conditions covered are: • **Adenoid vegetation** (2 RCTs) • **ADHD** (3 RCTs) • **Asthma** (2 RCTs) • **Acute otitis media** (1 RCT) • **Conjunctivitis** (1 RCT) • **Diarrhoea** (3 RCTs) • **Postoperative pain-agitation syndrome** (1 RCT) • **URTI** (2 RCTs) • **Warts** (1 RCT)	Level of evidence: Level I	Location/setting: NR (all included studies)
Intervention: Homeopathy regimen specified by authors (7 RCTs) Individualised homeopathy (9 RCT)	Comparator(s): Placebo (all included studies)	
Sample size: The number of patients enrolled in the RCTs ranged from 34 to 1306		

Population characteristics:

Adenoid vegetation

- Feuchter et al, 2001 (RCT): Patients with adenoid vegetation; Intervention and control group: mean age 6 years; 65% male
- Furuta et al, 2003 (RCT); Patients with adenoid vegetation; Intervention group and control group: 3-7 years old; 57% male

ADHD

- Strauss et al, 2000 (RCT): Patients with ADHD; "children"; 90% male
- Jacobs et al, 2005 (RCT): Patients with ADHD; Intervention group: mean age 9.5 years; Control group: mean age 9.0 years; 77% male
- Frei et al, 2005 (RCT): Patients with ADHD; Mean age 10 years; 89% male

Asthma

- Freitas et al, 1995 (RCT): Patients with asthma; 1-12 years old; 51% male
- White et al, 2003 (RCT): Patients with asthma; 5-15 years old; 54% male

Acute otitis media

- Jacobs et al, 2001 (RCT): Patients with acute otitis media; Intervention group: mean age 3.5 years; Control group: mean age 3.1 years; 41% male

Conjunctivitis

- Mokkapatti 1992 (RCT): Patients with conjunctivitis; 4-15 years old; gender not reported

Diarrhoea

- Jacobs et al, 2003 (RCT): Patients with diarrhoea; 6 months-5 years old; gender not reported
- Jacobs et al, 2004 (RCT): Patients with diarrhoea; Intervention group: mean age 1.6 years; Control group: mean age 1.5 years; gender not reported
- Jacobs et al, 2000 (RCT): Patients with diarrhoea; Intervention group: mean age 1.7 years; Control group: mean age 1.4 years; 67.5% male

Postoperative pain-agitation syndrome

- Alibeu and Jobert, 1990 (RCT): Patients with postoperative pain-agitation syndrome; Mean age 6 months-14 years; 72% male

URTI

- De Lange de Klerk et al, 1994 (RCT): Patients with recurrent URTI; Intervention group: mean age 4.2 years; Control group: mean age 3.6 years; 56% male
- Steinsbekk et al, 2005 (RCT): Patients with URTI; Intervention group: mean age 3.6 years; Control group: mean age 3.2 years; 41% male

Warts

- Kainz et al, 1996 (RCT): Patients with warts; Intervention group: mean age 8 years; Control group: mean age 9 years; gender not reported

Length of follow-up:	Outcome(s) measured:
• **Adenoid vegetation**: range from 3-4 months	• **Adenoid vegetation**: Need for adenoidectomy after 3 months of treatment; Size of adenoid vegetation; Symptom questionnaire; Adverse events
• **ADHD:** range from 6-18 weeks	• **ADHD:** PSQ, CCT, CGI-P; Adverse events
• **Asthma:** range from 6 months to 1 year	• **Asthma:** Intensity, frequency, duration of asthma attacks; Active quality of living subscale of Childhood Asthma Questionnaire; Adverse events
• **Acute otitis media:** 5 days or until improvement	• **Acute otitis media:** Symptom scores, treatment failures, presence of middle ear effusion; Adverse events
• **Conjunctivitis:** 3 days	• **Conjunctivitis:** Overall conjunctivitis severity score; Adverse events
• **Diarrhoea:** range from 3-5 days	• **Diarrhoea:** Number of days with diarrhoea, number of daily stools; Adverse events
• **Postoperative pain-agitation syndrome:** postoperative period	• **Postoperative pain-agitation syndrome:** Sedation of agitation 15 minutes after operation; Adverse events
• **URTI:** range from 12 weeks to 1 year	• **URTI:** Daily symptom scores, number of antibiotic treatment courses, adenoidectomies and tonsillectomies after 1 year follow up; Adverse events
• **Warts:** 8 weeks	• **Warts:** Number of responders (50% reduction in warts area); Adverse events

INTERNAL VALIDITY

Allocation:	Comparison of study groups:	Blinding:	Treatment/ measurement bias:	Follow-up (ITT):
Unclear for all included studies. Method for random sequence generation not specified	All included studies focused on homeopathy vs placebo in patients with a particular condition	Double-blind (all included studies)	Unclear for all included studies. Not specified by the authors	Unclear for all included studies. Not specified by the authors

Author-assessed quality of included studies:
Measure used: Jadad score
Jadad score 2 (3 RCTs); Jadad score 3 (1 RCT); Jadad score 4 (3 RCTs); Jadad score 5 (9 RCTs)

Overall quality assessment
Rating: 6/10 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed using the Jadad score and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were not stated

RESULTS

Adenoid vegetation:

- Overall: "homeopathic treatments were not effective for reducing the size of adenoid vegetations and preventing the need for adenoidectomy."

ADHD

- Overall: "Three RCTs tested homeopathic interventions for patients with ADHD. Two trials reported effects in favour of homeopathy for their respective main outcome measures, PSQ and CGI-P, compared with placebo. Another RCT reported no intergroup differences for CGI-P."

Asthma

- Overall: "Both RCTs reported no differences compared with placebo on several outcome measures, including the intensity, frequency and duration of asthma attacks."

Acute otitis media

- Overall: "A single RCT assessed patients with acute otitis media and reported a decrease in symptom scores compared with placebo as recorded by parent diaries. These data require independent replication."

Conjunctivitis

- Overall: "Single RCT conducted during a viral conjunctivitis epidemic assessed schoolchildren who were treated with Euphrasia 30C for 3 days. No significant difference was found in favour of homeopathy compared with placebo for preventing viral conjunctivitis."

Diarrhoea

- Overall: "Three RCTs which were similar in design and from the same research group, tested individualised homeopathy in acute childhood diarrhoea. Two RCTs reported effects in favour of homeopathy for the duration of diarrhoea and the number of unformed stools, whereas another RCT failed to show intergroup differences for these outcomes in its main analysis."

Postoperative pain-agitation syndrome

- Overall: "Patients were treated with standardised homeopathy as an adjunct to conventional premedication during surgical operations. This single RCT reported beneficial effects for postoperative agitation in children compared with placebo. These data require independent replication."

URTI

- Overall: "Two double-blind RCTs included patients aged 3-4 years. Neither of the studies reported significant differences compared with placebo for the main outcome measures."

Warts

- Overall: "A single RCT was identified for treating warts. It failed to demonstrate the effectiveness of individualised homeopathic treatment for reducing the size of warts."

Overall conclusion

"The evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition."

Individual study results

Trial (N) *Quality*	Intervention[a,b] (n)	Control (n)	Outcome	Results as reported in the systematic review
Adenoid vegetation				
Feuchter et al, 2001 N=97 *Jadad score 5*	Standardised homeopathy, material potencies, 3 months - Nux vomica D200 potency, 5 globules once at the start of the study - Okoubaka D3 potency, 15 globules daily before meals from the first day for 4 weeks - Tuberculinum D200 potency, 5 globules once 4 weeks after the start of the study - Barium iodatum D4 potency, 3 tablets daily before meals from weeks 4-8 - Barium iodatum, D6 potency, 3 tablets daily for 4 weeks from weeks 8-12 - Concomitant treatment: acute intercurrent diseases were treated homeopathically if possible so as not to	Placebo n=NR	Need for adenoidectomy after 3 months of treatment	No significant difference
			Adverse events	Main adverse events include acute inflammation of the middle ear (5H, 6P), influenza (4 both), acute tonsillitis (3H, 5P), cough (5H, none P), scarlet fever (2 both), rhinitis (2 both), digestive complaints (1 both)

	compromise the effect of homeopathic remedies n=NR			
Furuta et al, 2003 N=40 *Jadad score 4*	Standardised and individualised homeopathy, material potencies, 4 months, treatment regimen not reported - Agraphis nutans 6C potency - Thuya 6C potency - Adenoid 21C potency in addition to individualised remedies n=NR	Placebo n=NR	Size of adenoid vegetation	No significant difference
			Symptom questionnaire	No significant difference
			Adverse events	No adverse events
ADHD				
Strauss et al, 2000 N=20 *Jadad score 2*	Standardised homeopathy, material potencies, 2 months, treatment regimen not reported - Selenium-Homaccord (selenium in varying potencies of 10X, 15X, 30X and 200X and potassium phosphate in varying potencies of 2X, 10X, 30X and 200X) - Concomitant treatment: Methylphenidate (Ritalin in 10 patients) n=NR	Placebo n=NR	PSQ	Significant difference (P=0.01)
			CCT	"Intergroup differences for improvement compared with baseline for CCT" (P=NR)
Jacobs et al, 2005 N=43 *Jadad score 5*	Individualised homeopathy, 18 weeks, homeopathic remedies prescribed with no limit, doses and potencies not reported - 41 different remedies prescribed: Medorrhinum, Saccharum officinalis, Calcarea carbonica, Calcarea phosphorica, China officinalis, stramonium - Concomitant treatment: stimulant medications (5H; 4P) n=NR	Placebo n=NR	CGI-P	No significant difference
			Adverse events	No adverse events
Frei et al, 2005 N=62	Individualised homeopathy, material potencies, 6 weeks,	Placebo n=NR	CGI-P	Significant difference (P=0.048)

Jadad score 5	treatment regimen not reported - 17 different remedies prescribed, potencies between Q3 and Q42: Calcarea carbonica, sulphur, Chamomilla, Lycopodium, silica, Hepar-sulph., Nux vomica, China, Ignatia, Mercurius, Capsicum, Causticum, Hyoscyamus, phosphorous, phosphoric acid, sepia, Staphysagria n=NR		Adverse events	Main adverse events causing withdrawal were 1 increasing tics, 2 behavioural disorders, 1 reactive depression
Asthma				
Freitas et al, 1995 N=86 *Jadad score 4*	Standardised homeopathy, material potencies, 6 months - Blatta orientalis 6C potency, two globules delivered 3 times daily - Concomitant treatment: conventional asthma medicines (for prevention or crisis) n=NR	Placebo n=NR	Intensity of asthma attack	No significant difference
			Frequency of asthma attack	No significant difference
			Duration of asthma attack	No significant difference
White et al, 2003 N=93 *Jadad score 5*	Individualised homeopathy, potency not reported, 1 year - Various remedies in different potencies (no details reported). Homeopaths were free to practice in their usual way, combining homeopathic prescriptions with lifestyle suggestions and other advice - Concomitant treatment: β-Adrenergic inhalers (all patients), inhaled steroids (33H; 36P), sodium cromoglycate (6H; 2P), salbutamol nebules (1H) n=NR	Placebo n=NR	Active quality of living subscale of Childhood Asthma Questionnaire	No significant difference
			Adverse events	Main adverse events include exacerbation of eczema (4H, 2P0 and asthma (3 both), headache (3H), fever (1H), sickness (1H), rash (1P), depression and irritability (3P), sleeping difficulties (2P); 1 patients was withdrawn because of adverse events (cough, behaviour and sleeping disorders)
Acute otitis media				
Jacobs et al, 2001 N=75 *Jadad score 5*	Individualised homeopathy, non-material potencies, 5 days or until improvement - 8 different remedies in C30 potency; 4 most commonly used were Pulsatilla nigrans, Chamomilla, sulphur, Calcarea carbonica; 3-5	Placebo n=NR	Symptom scores	Significant difference ($P<0.05$)
			Treatment failures	No significant difference
			Presence of middle ear effusion	No significant difference
			Adverse events	None

	pellets 3 times daily - Concomitant treatment: Analgesics (10P; 5H) n=NR			
Conjunctivitis				
Mokkapatti, 1992 N=1306 *Jadad score 2*	Standardised homeopathy, non-material potencies, 3 days - Euphrasia 30C potency, a total amount of 5-6 pills - Concomitant treatment: not reported n=NR	Placebo n=NR	Overall conjunctivitis severity score	No significant difference
Diarrhoea				
Jacobs et al, 1993 N=34 *Jadad score 5*	Individualised homeopathy, non-material potencies, 3 days or until improvement - Various remedies in 30C potency (no details reported), 2 pills daily - Concomitant treatment: oral rehydration therapy, normal feeding; standard antiparasitic medication at the end of intervention if needed n=NR	Placebo n=NR	Number of days with diarrhoea	No significant difference
			Number of daily stools	No significant difference
Jacobs et al, 1994 N=92 *Jadad score 5*	Individualised homeopathy, non-material potencies, 5 days - 18 different remedies in 30C potency, one dose after every unformed stool: Podophyllum, Chamomilla, Arsenicum album, Calcarea carbonica, sulphur, Mercurius vivus, Pulsatilla, phosphorus, China, Gambogia, Aethusia, aloe, belladonna, Bryonia, Colchicum, Croton tiglium, Dulcamara, Nux vomica - Concomitant treatment: oral rehydration therapy, normal feeding; standard antiparasitic medication at the end of intervention if needed; 11 children were given antidiarrheal medication by their patents (6P; 5H) n=NR	Placebo n=NR	Number of days with diarrhoea	Significant difference (P=0.048)
			Number of daily stools	Significant difference (P<0.05)
			Adverse events	No adverse evnets
Jacobs et al, 2000 N=126 *Jadad score 5*	Individualised homeopathy, non-material potencies, 5 days - 19 different remedies in 30C potency, one dose after every unformed stool; 5 most	Placebo n=NR	Number of days with diarrhoea	Significant difference (P=0.04)
			Number of daily stools	Significant difference (P=0.02)

	commonly listed: Podophyllum, sulphur, Arsenicum album, Calcarea carbonica, Chamomilla - Concomitant treatment: oral rehydration therapy, normal feeding; standard antiparasitic medication at the end of intervention, if needed n=NR			
Postoperative pain-agitation syndrome				
Alibeu and Jobert, 1990 N=50 *Jadad score 2*	Standardised homeopathy, potency not reported, postoperative period - Aconite, dose not reported, dose not reported, administered at least once, to be repeated as many times as necessary - Concomitant treatment: Halothane (1.5%), nitric oxide, Alimemazine (1 mg/kg), methohexital (25 mg/kg intrarectally) n=NR	Placebo n=NR	Sedation of agitation 15 minutes after operation	Significant difference (P<0.05)
URTI				
de Lange et al, 1994 N=170 *Jadad score 3*	Individualised homeopathy, material potencies, 1 year - Remedies in various potencies, mainly D6, D30 and D200 (remedies not reported). Homeopathic medicines and follow up prescriptions were based on the clinical course - Concomitant treatment: adequate nutrition advice, antibiotics, adenoidectomy, tonsillectomy if needed n=NR	Placebo n=NR	Daily symptom scores	No significant difference
			Number of antibiotic treatment courses	No significant difference
			Adenoidectomies and tonsillectomies after 1 year follow up	No significant difference
Steinsbekk et al, 2005 N=251 *Jadad score 5*	Standardised homeopathy, non-material potencies, 12 weeks - Calcarea carbonica, Pulsatilla, sulfur in C30 potency; 2 pills 2 days per week. In addition, 1 pill up to once every hour if the child had an acute episode of URTI but reduce the intake if the URTI was mild or when there was an improvement - Concomitant treatment:	Placebo n=NR	Total daily symptom score	No significant difference
			Adverse events	"Mild and transient" adverse events in 4P, 9H.

	antibiotics, painkiller/antipyretic drugs if needed n=NR			
Warts				
Kainz et al, 1996 N=60 *Jadad score 4*	Individualised homeopathy, material potencies, 8 weeks - 10 different remedies were preselected: sulfur 12X potency, Calcium carbonicum 30X potency, Natrium muriaticum 30X potency, sepia 12X potency, Causticum 12X potency, Staphysagria 12X potency, Thuja 12X potency. Globuli 12X potency were administered once a day; globuli 30X potency every other day n=NR	Placebo n=NR	Number of responders (50% reduction in warts area)	No significant difference
			Adverse events	Main adverse events include thrombosis of a capillary hemangioma (1P), exacerbation (1 both)
EXTERNAL VALIDITY				
Generalisability: Participants in the included RCTs were children and/or adolescents of variable age. The location of the included studies was not specified				
Comments: None				

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CCT, Children's Checking Task; CGI-P, Conners' Global Index-Parent; H, homeopathy; ITT, intention-to-treat; NR, not reported; P, placebo; PSQ, Conners' Parent Symptom Questionnaire; RCT, randomised controlled trial; URTI, upper respiratory tract infection

[a] Standardised homeopathy indicates the same remedy for all patients. Individualised homeopathy indicates remedies that best match the symptom picture of a patient

[b] Material potencies are dilutions above Avogadro's number. Non-material potencies are dilutions below Avogadro's number

Citation: Altunc U, Pittler MH, Ernst E (2007) Homeopathy for childhood and adolescence ailments: Systematic review of randomized clinical trials. Mayo Clin Proc 82(1):69-75.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**6/10**	

STUDY DETAILS				
Reference: Baranowsky J, Klose P, Musial F, Hauser W, Dobos G, Langhorst J (2009) Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia. Rheumatol Int 30(1):1-21.				
Affiliation/source of funds: NR Conflicts of interest: NR				
Study design: Systematic review of 1 RCT		Level of evidence: Level I	Location/setting: NR	
Intervention: Individualised homeopathy		Comparator(s): Placebo (oral daily liquid)		
Sample size: Included trial recruited 62 participants				
Population characteristics: Fibromyalgia patients				
Length of follow-up: 4 months		Outcome(s) measured: TP count, TP pain on palpation, McGill pain ratings, appraisal of FM quality of life scale, POMS, global health self-rating, treatment helpfulness rating		
INTERNAL VALIDITY				
Allocation: Randomised – method of randomisation not clear	Comparison of study groups: Limited patient characteristics provided. All FM patients.	Blinding: Double-blind	Treatment/ measurement bias: NR	Follow-up (ITT): NR
Author-assessed quality of included studies: Quality evaluated according to 16 formal criteria – included study scored 57.5/100				
Overall quality assessment Rating: 5/10 according to the AMSTAR criteria Description: Comprehensive literature search (six databases searched); no information about duplicate study selection and data extraction; limited information about patient characteristics (age, sex, disease severity, etc) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was considered when drawing conclusions; publication bias and conflict of interest were not discussed.				
RESULTS				
Overall: • Significant improvement in active group in TPC and TP pain on palpation, appraisal of FM scores, global health ratings and helpfulness of treatment as compared to placebo group • **Homeopathy is a promising option in the treatment of fibromyalgia, although further studies are needed to confirm the findings**				
Individual study results				
Trial (N) *Quality*[b]	Intervention	Control	Outcome	Results as reported in the systematic review
Bell 2004 N=62 *57.5/100*	Individually prescribed homeopathic remedies of daily oral liquid, flexibly dosed LM potencies[a]	Placebo (oral daily liquid)	TPC	Significant improvement in active group compared to placebo; p-value NR
			TP pain on palpation	Significant improvement in active group compared to

				placebo; p-value NR
			McGill pain ratings	NR
			FM quality of life scores	Significant improvement in active group compared to placebo; p-value NR
			POMS	NR
			Global health self-rating	Significant improvement in active group compared to placebo; p-value NR
			Treatment helpfulness rating	Significant improvement in active group compared to placebo; p-value NR
EXTERNAL VALIDITY				
Generalisability:				
Comments: Only one homeopathy study included in the review – the review was more broadly about complementary and alternative medicines for fibromyalgia. However the one included study yielded a significant improvement in favour of homeopathy over placebo on most outcome measures.				

Abbreviations: FM, fibromyalgia; ITT, intention-to-treat; NR, not reported; POMS, Profile of Mood States scale; RCT, randomised controlled trial; TP, tender point; TPC, tender point count.

[a] Homepaths were permitted to change prescription after a homeopathic visit at 2 months

[b] Scored out of 100 according to 16 formal criteria

Citation: Baranowsky J, Klose P, Musial F, Hauser W, Dobos G, Langhorst J (2009) Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia. Rheumatol Int 30(1):1-21.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**5/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Barnes J, Resch KL, Ernst E (1997) Homeopathy for postoperative ileus?: A meta-analysis. J Clin Gastroenterol 25(4):628-33.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: not reported
Conflicts of interest: not reported</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 7 RCTs</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
Various</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy (6 RCTs); NR (1 RCT)</td><td colspan="3">Comparator(s):
Placebo (5 RCTs); Opium 15C + Raphanus sativus 5C (1 RCT); NR (1 RCT)</td></tr>
<tr><td colspan="2">Sample size (intervention arm): The number of patients enrolled in the intervention arm of the RCTs ranged from 10 to 150</td><td colspan="3">Sample size (control arm): The number of patients enrolled in the control arm of the RCTs ranged from 10 to 150</td></tr>
<tr><td colspan="5">Population characteristics:
All studies enrolled patients who had undergone abdominal or gynaecologic surgery in order to treat postoperative ileus</td></tr>
<tr><td colspan="2">Length of follow-up: NR (7 RCTs)</td><td colspan="3">Outcome(s) measured:
Time to first flatus; time to first faeces; number of patients who passed flatus on a particular postoperative day[a]</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: All studies randomised – method of allocation/concealment was not clear</td><td>Comparison of study groups: NR</td><td>Blinding: NR</td><td>Treatment/ measurement bias: NR</td><td>Follow-up (ITT): NR</td></tr>
<tr><td colspan="5">Author-assessed quality of included trials:
Method used: Quality scoring system described by Kleijnen et al. A score of ≥55 indicates a study of higher quality
Quality of six studies included in meta-analysis: 20, 50, 58, 75, 80, 90.</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 6/11 according to the AMSTAR criteria
Description: Comprehensive literature search (ten databases searched); no information about duplicate study selection and data extraction; limited information about patient characteristics (age, sex, disease severity, etc) was provided; meta-analysis conducted but some studies excluded to minimise heterogeneity; scientific quality of included trials was considered when drawing conclusions; publication bias was discussed but no graphical aids included; conflict of interest was not discussed</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall
Of the six studies included in the meta-analysis, five reported a “positive” effect for homeopathy compared with placebo on the time to first flatus. One study reported “no effect” for homeopathy on that measure.
Two of four studies reported a significant reduction in time to first faeces in the homeopathy versus placebo groups; one study reported a non-significant trend towards a reduction in mean time to first faeces of 20 hours in the homeopathy-treated group; one study reported no difference between homeopathy and placebo
Statistically significant (p<0.05) weighted mean difference (WMD) in favour of homeopathy (compared with placebo) on the time to first flatus
No significant difference between homeopathic remedies ≥12C versus placebo (p>0.05) on the time to first flatus; significant difference in favour of homeopathic remedies <12C versus placebo (p<0.05) WMD.
Excluding methodologically weak trials did not substantially change any of the results
There is some evidence to support the administration of a homeopathic remedy immediate after surgery to reduce the duration of ileus. However, there is no evidence to support the use of a particular homeopathic remedy or for a combination of remedies</td></tr>
</table>

- The authors acknowledge that their overall result could be a false-positive due to inherent flaws in the original studies and the meta-analysis

Individual study results

Trial (N) *Quality*[b]	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Castelin 1979 *Quality: 20/100* N=20	*Opium* 15C (n=10)	Placebo (unmedicated granules) (n=10)	Time to first flatus (mean, SD) (hr)	Intervention group: 24.9 (8.6); Control group: 34.8 (14.2)
			Time to first faeces (mean, SD) (hr)	Intervention group: 83.7 (21.6); Control group: 110.8 (37.1)
Valero 1981 *Quality: 80/100* N=80	*Raphanus sativus* 7C (n=37)	Placebo (unmedicated granules) (n=43)	Time to first flatus (mean, SD) (hr)	Intervention group: 53.3 (25.02); Control group: 58.6 (22.27)
Chevrel 1984 *Quality: 58/100* N=96	*Opium* 15C (n=50)	Placebo (unmedicated granules) (n=46)	Time to first flatus (mean, SD) (hr)	Intervention group: 42.65 (21.87); Control group: 52.01 (21.96)
			Time to first faeces (mean, SD) (hr)	No significant inter-group differences. Intervention group: 78.2 (30.5); Control group: 99.9 (37.9).
Aulagnier 1985 *Quality: 75/100* N=200	*Opium* 9C + *Arnica Montana* 9C + *Raphanus sativus* 9C (n=100)	Placebo (unmedicated granules) (n=100)	Time to first flatus (mean, SD) (hr)	Intervention group: 59.28 (21.36); Control group: 76.08 (30)
			Time to first faeces (mean, SD) (hr)	Intervention group: 96.96 (34.08); Control group: 117.12 (38.4)
GRECHO 1989 *Quality: 90/100* N=NR	*Opium* 15C	*Opium* 15C + *Raphanus sativus* 5C (n=150)	Time to first flatus (mean, SD) (hr)	Intervention group: 54.2 (24.7); Control group: 52.3 (26.8)
			Time to first faeces (mean, SD) (hr)	Intervention group: 96.2 (39.8); Control group: 94.4 (40.7)
	Opium 15C + *Raphanus sativus* 5C	*Opium* 15C + *Raphanus sativus* 5C (n=150)	Time to first flatus (mean, SD) (hr)	Intervention group: 54.8 (26.1); Control group: 56.6 (26.3)
			Time to first faeces (mean, SD) (hr)	Intervention group: 98.8 (42); Control group: 95.4 (23.7)
Dorfman 1992 *Quality: 50/100* N=80	*China regia* 5C + *Arnica montana* 9C + *Raphanus sativus* 5C (n=40)	Placebo (drops – alcohol diluted in water) (n=40)	Time to first flatus (mean, SD) (hr)	Intervention group: 46.5 (23.5); Control group: 62 (28)
Estrangin 1979	NR	NR	NR	NR

Meta-analysis

Outcome:	n	Measure of effect	Effect size	p-value	95% CI
Time to first flatus (relative to placebo) – *all studies*	776	WMD	-7.4 hours	<0.05	-4.0, -10.8
Time to first flatus (relative to placebo) – *excluding low*	676	WMD	-6.11 hours	<0.05	-2.31, -9.91

quality studies					
Time to first flatus, homeopathic remedy of <12C potency (relative to placebo	660	WMD	-6.6 hours	<0.05	-2.6, -10.5
Time to first flatus, homeopathic remedy of ≥12C potency (relative to placebo	416	WMD	-3.1 hours	ns	-7.5, 1.3
EXTERNAL VALIDITY					
Generalisability: Due to the range of homeopathic treatments used, it could be argued that the studies were not homogenous and should not have been pooled for meta-analysis, meaning that the overall treatment effect cannot be attributed to any particular homeopathic remedy.					
Comments: Results are potentially affected by retrieval bias, selection bias (for studies included in the meta-analysis) and/or publication bias.					

Abbreviations: ITT, intention-to-treat; NNT, number needed to treat; NR, not reported; ns, not significant; SD, standard deviation; WMD, weighted mean difference

Note: Homeopathic remedies of <12C potency are dilutions likely to contain molecules of the "mother tincture"; remedies of ≥12C potency are "immaterial dilutions" that are unlikely to contain even a single molecule of the original compound.

Abbreviations: WMD, weighted mean difference

[a] The study by Estrangin was excluded from the meta-analysis, as the results were expressed in an inappropriate form for meta-analysis. The results were reported as the number of patients who passed flatus on a particular postoperative day, and therefore there was no accurate indication of time to first flatus

[b] Based on quality scoring system described by Kleijnen et al (a score of ≥55 indicates a study of higher quality)

Citation: Barnes J, Resch KL, Ernst E (1997) Homeopathy for postoperative ileus?: A meta-analysis. J Clin Gastroenterol 25(4):628-33.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
	✓	Can't answer
		Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**6/11**	

<table>
<tr><th colspan="3">STUDY DETAILS</th></tr>
<tr><td colspan="3">Reference: Bellavite P, Marzotto M, Chirumbolo S, Conforti A (2011) Advances in homeopathy and immunology: a review of clinical research. Front Biosci (Schol Ed) 3:1363-89.
Ref ID: 492</td></tr>
<tr><td colspan="3">Affiliation/source of funds: The study was financed by a grant from Boiron Laboratories (Milano) to University of Verona and in part by the Italian Ministry of University Research.
Conflicts of interest: The authors declared that they have no competing interests</td></tr>
<tr><td>Study design:
Systematic review of 50 RCTs, and 12 non-randomised, controlled trials (CTs). The therapeutic areas included in the systematic review are:
• Infections of upper airways and ear-nose-throat ailments (19 RCTs; 7 CTs)
• Respiratory allergies (18 RCTs; 3 CTs)
• Arthrorheumatic diseases and osteoarthritis (13 RCTs; 2 CTs)</td><td>Level of evidence:
Level I/III</td><td>Location/setting:
France (1 RCT); Israel (1 RCT); NR (48 RCTs; 12 CTs)</td></tr>
<tr><td>Intervention:
Infections of upper airways and ear-nose-throat ailments
Homeopathy – including 4 homeopathic regimens used for prophylaxis of upper respiratory conditions (19 RCTs; 7 CTs)

Respiratory allergies
Homeopathy (18 RCTs; 3 CTs)

Arthrorheumatic diseases and osteoarthritis
Homeopathy (12 RCTs; 2 CTs); Homeopathy + NSAIDS (1 RCT)</td><td colspan="2">Comparator(s):
Infections of upper airways and ear-nose-throat ailments
Placebo (11 RCTs); Aspirin (2 RCT); Allopathy (antibiotics, secretolytics, antipyretics, mucolytics) (5 CTs; 1 RCT); Anti-inflammatory agents (1 CT); Xylometazoline (1 CT); NR (4 RCTs); parent-selected medicines (1 RCT)

Respiratory allergies
Placebo (15 RCTs); Chromolyn sodium (1 RCT); Placebo + allopathy (1 RCT); NR (1 RCT); Conventional therapy (3 CTs)

Arthrorheumatic diseases and osteoarthritis
Placebo (7 RCTs); Placebo or fenoprofen (1 RCT); Placebo + NSAIDS (1 RCT); Hyaluronic acid (1 RCT); Acetaminofen (1 RCT); piroxicam gel (1 RCT); Conventional treatment (1 RCT); COX-2 inhibitors (1 CT); Salicylate + placebo (1 CT)</td></tr>
<tr><td colspan="3">Sample size:
Infections of upper airways and ear-nose-throat ailments
The number of patients enrolled ranged from 30 to 478 in the RCTs and from 126 to 1,557 in the CTs

Respiratory allergies
The number of patients enrolled ranged from 19 to 164 in the RCTs and from 12 to 178 in the CTs

Arthrorheumatic diseases and osteoarthritis
The number of patients enrolled ranged from 24 to 172 in the RCTs and from 195 to 592 in the CTs.</td></tr>
<tr><td colspan="3">Population characteristics:
Infections of upper airways and ear-nose-throat ailments
Patients with:
• Acute rhinitis/ nasal obstruction
• Chronic rhinitis</td></tr>
</table>

<table>
<tr><td colspan="2">
• Upper respiratory tract infections
• Influenza-like syndrome
• Acute or chronic sinusitis
• Pharyngitis and/or tonsillitis
• Common cold and cough
• Otitis media
• Chemotherapy-associated stomatitis who had undergone stem cell transplantation
• Maxillary sinusitis
• Aphthous ulcer
• Oral lichen planus

Respiratory allergies
Patients with:
• Allergic oculorhinitis
• Allergic asthma
• Allergic rhinitis

Arthrorheumatic diseases and osteoarthritis
Patients with:
• Rheumatoid arthritis
• Hip and/or knee osteoarthritis
• Fibromyalgia
• Chronic polyarthritis
• Ankylosing spondylitis
• Back pain
</td></tr>
<tr><td>
Length of follow-up:
Infections of upper airways and ear-nose-throat ailments
Of the studies that reported on length of follow up the durations ranged from 4 days to 4 months

Respiratory allergies
Of the studies that reported on length of follow up the durations ranged from 1 to 12 months

Arthrorheumatic diseases and osteoarthritis
Of the studies that reported on length of follow up the durations ranged from 4 weeks to 12 months
</td><td>
Outcome(s) measured:
Infections of upper airways and ear-nose-throat ailments
Symptoms severity score; symptoms; temperature shivering and myalgia; physician's judgment of the therapy; global evaluation; healing rate at 48 hours after diagnosis based on rectal temperature and two of the following symptoms: headache, stiffness, lumbar pain, articular ache, shivering; rhinomanometry; functional tests; frequency, duration and severity of rhinitis, pharingytis episodes; duration of pain and therapy; healing or major improvement after 14 days of treatment, adverse effects; treatment failure; stomatitis development and scores; prevention of new episodes; pain and ulcer size; pain and lesion size; quality of life; number of episodes during 6 months before and after treatment

Respiratory allergies
Symptoms (VAS); eye and nose symptoms; respiratory tests; spirometry parameters and immunological markers; general assessment; attack intensity; use of allopathic drugs, laboratory and spirometric tests; quality-of-life questionnaire; nasal air flux tests; symptoms scores; expiration flux (FEV); costs

Arthrorheumatic diseases and osteoarthritis
Medical assessment; pain and articular index; symptoms; pain symptoms; clinical measurement and general medical assessment; inflammation markers, functional indexes, allopathic drugs consumption, general assessment; pain during motion (subjective scores), tolerability; motion tenderness (VAS); questionnaire on arthritis; arthritis index;
</td></tr>
</table>

<table>
<tr><td colspan="2"></td><td colspan="3">articular index; symptoms scores; quality of life; Fibromyalgia Impact Questionnaire (FIQ)</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: Randomised, method of allocation/concealment not specified (50 RCTs); non-randomised, controlled, method of allocation not clear (10 CTs)</td><td>Comparison of study groups: NR</td><td>Blinding:
Double blind (40 RCTs)
Non-blinded (10 RCTs)
NR (12 CTs)</td><td>Treatment/ measurement bias: NR</td><td>Follow-up (ITT): NR</td></tr>
<tr><td colspan="5">Author assessed quality of included studies:
NR</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 5/10 according to the AMSTAR criteria</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
Infections of upper airways and ear-nose-throat ailments
Good positive evidence[b]
• Individualised homeopathy in otitis. Positive evidence from one RCT, three non-randomised controlled studies, and two non-randomised, non-controlled studies
• Anas barbariae 200K in therapy of influenza like-syndromes. Positive evidence from three RCTs. Little effect demonstrated in one review (Vickers and Smith 2009)
• Euphorbium compositum in rhinitis-sinusitis. Positive evidence from one RCT, one non-randomised, controlled study, and two non-randomised, non-controlled studies
Unclear or conflicting evidence[c]
• Individualised homeopathy in upper respiratory tract infections. Positive evidence from one RCT, three non-randomised, controlled trials and two non-randomised, non-controlled trials; Little evidence from one RCT; No evidence from one RCT
Negative scientific evidnece[d]
• Homeopathic complex: Luffa + Cinnabaris + Kalium Bichromicum. No evidence from one RCT

Respiratory allergies
Strong positive evidence[a]
• Galphimia glauca (low homeopathic dilutions) in allergic oculorhinitis. Positive evidence from six RCTs
Good positive evidence[b]
• Individualised homeopathy in allergic rhinitis and asthma. Positive evidence from two RCTs, four non-randomised, controlled studies, and two non-randomised, non-controlled studies; No evidence from one RCT
Unclear or conflicting evidence[c]
• Homeopathic immunotherapy of allergic rhinitis and asthma. Positive evidence from six RCTs and one non-randomised, non-controlled study; No evidence from four RCTs and one non-randomised, non-controlled study

Arthrorheumatic diseases and osteoarthritis
Good positive evidence[b]
• Individualised homeopathy in fibromyalgia. Positive evidence from three RCTs and one review; Positive but insufficient evidence from one review
• Zeel compositum-N in osteoarthritis. Positive evidence from one RCT, one non-randomised, controlled trial, and one review
Unclear or conflicting evidence[c]
• Individualised homeopathy in rheumatoid arthritis. Positive evidence from one RCT and one non-randomised, controlled trial. No evidence from two RCTs</td></tr>
</table>

Negative scientific evidence[d] • *Arnica, Rhus tox, Bryonia* 6C in fibromyalgia. No evidence from one RCT • *Rhus toxicodendron* 6C in osteoarthritis. No evidence from one RCT • *Formica rufa* 6X in ankylosing spondylitis. No evidence from one RCT				
Individual study results				
Trial (N) *Quality*	Intervention	Comparator	Outcome	Results as reported in the systematic review
Acute rhinitis				
Gassinger et al 1981 N=53 *Quality not specified*	*Eupatorium perfoliatum* 2x	Aspirin	Symptom severity score	Equivalence between homeopathy and allopathy
Maiwald 1988 N=170 *Quality not specified*	Homeopathic complex *Grippheel*	Aspirin	Symptom severity score	Equivalence between homeopathy and allopathy
Schmiedel and Klein 2006 N=397 *Quality not specified*	Homeopathic complex *Engystol*	Conventional treatment (antihistamines, antitussives, and nonsteroidal anti-inflammatory drugs)	Patient-reported improvement within 3 days	Significant benefit in homeopathy group ($p<0.05$). Homeopathy group: 77.1%; Conventional treatment group: 61.7%
			General and local symptoms	Homeopathic medicine equivalent to the conventional treatment
Upper respiratory tract infections				
Lecoq 1985 N=60 *Quality not specified*	Homeopathic complex *L52*	Placebo	Symptom severity score	Patients rated more relief in verum group
Rabe et al 2004 N=485 *Quality not specified*	Homeopathic complex *Grippheel*	Anti-inflammatory agents	Symptoms	Equivalence between homeopathy and allopathy
Steinsbekk et al 2005 N=169 *Quality not specified*	Individualised homeopathy	Conventional care	Symptom score	Decrease of days with symptoms in homeopathic group
Steinsbekk et al 2005 N=251 *Quality not specified*	Parents-selected homeopathic medicines	Placebo	Prevention of new episodes, symptoms score	No effectiveness of homeopathy over placebo
Steinsbekk et al 2007 N=208 *Quality not specified*	Individualised homeopathy	Parents-selected medicines	Prevention of new episodes, symptoms scores	No difference between the two methods of prescription
Haidvogl et al 2007 N=1,557 *Quality not specified*	Homeopathic strategy	Allopathic (e.g. anti-inflammatory drugs, antibiotics)	Healing or major improvement after 14 days of treatment	Homeopathic treatment not inferior to allopathic treatment and best tolerated
Cough				
Bordes and Dorfman 1986 N=60 *Quality not specified*	Low-dilution (3C) homeopathic complex in syrup (*Drosera*)	Placebo	Number of patients with significant reduction or disappearance of	Homeopathy group: 20/30 patients (66.67%); Placebo group: 8/30 patients

			symptoms after one week	(26.67%). No level of significant reported.
Influenza-like syndrome				
Papp et al 1998 N=372 *Quality not specified*	*Oscillococcinum* (*Anas barbariae* 200k) 1 dose, 3 times per day for 3 days	NR	Evaluation of symptoms after treatment	Statistically significant reduction of symptoms after 48 hours in the verum group
Casanova and Gerard 1988 N=300 *Quality not specified*	*Oscillococcinum* (*Anas barbariae* 200K), one dose in the morning and one dose in the evening for 3-4 days	NR	Temperature shivering and myalgia	In the verum group: faster temperature reduction, significantly less shivering and less myalgia after 4 days
Ferley et al 1989 N=478 *Quality not specified*	*Oscillococcinum* (*Anas barbariae* 200k) 5 doses, one every 12 hours	NR	Healing rate at 48 hours after diagnosis based on rectal temperature and two of the following symptoms: headache, stiffness, lumbar pain, articular ache, shivering	Clinical healing after 48 hours and rate of temperature reduction better in the verum group
Sinusitis				
Wiesenauer et al 1989 N=152 *Quality not specified*	Low-dilution (3x-4x) homeopathic complex *Luffa, Cinnabaris, Kalium bichromicum*	Placebo	Global evaluation and symptoms	No effect over placebo
Weiser and Clasen 1994 N=155 *Quality not specified*	*Euphorbium compositum*	Placebo	Overall percentage improvement	Significantly greater improvement in homeopathy group (21.1%) compared to placebo (14.4%); p=0.016
Zabolotnyi et al 2007 N=113 *Quality not specified*	Homeopathic complex *Sinfrontal*	Placebo	Symptoms	Significant improvement over placebo
Common cold and flu				
Heilmann 1994 N=102 *Quality not specified*	*Engystol-N* i.v. injection	Placebo	Symptoms	No change in frequency of attacks; decrease of symptoms and their duration
Pharyngitis and tonsillitis				
de Lange et al 1994 N=170 *Quality not specified*	Individualised homeopathy	Placebo	Mean number of infective episodes	No significant inter-group differences. Homeopathy group: 7.9/year; Placebo group: 8.4/year
			Percentage of children not requiring	Homeopathy group: 62%; Placebo group:

			antibiotics	49%. Significance of results not reported.
Otitis media				
Friese et al 1997 N=131 *Quality not specified*	Individualised homeopathy	Allopathy (antibiotics, mucolytics, antipyretics)	Mean duration of pain	No significant inter-group differences. Homeopathy group: 3 days; Placebo group: 4 days
Kruse 1998 N=126 *Quality not specified*	Individualised homeopathy	Allopathy (antibiotics, secretolytics, antipyretics and nasal sprays)	Duration of pain and therapy	"Equivalent efficacy" (3 days in homeopathy group; 4 days in allopathy group)
			Recurrence	No significant difference (70.7% in the homeopathy group; 64% in the allopathy group)
Jacobs et al 2001 N=75 *Quality not specified*	Individualised homeopathy	Placebo	Treatment failure (5 days, 2 weeks, 6 weeks)	Less failure in verum group, non-significant
			Diary symptom scores	Significant decrease in symptoms in verum group compared to placebo ($p<0.05$) at 24 and 64 hours
Respiratory tract or ear complains				
Riley et al 2001 N=456 *Quality not specified*	Individualised homeopathy	Allopathy	Healing or major improvement after 14 days of treatment	Homeopathy group: 82.6%; Allopathy group: 68%. Significance of results not reported
			Rate of adverse events	Homeopathy group: 7.8%; Allopathy group: 22.3%. Significance of results not reported
Chemotherapy-associated stomatitis				
Oberbaum et al 2001 N=32 *Quality not specified*	Homeopathic complex *Traumeel-S*	Placebo (local therapy with mouth rinsing)	Percentage of patients who did not develop stomatitis	Homeopathy group: 33%; Allopathy group: 7%. Significance of results not reported
			Mean AUC of stomatitis scores	Significant difference between groups ($p<0.01$). Homeopathy group: 10.4; Placebo group: 24.3.
Rhinitis and sinusitis				
Ammerschlager et al 2005	Low-dilution homeopathic complex	Xylometazoline	Disease specific symptoms; tolerability	Equivalent efficacy. Clinically relevant

N=739 *Quality not specified*	formulation *Euphorbium compositum* (nasal spray)			reductions observed in both groups. Non-inferiority of the homeopathic complex shown for all studied variables.
Aphthous ulcer				
Mousavi et al 2009 N=100 *Quality not specified*	Individualised homeopathy	Placebo	Pain and ulcer size	Significant improvement after 4-6 days of treatment
Oral lichen planus				
Mousavi et al 2009 N=30 *Quality not specified*	*Ignatia* 30c	NR	Pain and lesion size	Significant improvement after 4 months of treatment
Allergic oculorhinitis/hay fever				
Hardy 1984 N=70 *Quality not specified*	Homeopathic immunotherapy (H.I.T.) made with house dust potencies	Placebo	Symptoms	H.I.T. better than placebo
Wiesenauer and Gaus 1985 N=164 *Quality not specified*	*Galphimia glauca* 6x dynamised	Placebo (e *Galphimia glauca* 6x non-dynamised)	Eye and nose symptoms	Trend to better improvement in the homeopathic group; not statistically significant; less symptoms in patients taking dynamized verum medicine than other groups
Reilly et al 1986 N=144 *Quality not specified*	*Pollens* 30c (H.I.T.)	Placebo	Symptoms (VAS)	H.I.T. better than placebo
Wiesenauer and Ludtke 1987 N=132 *Quality not specified*	*Galphimia* 2c	Placebo	Eye and nose symptoms	Significantly less eye symptoms in verum group
Wiesenauer and Ludtke 1995 N=115 *Quality not specified*	*Galphima* 4x	Placebo	Eye and nose symptoms	Significant relief in verum group
Micciche et al 1998 N=70 *Quality not specified*	Homeopathic protocol based on three low-dilution drugs	Conventional therapy (anti-histaminic and cortisone treatment)	General assessment	Trend to better improvement in the homeopathic group
Allergic asthma				
Campbell et al 1990 and Reilly et al 1994 N=28 *Quality not specified*	Allopathy + allergen 30c (H.I.T.)	Allopathy + placebo	Symptoms (VAS) and respiratory tests	Less symptoms in the verum group than placebo, no differences in tests
Matusiewicz 1995-1997 N=40 *Quality not specified*	Homeopathic complex *Engystol-N*	Placebo	Respiratory tests	Clinical improvement only in verum group

Lara-Marquez et al 1997 N=19 *Quality not specified*	Individualised homeopathy	Placebo	Symptoms, spirometry parameters and immunological markers	Verum better than placebo, significant changes of laboratory markers
Riveron-Garrote et al 1998 N=80 *Quality not specified*	Individualised homeopathy	Placebo	General symptoms and attack intensity	Higher reduction of asthma attacks in verum group
Matusiewicz et al 1999 N=146 *Quality not specified*	Homeopathic complex *Asthma H Inj. Plfugerplex*, subcutaneously	Placebo	Use of allopathic drugs, laboratory and spirometric tests	Slight decrease of conventional medication and infections; no change in spirometric tests
Lewith et al 2002 N=242 *Quality not specified*	Allergen (dust mite) 30c	Placebo H.I.T.	Symptoms (VAS) and expiration flux (FEV)	No final therapeutic effect, initial aggravation
Li et al 2003 N=12 *Quality not specified*	H.I.T. prepared from individual allergen	Placebo	Spirometric tests	No improvement after treatment
Allergic rhinitis				
Weiser et al 1999 N=146 *Quality not specified*	Low dilution homeopathic complex formulation *Luffa compositum*	Standard intranasal therapy based on cromolyn sodium	Symptoms and quality-of-life questionnaire	Equivalence of homeopathy and allopathy
Taylor et al 2000 N=50 *Quality not specified*	Individual allergen	Placebo (H.I.T.)	Symptoms (VAS) and nasal air flux tests	Slightly better outcomes in verum group
Aabel et al 2000 N=66 *Quality not specified*	Homeopathic birch pollen *Betula* 30c	Placebo	Symptoms scores	Slightly less symptoms during 10 days; aggravation after taking verum
Aabel 2000 N=73 *Quality not specified*	Homeopathic birch pollen *Betula* 30c	Placebo	Symptoms (VAS)	Verum significantly worse than placebo
Aabel 2001 N=51 *Quality not specified*	Homeopathic birch pollen *Betula* 30c	Placebo	Symptoms (VAS)	Similar improvement in verum and placebo
Kim et al 2005 N=40 *Quality not specified*	H.I.T. prepared from individual allergen	Placebo	Symptoms, quality-of-life questionnaires	Better clinical changes in verum group as compared with placebo
Asthma				
White et al 2003 N=96 *Quality not specified*	Individualised homeopathy	Placebo	Quality-of-life questionnaires, symptoms and tests	No changes in quality of life, small not significant improvement of symptoms in verum group
Allergic diseases including rhinitis and asthma				
Witt et al 2005 N=178	Classic homeopathy	Conventional care	Symptoms, quality-of-life questionnaires,	Better outcomes in homeopathic group

Quality not specified			costs	
Rheumatoid arthritis				
Gibson et al 1978 N=195 *Quality not specified*	Individualised homeopathic prescription	Salicylate and placebo	Medical assessment	Better relief in the homeopathic group compared to the allopathic and placebo. High incidence of drop-out
Gibson et al 1980 N=46 *Quality not specified*	Individualised homeopathic prescription	Placebo	Improvement in symptoms (spontaneous pain, stiffness in the joint, prensile strength)	Homeopathy group: 83%; Placebo group: 22%. Significance of results not reported
Andrade et al 1991 N=44 *Quality not specified*	Individualised homeopathic prescription	Placebo	Overall improvement assessed by physicians	Homeopathy group: 59%; Placebo group: 44%. Significance of results not reported
Fisher and Scott 2001 N=112 *Quality not specified*	NSAIDS + individualised homeopathic prescription	NSAIDS + placebo	Pain and articular index	No effect of homeopathy over the placebo
Osteoarthritis				
Shipley et al 1983 N=36 *Quality not specified*	*Rhus toxicodendron* 6x	Placebo and fenoprofen	Symptoms	No effect of homeopathy versus placebo; fenoprofen better than homeopathy and placebo
Nahler et al 1996 N=114 *Quality not specified*	*Zeel compositum-N*	Hyaluronic acid, intrarticular injection	Pain during motion (subjective scores), tolerability	Equivalence of the homeopathic complex and hyaluronic acid
Shealy et al 1998 N=65 *Quality not specified*	Complex homeopathic formulation – *Rhus toxicodendron, Causticum,* and *Lac vaccinum*	Acetaminofen	Motion tenderness (VAS)	Equivalence of homeopathic and allopathic medicines
van Haselen and Fisher 2000 N=172 *Quality not specified*	Local application of a homeopathic gel	Piroxicam gel	Pain reduction (VAS)	No significant inter-group differences. Homeopathy group: 16.5mm; Control group: 8.1mm
Birnesser et al 2003 N=592 *Quality not specified*	*Zeel compositum-N*	COX-2 inhibitors	Symptoms scores	Equivalence of homeopathic and allopathic medicines
Fibromyalgia				
Fisher 1986 N=24 *Quality not specified*	*Arnica, Rhus tox, Bryonia* 6c	Placebo	Pain symptoms	Trend to better improvement in the homeopathic group, not statistically significant

Fisher et al 1989 N=30 *Quality not specified*	*Rhus tox* (individualised)	Placebo	Pain symptoms	Slightly positive therapeutic effect in most patients in the verum group versus placebo
Bell et al 2004 N=62 *Quality not specified*	Individualised homeopathic prescription	Placebo	Pain, motion tenderness, quality of life	Significantly better outcomes of the homeopathy group vs the placebo
Relton et al 2009 N=47 *Quality not specified*	Individualised homeopathic prescription	Conventional treatment	Fibromyalgia Impact Questionnaire	Better reduction of symptoms in patients treated with homeopathy vs control; no adverse effects
Chronic polyarthritis				
Wiesenauer and Gaus 1991 N=111 *Quality not specified*	Homeopathic preparation *'Rheumaselect'*	Placebo	Inflammation markers, functional indexes, allopathic drugs consumption, general assessment	Slightly better outcomes in the verum group
Anklosing spondylitis				
Schirmer et al 2000 N=104 *Quality not specified*	Intramuscular treatment with a combination of low homeopathic potencies of *Formica rufa* and the patient's own blood	Placebo (injection of saline)	Questionnaire on arthritis and general physician assessment	No difference compared to placebo
EXTERNAL VALIDITY				
Generalisability:				
Comments:				

Note: Individual homeopathy interventions are commonly one of the following remedies: *Aconitum, Apis, Belladonna, Calcium carbonicum, Capsicum, Chamomilla, Lachesis, Phosphorus, Pulsatilla, Silicea, Sulphur, Lycopodium*

Abbreviations: AUC, area under curve; FEV, forced expiratory volume; H.I.T, homeopathic immunotherapy; NR, not reported; VAS, visual analogue scale.

[a] significant evidence of a clear benefit from >2 properly randomised trials, or from one properly conducted meta-analysis on homogenous trials

[b] statistically significant evidence of a benefit from 1-2 properly randomised trials, or evidence of benefit from at least 1 randomised trial plus >1 observational cohort/case-control/non-randomised trial

[c] conflicting evidence from multiple trials or observational studies without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness

[d] statistically significant negative evidence (i.e., lack of evidence of benefit) from 1 or more randomised trials or >1 non-randomised trials

Citation: Bellavite P, Marzotto M, Chirumbolo S, Conforti A (2011) Advances in homeopathy and immunology: a review of clinical research. Front Biosci (Schol Ed) 3:1363-89. Ref ID: 492		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**5/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Cooper KL, Relton C (2010) Homeopathy for insomnia: a systematic review of research evidence. Sleep Med Rev 14(5):329-37.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: Not reported
Conflicts of interest: Not reported</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 4 RCTs</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
Brazil (1 RCT); France (1 RCT); Germany (1 RCT); South Africa (1 RCT)</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy (4 RCTs)</td><td colspan="3">Comparator(s):
Placebo (4 RCTs)</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 29 to 96.</td></tr>
<tr><td colspan="5">Population characteristics:
Patients with severe insomnia (1 RCT); patients with insomnia who had received low-dose benzodiazepines for ≥3 months; mean age: 54 years (1 RCT); patients with difficulties falling asleep or staying asleep. Both groups had an average of 8 hours sleep per night at baseline; age range: 19-73 (1 RCT); people with insomnia >1 year, with difficulty in falling asleep due to nervous excitability and flow of ideas. Patients taking medication for insomnia were excluded; mean age: 32-33 years (1 RCT)</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: range – 1 month to 90 days (45 days per treatment)</td><td colspan="3">Outcome(s) measured:
Sleep duration; sleep latency; sleep quality; clinical evaluation by homeopaths; improvement, or no change in symptoms on Clinical Global Impression Improvement scale; proportion of patients reporting improvement; night waking; improvement in sleep patterns; daytime fatigue</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
Adequate concealment of allocation (2 RCTs); allocation method NR (1 RCT); poor/inadequate randomisation – patients chose a homeopathic or placebo bottle (1 RCT)</td><td>Comparison of study groups:
NR</td><td>Blinding:
Double-blind (4 RCTs)</td><td>Treatment/ measurement bias: Most studies did not use the ITT population for analyses</td><td>Follow-up (ITT): ITT analysis (1 RCT); analysis only included patients with full follow-up data (59%) (1 RCT); 36% excluded from analysis due to violation of entry criteria, 31% of remaining participants withdrew from treatment (1 RCT); one participant (3%) not included in main analysis (1 RCT)</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: Standard appraisal form based on criteria recommended by the Centre for Reviews and Dissemination
Quality: scores of individual included studies were not reported</td></tr>
<tr><td colspan="5">Overall quality assessment</td></tr>
</table>

Rating: 7/10 according to the AMSTAR criteria
Description: Comprehensive literature search (twelve databases searched); study selection and data extraction was conducted by two independent researchers; sufficient information about patient characteristics (age, disease severity, etc) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was considered when drawing conclusions; publication bias and conflict of interest were not discussed.

RESULTS

Overall:

- **The limited evidence available does not demonstrate a statistically significant effect of homeopathic medicines for insomnia treatment**
- Two studies showed a trend towards better outcomes in the homeopathy group, however the differences were non-significant
- Major flaws existed in the RCTs in terms of concealment of allocation, accrual of participants to sufficiently power the studies, and reporting of statistical differences (eg. in one studies it was unclear whether the p-values referred to differences between groups or from baseline, in another the p-values were misinterpreted).
- All four RCTs involved small patient numbers, with the largest reporting a lack of statistical power due to accrual difficulties. The included RCTs were poorly reported with high patient withdrawal rates

Individual study results

Trial (N) *Quality*	Intervention	Control	Outcome	Results as reported in the systematic review
Carlini 1987 N=44 *Quality not specified*	Individualised homeopathic medicine (agreed by 2 homeopaths)	Placebo	Sleep duration	Both groups showed significant improvement from baseline to Day 15 and at all timepoints until 3 months. No significant difference between patients starting on intervention or placebo
			Sleep latency	Both groups showed significant improvement from baseline to Day 15 and at all timepoints until 3 months. No significant difference between patients starting on intervention or placebo
			Sleep quality	Both groups showed significant improvement from baseline to Day 15 and at all timepoints until 3 months. No significant difference between patients starting on

				intervention or placebo
			Clinical evaluation by a homeopath	Both groups showed significant improvement from baseline to Day 15 and at all timepoints until 3 months. No significant difference between patients starting on intervention or placebo
Cialdella 2001 N=96 *Quality not specified*	Formulaic homeopathic medicines: Homeogene-46[a] or Sedatif-PC[b]	Placebo	Proportion of patients completing the study and showing improvement or no change in symptoms at 1 month	No significant intergroup differences. Homeogene-46: 10/15 (67%); Sedatif-PC: 12/20 (60%); Placebo 13/36 (50%)
			Proportion of patients preferring: (i) study treatment (ii) prior BZD treatment (iii) no treatment/other treatment/no preference	Homeopathy groups: (i) 33% (ii) 30% (iii) 37% Placebo group: (i) 19% (ii) 38% (iii) 43%
			Number of patients requesting a return to BZD treatment	No significant difference between patients in the homeopathy compared to placebo groups
			Clinical Global Impression Improvement scale	No significant difference between patients in the homeopathy compared to placebo groups
Wolf 1992 N=29 *Quality not specified*	Formulaic homeopathic medicine: Requiesan[c]	Placebo	Patient- reported improvement	No significant difference between groups, although a higher proportion of patients in the homeopathy group reported improvement (n=8/14; 57%) compared to the placebo group (n=4/14; 29%)
			Increase in sleep time	No significant difference between

				groups, although the homeopathy group had an increase of 30 minutes, and the placebo group had no change
			Decrease in sleep latency (baseline; 1 month)	Both groups experienced significant decreases from baseline (homeopathy: 1 hour to 30 minutes; placebo: 30 minutes to 20 minutes), although no significant inter-group differences were reported.
			Sleep quality – measure not specified	Both groups experienced significant improvement from baseline; no significant inter-group differences were reported
			Night waking	Both groups experienced significant improvement from baseline to 1 month; no significant inter-group differences were reported
Kolia-Adam 2008 N=30 *Quality not specified*	Formulaic homeopathic medicine: *Coffea cruda* 200c	Placebo	Increase in sleep duration compared to baseline	Significant improvement compared to baseline (homeopathy: 38 minutes, p=0.003; placebo: 35 minutes, p=0.007). No significant inter-group differences were reported
			Improvement in sleep pattern	Both groups experienced a significant improvement from baseline. No inter-group differences reported
EXTERNAL VALIDITY				

Generalisability:
Comments:

Abbreviations: BZD, benzodiazepines; ITT, intention-to-treat; N/A, not applicable; NR, not reported; RCT, randomised controlled trial; UC, uncontrolled.

[a] contains Stramonium 3DH, Hyoscyamus niger 3DH, Passiflora incarnata 3DH, Ballota foetida 3DH and Nux moschata 4CH

[b] contains Aconitum napellus 6CH, Belladonna 6CH, Calendula officinalis 6CH, Abrus precatorius 6CH, Chelidonium majus 6CH and Viburnum opulus 6CH

[c] contains two herbal medicines: California sleep poppy (Radix Eschscholzia californica) and green oats (Avena sativa), and two homeopathic medicines: Coffea D3 and Arnica D3

[d] contains Passiflora incarnata D2, Avena sativa D2, Coffea arabica D12 and Zincum isovalerianicum D4.

Citation: Cooper KL, Relton C (2010) Homeopathy for insomnia: a systematic review of research evidence. Sleep Med Rev 14(5):329-37.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**7/10**	

<table>
<tr><th colspan="3">STUDY DETAILS</th></tr>
<tr><td colspan="3">Reference: Cucherat M, Haugh MC, Gooch M, Boissel JP (2000) Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials. Eur J Clin Pharmacol 56(1):27-33.</td></tr>
<tr><td colspan="3">Affiliation/source of funds: The Commission of the European Communities
Conflicts of interest: not reported</td></tr>
<tr><td>Study design:
Systematic review of 16 RCTs (Level II). The therapeutic conditions covered are:
• Boils and pyoderma (1 RCT)
• Dystocia (1 RCT)
• Acute hay fever (1 RCT)
• Post-surgery ileus (1 RCT)
• Acute ankle sprains (1 RCT)
• Influenza-like syndrome (2 RCTs)
• Post-operative pain agitation (1 RCT)
• Knee joint haematoma (1 RCT)
• Burns (1 RCT)
• Rheumatoid arthritis (1 RCT)
• Headache (1 RCT)
• Acute childhood diarrhoea (1 RCT)
• Allergic asthma (1 RCT)
• Chronic sinusitis (1 RCT)
• Bronchitis (1 RCT)</td><td>Level of evidence:
Level I</td><td>Location/setting:
NR (all included studies)</td></tr>
<tr><td>Intervention:
Homeopathy regimen specified by authors (13 RCTs)
Individualised homeopathy (3 RCTs)</td><td colspan="2">Comparator(s):
Placebo (10 RCTs)
Identically prepared globules or ointment base but without active constituent (4 RCTs)
Intraarticular injections of sodium chloride (1 RCT)
Vaseline (1 RCT)</td></tr>
<tr><td colspan="3">Sample size:
The number of patients enrolled in the RCTs ranged from 34 to 478. The number of patients evaluated in the RCTs ranged from 34 to 462</td></tr>
<tr><td colspan="3">Population characteristics:
• Patients with boils and pyoderma (Mossinger 1980)
• Patients with dystocia (Couldert 1981)
• Patients with acute hay fever (Reilly 1986)
• Patients with post-surgery ileus (Grecho 1988)
• Patients with acute ankle sprains (Zell 1988)
• Patients with influenza-like syndrome (Ferley 1989; Papp 1998)
• Patients with post-operative pain agitation (Alibeu 1990)
• Patients with knee joint haematoma (Thiel 1991)
• Patients with 2nd and 3rd degree burns (Lievre 1992)
• Patients with rheumatoid arthritis (Gaus 1993)
• Patients with headache (Whitmarsh 1993)
• Patients with acute childhood diarrhoea (Jacobs 1994)
• Patients with allergic asthma (Reilly 1994)
• Patients with chronic sinusitis (Weiser and Clasen 1994)
• Patients with bronchitis (Diefenbach 1997)</td></tr>
<tr><td colspan="2">Length of follow-up:
NR in 13 RCTs. Of the 3 RCTs that did report on length of follow</td><td>Outcome(s) measured:
Boils and pyoderma: healing time</td></tr>
</table>

<table>
<tr><td colspan="3">up, the times ranged from 15 minutes (post-operative pain agitation) to 48 hours (influenza-like syndrome)</td><td colspan="3">Dystocia: success within 2 hours
Acute hay fever: VAS of overall symptom intensity
Post-surgery ileus: delay to the first stool
Acute ankle sprain: composite criteria of treatment success
Influenza-like syndrome: recovery rate within 48 h of treatment; multiple endpoint: rate of patients affected and duration of disease
Post-operative pain agitation: sedation within 15 minutes
Knee joint haematoma: joint mobility
Burns: composite criteria of treatment success
Rheumatoid arthritis: composite criteria of treatment success
Headache: change in mean attach frequency over the course of the trial
Acute child diarrhoea: duration of diarrhoea
Allergic asthma: VAS of overall symptom intensity
Chronic sinusitis: cumulative score
Bronchitis: length of productive cough</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
Unclear for all included RCTs. Method for random sequence allocation not specified</td><td>Comparison of study groups:
All of the RCTs focused on homeopathy vs placebo in patients with a particular condition</td><td>Blinding:
Double-blind (15 RCTs); Open-blind (1 RCT for burns)</td><td>Treatment/ measurement bias:
Unclear for all included studies. Not specified by authors.</td><td>Follow-up (ITT):
Loss to follow up was reported for all included studies</td></tr>
<tr><td colspan="6">Author-assessed quality of included studies:
Quality of included studies was not formally assessed by the authors. The authors noted that “the only criterion for quality used for selection was adequate concealment of treatment allocation (by a suitable randomisation method).”</td></tr>
<tr><td colspan="6">Overall quality assessment
Rating: 10/11 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. The status of publication was used as an inclusion criterion. A list of included and excluded studies was provided. Characteristics of the included studies were reported. Scientific quality of the included studies was not formally assessed but the “overall low quality of the trial designs and reporting” was considered in formulating conclusions. The results of findings were pooled and assessed using the weighted sum of Zs. The likelihood of publication bias was assessed. Conflicts of interest were not stated</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td colspan="6">Pooled P values obtained from all eight methods investigated for the 17 comparisons
• Weighted sum Z: P value (two tailed) 0.000036
• Mean P: P value (two tailed) 1.7x10^-6
• Mean Z: P value (two tailed) 7.8x10^-8
• Logit: P value (two tailed) 8.7x10^-12
• Sum log: P value (two tailed) 4.7x10^-12
• Sum Z: P value (two tailed) 5.9x10^-12
• Sum t: P value (two tailed) 3.2x10^-13
• Count: P value (two tailed) 2.8x10^-29</td></tr>
</table>

Overall:

- "From the available evidence, it is likely that among the tested homeopathic treatments tested at least one shows an added effect relative to placebo. The meta-analysis method used does not allow any conclusion on what homeopathic treatment is effective in which diagnosis or against which symptoms."
- "There is some evidence that homeopathic treatments are more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies. Further high quality studies are needed to confirm these results."
- "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."

Individual study results

Trial (N=no. randomised/no. evaluated) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Boils and pyoderma				
Mossinger 1980 N=NR/46 *Quality not assessed*	Hepar sulfuris calcareum D4 n=NR	Placebo n=NR	Healing time	No significant difference (P=0.318)
Dystocia				
Couldert 1981 N=34/34 *Quality not assessed*	Caulophyllum 5 °C n=NR	Placebo n=NR	Success within 2 hours	Significant difference in favour of homeopathy (P=0.00055)
Acute hay fever				
Reilly 1986 N=158/102 *Quality not assessed*	Fixed, mixed grass pollens 30 °C n=NR	Placebo n=NR	VAS of overall symptom intensity	Significant difference in favour of homeopathy (P=0.018)
Post-surgery ileus				
Grecho 1988 N=300/300 *Quality not assessed*	Opium 15 °C n=NR	Identically prepared globules but without active constituent n=NR	Delay to the first stool	No significant difference (P=0.699)
	Raphanus 15 °C and Opium 15 °C n=NR	Identically prepared globules but without active constituent n=NR	Delay to the first stool	No significant difference (P=0.358)
Acute ankle sprains				
Zell 1988 N=NR/69 *Quality not assessed*	Traumel ointment n=NR	Ointment base without active constituent n=NR	Composite criteria of treatment success	Significant difference in favour of homeopathy (P=0.028)
Influenza-like syndrome				
Ferley 1989 N=478/462 *Quality not assessed*	Fixed, Oscillococcinum n=NR	Placebo n=NR	Recovery rate within 48 hours of treatment	Significant difference in favour of homeopathy (P=0.032)
Papp 1998 N=372/334 *Quality not assessed*	Oscillococcinum n=NR	Placebo n=NR	Multiple endpoint: rate of patients affected and duration of disease	Significant difference in favour of homeopathy (P=0.0257)

Post-operative pain agitation				
Alibeu 1990 N=50/47 *Quality not assessed*	Aconit 4 °C n=NR	Placebo n=NR	Sedation within 15 minutes	Significant difference in favour of homeopathy (P=0.002)
Knee joint haematoma				
Thiel 1991 N=80/73 *Quality not assessed*	Intraarticular Traumel R n=NR	Intraarticular injections of sodium chloride n=NR	Joint mobility	Significant difference in favour of homeopathy (P=0.026)
2nd and 3rd degree burns				
Lievre 1992 N=103/103 *Quality not assessed*	Calendula n=NR	Vaseline n=NR	Composite criteria of treatment success	No significant difference (P=0.147)
Rheumatoid arthritis				
Gaus 1993 N=176/176 *Quality not assessed*	Rheumaselect n=NR	Placebo n=NR	Composite criteria of treatment success	Significant difference in favour of homeopathy (P=0.018)
Headache				
Whitmarsh 1993 N=64/NR *Quality not assessed*	Individualised homeopathy n=NR	Placebo n=NR	Change in mean attack frequency over the course of the trial	No significant difference (P=0.83)
Acute childhood diarrhoea				
Jacobs 1994 N=92/81 *Quality not assessed*	Individualised homeopathy n=NR	Placebo n=NR	Duration of diarrhoea	Significant difference in favour of homeopathy (P=0.048)
Allergic asthma				
Reilly 1994 N=28/24 *Quality not assessed*	Individualised homeopathic immunotherapy n=NR	Identically prepared globules but without active constituent n=NR	VAS of overall symptom intensity	Significant difference in favour of homeopathy (P=0.003)
Chronic sinusitis				
Weiser and Clasen 1994 N=172/155 *Quality not assessed*	Euphorbium compositum S nasal spray n=NR	Placebo n=NR	Cumulative score	Significant difference in favour of homeopathy (P=0.016)
Bronchitis				
Diefenbach 1997 N=258/209 *Quality not assessed*	Bronchiselect n=NR	Placebo n=NR	Length of productive cough	No significant difference (P=0.86)

Assessment of pooled results using the weighted sum of Zs		
Class	No. of trials	Combined 2-tailed *P* value
Randomised, blind or open	17	0.000036
Randomised, double-blind	16	0.000068

Randomised, double-blind with less than 10% of lost to follow up	9	0.0084
Randomised, double-blind with less than 5% of lost to follow up	5	0.082
Individualised treatment	3	0.021
Fixed preparation	14	0.00011
EXTERNAL VALIDITY		
Generalisability: The age of participants within the included RCTs was not reported by the systematic reviewers		
Comments:		

Abbreviations: ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; VAS, visual analogue scale.

Citation: Cucherat M, Haugh MC, Gooch M, Boissel JP (2000) Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials. Eur J Clin Pharmacol 56(1):27-33.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	✓	Yes
		No
		Can't answer
		Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**10/11**	

<table>
<tr><th colspan="3">STUDY DETAILS</th></tr>
<tr><td colspan="3">Reference: Davidson JRT, Crawford C, Ives JA, Jonas WB (2011) Homeopathic treatments in psychiatry: A systematic review of randomized placebo-controlled studies. J Clin Psychiatry 72(6):795-805.</td></tr>
<tr><td colspan="3">Affiliation/source of funds: Project was partially supported by an award from the United States Army Medical Research Acquisition Activity.
Conflicts of interest: Dr Davidson has received consulting fees from AstraZeneca and Euthymics Bioscience and royalties from the Davison Trauma Scale, Social Phobia Inventory, Connor-Davidson Resilience Scale, Guilford Publication, and American Psychiatric Press.</td></tr>
<tr><td>Study design:
Systematic review of 25 RCTs. The therapeutic areas included in the systematic review are:
• Anxiety or stress-related conditions (6 RCTs)
• Sleep or circadian rhythm disturbances (5 RCTs)
• Premenstrual problems (PMS) (4 RCTs)
• Attention-deficit/hyperactivity disorder (ADHD) (3 RCTs)
• Mild traumatic brain injury (TBI) (1 RCT)
• Functional somatic syndromes (6 RCTs)</td><td>Level of evidence:
Level I</td><td>Location/setting:
Various</td></tr>
<tr><td>Intervention:
Anxiety or stress-related conditions
Homeopathy (6 RCTs)

Sleep or circadian rhythm disturbances
Homeopathy (5 RCTs)

Premenstrual problems (PMS)
Homeopathy (4 RCTs)

Attention-deficit/hyperactivity disorder (ADHD)
Homeopathy (3 RCTs)

Mild traumatic brain injury (TBI)
Homeopathy (1 RCT)

Functional somatic syndromes
Homeopathy (6 RCTs)</td><td colspan="2">Comparator(s):
Anxiety or stress-related conditions
Placebo (5 RCTs); Placebo or cognitive-behavioural therapy (CBT) (1 RCT)

Sleep or circadian rhythm disturbances
Placebo (5 RCTs)

Premenstrual problems (PMS)
Placebo (4 RCTs)

Attention-deficit/hyperactivity disorder (ADHD)
Placebo (3 RCTs)

Mild traumatic brain injury (TBI)
Placebo (1 RCT)

Functional somatic syndromes
Placebo (6 RCTs)</td></tr>
<tr><td colspan="3">Population characteristics:
Patients with:
• Generalised Anxiety Disorder (GAD) (2 RCTs)
• Test anxiety (2 RCTs)
• High trait anxiety (1 RCT)
• Job-related burnout (1 RCT)
• Severe snoring (1 RCT)
• Insomnia (2 RCTs)
• Jet lag (1 RCT)
• Shift lag in night shift workers (1 RCT)
• PMS (4 RCTs)
• ADHD (3 RCTs)
• Mild TBI (1 RCT)
• Fibromyalgia (3 RCTs)
• Chronic Fatigue Syndrome (CFS) (3 RCTs)</td></tr>
</table>

Length of follow-up: **Anxiety or stress-related conditions** Range: 4 days to 10 weeks **Sleep or circadian rhythm disturbances** Range: 24 hours (per treatment, cross-over design) to 4 weeks **Premenstrual problems (PMS)** Range: 3 months to 6 months **Attention-deficit/hyperactivity disorder (ADHD)** Range: 6 weeks (per treatment, cross-over design) to 18 weeks **Mild traumatic brain injury (TBI)** 4 months **Functional somatic syndromes** Range: 4 weeks (per treatment arm, cross-over design) to 12 months	Outcome(s) measured: **Anxiety or stress-related conditions** HARS; BAI; PPQ; RTA; STAI(T); STAI(S); sleep; pulse; feelings of anxiety; thought interference; MBI subscales **Sleep or circadian rhythm disturbances** Snoring daily score; sleep diary; SII; DBAS; POMS-Fatigue; POMS-Vigor; CAVT, IIQ; hours of sleep; sleep satisfaction; change in sleep pattern **Premenstrual problems (PMS)** Rate of response; MDQ; each item on MDQ; PAF **Attention-deficit/hyperactivity disorder (ADHD)** Conners Global Index-Parent; CPSQ; CCT **Mild traumatic brain injury (TBI)** MANOVA for FA **Functional somatic syndromes** VAS pain; VAS sleep; number of tender spots; analgesic use; global response; 5 MFI scales (general fatigue, physical fatigue, mental fatigue, reduced activity, reduced motivation); tender point pain on palpation; tender point count; MAP; MSP; AF; CFS-Q; F-VAS

INTERNAL VALIDITY

Allocation: In all studies participants were randomised, but the method of allocation was not reported	Comparison of study groups: NR	Blinding: All 25 RCTs were double-blinded	Treatment/ measurement bias: NR	Follow-up (ITT): High drop-out/withdrawal rates in many studies – ITT vs per protocol analysis unclear

Author-assessed quality of included studies:
Method used: Scottish Intercollegiate Guidelines Network (SIGN) quality analysis
Quality: 10 RCTs were deemed to be 'poor' quality; 9 RCTs were 'fair'; 6 RCTs were 'good'

Overall quality assessment
Rating: 8/10 according to the AMSTAR criteria
Description: Comprehensive literature search (six databases searched); limited information about patient characteristics (age, sex, disease severity, etc) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was not discussed in detail; a funnel plot was created to examine the likelihood of publication bias; affiliations and source of funds were acknowledged

RESULTS

Overall:

- No support for efficacy of homeopathy in anxiety- or stress-related conditions. Only one study showed significant on a sleep measure
- There is mixed evidence for sleep- and circadian rhythm-related problems. Two studies (with relatively high scores on GRADE evaluation) yielded predominantly positive results. However they addressed different conditions, so it is difficult to generalise positive results to the whole clinical area

- Little evidence of efficacy of homeopathy for premenstrual problems, other than in one study with a small sample size
- Mixed results for ADHD
- Weakly positive results in favour of homeopathy for mild TBI
- All except one of the six FSS studies yielded positive evidence that homeopathy was superior to placebo and that one was one of the smallest and methodologically weakest
- **Results do not preclude the possibility of some benefit – Efficacy was found for the functional somatic syndromes group (fibromyalgia and chronic fatigue syndrome), but not for anxiety or stress. For other disorders, homeopathy produced mixed effects**

Individual study results				
Trial *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Generalised anxiety disorder				
Bonne et al 2003 *Fair quality*	Individualised homeopathy (n=22)	Placebo (n=22)	Rate of response	No statistically significant difference between treatment groups ("results unlikely to be different with a larger sample size"). Homeopathy group: 40%; Control group: 42%
Ngobese 2006 *Fair quality*	Individualised homeopathy (n=14)	Placebo (n=13) or cognitive-behavioural therapy (CBT) (n=14)	HARS, BAI, PPQ	No significant difference "A proven treatment for GAD, cognitive therapy, failed to work; study can be regarded as a "failed" study rather than a negative study for homeopathy. In other words, it is not informative. Length of treatment may have been inadequate".
Test anxiety				
Baker et al 2003 *Fair quality*	*Argentum nitricum* (n=21[a])	Placebo (n=41[a])	RTA	Results favoured placebo (weak ES)
Traub 2000 *Poor quality*	Combined 3-remedy product (n=14[a])	Placebo (n=18[a])	Unclear	No effect on the total scores of the primary measures. Weak evidence for homeopathy on scale items
High trait anxiety				
McCutcheon 1996 *Fair quality*	Combined 9-remedy product (n=38)	Placebo (n=39)	STAI(T), STAI(S), sleep, pulse	Mixed results; significant improvement on sleep, but no benefit on state anxiety

Job-related burnout				
Vaithilingam 2005 *Poor quality*	Individualised homeopathy (n=14[a])	Placebo (n=16[a])	MBI subscales	Homeopathy worse than placebo on depersonalisation scale of MBI
Severe snoring				
Lipman et al 1999 *Fair quality*	Combined 9-remedy product (n=44[a])	Placebo (n=46[a])	Snoring daily score	Statistically significant difference favouring homeopathy. Homeopathy group: 80%; Control group: 46%; p<0.001
			Global rating	NNT: 2.95
Insomnia				
Naude et al 2010 *Fair quality*	Individualised homeopathy (n=16)	Placebo (n=17)	Sleep diary	Benefit for homeopathy (p<0.05)
			SII	Effect size (95% CI): 2.40 (1.46, 3.34). Benefit for homeopathy (p<0.0001)
			DBAS	No significant difference between treatment arms
Kolia-Adam combined publication 2008 *Poor quality*	*Coffea cruda* 200C (n=15)	Placebo (n=15)	Unclear	"Rate of response": homeopathy 33%; placebo 50%. Significance not reported
			Hours of sleep	No significant difference between treatment groups. Effect size (95% CI): 0.24 (-0.53, 1.02)
			Sleep satisfaction	No significant difference between treatment groups. NNT: -5.99 (placebo was more effective)
			Change in sleep pattern	No significant difference between treatment groups
Jet lag				
Kumar 2010 *Poor quality*	Combined multiple remedy product (n=23)	Placebo (n=23)	POMS-Fatigue	Results favour homeopathy (p<0.05) Effect size: 0.24
			POMS-Vigor	No significant difference between treatment arms. Inconsistently reported p-values; ambiguous, but results warrant further

				study Effect size: 0.17
Shift lag				
La Pine et al 2006 *Poor quality*	Combined 5-remedy product (n=34)	Placebo (n=34)	CAVT	No significant difference between treatment groups
			IIQ	No significant difference between treatment groups
			Fatigue	Effect size: 0.03 (-0.49, 0.56)
PMS				
Chapman et al 1994 *Fair quality*	Individualised homeopathy (n=5)	Placebo (n=5)	Rate of response	No significant difference between treatment groups. High placebo response rate. Homeopathy: 40%; Placebo: 60%
Yakir et al 2010 *Fair quality*	Individualised homeopathy (n=13)	Placebo (n=10)	MDQ	Suggestive of greater benefit for homeopathy, but small sample size
Laister 2008 *Good quality*	Individualised homeopathy (n=18)	Placebo (n=21)	MDQ	Homeopathic simillimum not effective in treating PMS
Kirtland 1994 *Poor quality*	*Folliculinum* 15C (n=16[a])	Placebo (n=15[a])	Each item on MDQ, PAF	Suggests an effect for homeopathy
ADHD				
Jacobs et al 2005 *Good quality*	Individualised homeopathy (n=22)	Placebo (n=21)	NR	Placebo tended to be better than homeopathy, but not significantly so
Frei et al 2005 *Good quality*	Individualised homeopathy (n=31)	Placebo (n=31)	NR	Results suggest effectiveness for homeopathy, particularly in behavioural and cognitive functions
Strauss 2000 *Poor quality*	Individualised homeopathy (n=10[a])	Placebo (n=10[a])	Unclear	Overall hyperactivity improved more on homeopathy than placebo; however effect was very weak
Mild TBI				
Chapman et al 1999 *Good quality*	Individualised homeopathy (n=33)	Placebo (n=28)	MANOVA for FA	Significant improvement favouring homeopathy
Fibromyalgia				
Fisher 1986	*Rhus toxicodendron,*	Placebo (n=12[a])	Pain (VAS)	Analysis gave

Poor quality	*Bryonia alba or Arnica montana* (n=12[a])			significant differences on pain for indicated remedy
			Sleep (VAS)	Analysis gave significant differences on sleep for indicated remedy
Fisher et al 1989 *Poor quality*	*Rhus toxicodendron* 6C (n=30[a])	Placebo (n=30[a])	Unclear	Positive results for homeopathy, especially on tender points
Bell et al 2004 *Good quality*	Individualised homeopathy (n=30)	Placebo (n=32)	25% improvement in tender point pain on palpation	Statistically significant difference between groups, favouring homeopathy. Homeopathy group: 50%; Placebo: 15%; (p<0.01)
			Tender point count	Significant improvement compared to placebo (p<0.05)
			MAP	Significant improvement compared to placebo (p<0.01)
			AF	Significant improvement compared to placebo (p<0.05)
			MSP	No significant difference between treatment arms
Chronic fatigue syndrome				
Awdry 1996 *Fair quality*	Individualised homeopathy (n=32)	Placebo (n=32)	Global response	Homeopathy group 43%; placebo group 4%. "Advantages seem evidence on many measures, but statistical analysis not carried out"
			NNT	2.49
Weatherley-Jones et al 2004 *Good quality*	Individualised homeopathy (n=53)	Placebo (n=50)	5 MFI scales: general fatigue, physical fatigue, mental fatigue, reduced activity, reduced motivation	Mixed results, but the most rigorous measure supports homeopathy – no further information provided
			Effect size (95% CI) and NNT based on	ES (95% CI): 0.40 (-0.03 to 0.83)

			Multidimensional Fatigue Inventory – fatigue	NNT: 6.14
			Effect size (95% CI) based on Multidimensional Fatigue Inventory – reduced motivation	ES (95% CI): -0.08 (-0.34 to 0.50)
Saul 2005 *Poor quality*	Individualised homeopathy (n=15[a])	Placebo (n=15)	CFS-Q; F-VAS	No benefit for homeopathy
EXTERNAL VALIDITY				
Generalisability:				
Comments: The authors state that a major limitation was an inability to provide information about major depression, which is such a large health problem worldwide				

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AF, Appraisal of Fibromyalgia; BAI, Beck Anxiety Inventory; CAVT, Computer Assisted Vigilance Test; CBT, cognitive-behavioural therapy; CCT, Children's Checking Test; CFS-Q, Chronic Fatigue Syndrome Questionnaire; CPSQ, Conners Parents Symptom Questionnaire; DBAS, Dysfunctional Beliefs About Sleep; ES, effect size; FA, Functional assessment; F-VAS, Fatigue Visual Analogue Scale; GAD, generalised anxiety disorder; HARS, Hamilton Anxiety Rating Scale; IIQ, Impact of Intervention Questionnaire; MANOVA, multivariate analysis of variance; MAP, McGill Affective Pain; MBI, Maslach Burnout Inventory; MDQ, Menstrual Distress Questionnaire; MSP, McGill Sensory Pain; NNT, number needed to treat; PAF, Premenstrual Assessment Form; PMS, premenstrual syndrome; POMS, Profile of Mood Score; PPQ, Patient Perception Questionnaire; RTA, Revised Test Anxiety Scale; SII, Severity of Insomnia Index; STAI(S), State Trait Anxiety Inventory (state); STAI(T), State Trait Anxiety Inventory (trait); TBI, traumatic brain injury; VAS, visual analogue scale

[a] Number of patients enrolled was not reported. The sample size refers to the number of patients who completed the study.

Citation: Davidson JRT, Crawford C, Ives JA, Jonas WB (2011) Homeopathic treatments in psychiatry: A systematic review of randomized placebo-controlled studies. J Clin Psychiatry 72(6):795-805.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**8/10**	

STUDY DETAILS		
Reference: De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (2010) Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: A systematic review. Rheumatology (UK) 49(6):1063-8.		
Affiliation/source of funds: Arthritis Research Campaign, Chesterfield, United Kingdom Conflicts of interest: The authors have declared no conflicts of interest		
Study design: Systematic review of 3 RCTs (Level II)	Level of evidence: Level I	Location/setting: NR in all included studies
Intervention: Homeopathy regimen specified by authors (2 RCTs) Individualised homeopathy (1 RCT)	Comparator(s): Placebo (all included studies)	
Sample size: The number of patients enrolled in the RCTs ranged from 24 to 62.		
Population characteristics: • Fisher et al 1989 (RCT): Patients with fibromyalgia; Only patients in whom *R. toxicodendron* was positively indicated after a homeopathic consultation were included • Fisher 1986 (RCT): Patients with fibromyalgia • Bell et al 2004 (RCT): Patients with fibromyalgia		
Length of follow-up: RCTs: ranged from 2-4 months	Outcome(s) measured: Tenderness; Pain; Sleep disturbance; Tender point pain; Tender point count; Quality of life; Global health; Depression	

INTERNAL VALIDITY				
Allocation: Unclear – method for random sequence generation not specified (3 RCTs)	Comparison of study groups: Homeopathy vs placebo in patients with fibromyalgia (3 RCTs)	Blinding: Unclear – not specified by the authors (3 RCTs)	Treatment/ measurement bias: Unclear – not specified by the authors (3 RCTs)	Follow-up (ITT): Unclear – not specified by the authors (3 RCTs)
Author-assessed quality of included studies: Method used: Jadad score. 1 RCT had a Jadad score of 1, 1 RCT had a Jadad score of 3, 1 RCT had a Jadad score of 5				
Overall quality assessment Rating: 7/10 according to the AMSTAR criteria Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided but there were no details on the characteristics of participants. Scientific quality of the included studies was assessed using the Jadad score and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were stated.				

RESULTS

Overall:

- "There was some evidence from three small studies regarding three different homeopathic approaches. Each demonstrated an improvement in pain in those receiving the standardised or individualised homeopathic remedy (compared with placebo) and two studies demonstrated improvement in sleep. While one of these trials received the lowest of all Jadad scores (Fisher 1986), another received the maximum score (Bell et al, 2004). The third study has been independently re-analysed and no firm support for the efficacy of homeopathic treatment as found".

Individual study results

Trial (N)	Intervention	Control	Outcome	Results as reported in

Quality				the systematic review
Fisher et al 1989 N=30 *Jadad score 3*	*R. toxicodendron* (6c potency) put up on 125 mg lactose taken three times per day. This was a cross-over study with treatment phases of 1 month each in random sequence	Placebo	Tenderness	"Homeopathic treatments significantly improved tenderness as assessed by VAS" (P<0.005)
			Pain	"Homeopathic treatments significantly improved pain as assessed by VAS" (P<0.005)
			Sleep disturbance	"Homeopathic treatments significantly improved sleep disturbance as assessed by VAS" (P<0.005)
Fisher 1986 N=24 *Jadad score 1*	One remedy from *Arnica montana*, *Bryonia alba* and *R. toxicodendron* (all of 6c potency). All the patients received the same treatment throughout a 3 month period	Placebo	Pain	Homeopathic treatments significantly improved pain compared with placebo as assessed by VAS (P<0.05)
			Sleep	Homeopathic treatments significantly improved sleep compared with placebo as assessed by VAS (P<0.05)
Bell et al 2004 N=62 *Jadad score 5*	Individually selected homeopathic remedy	Placebo	Tenderness	NR
			Tender point pain	Significant improvement in favour of homeopathy (P=NR)
			Tender point count	Significant improvement in favour of homeopathy (P=NR)
			Quality of life	Significant improvement in favour of homeopathy (P=NR)
			Global health	Significant improvement in favour of homeopathy (P=NR)
			Depression	Significant improvement in favour of homeopathy (P=NR)
EXTERNAL VALIDITY				
Generalisability: The age of participants within the included RCTs were not reported by the systematic reviewers. Location of the included studies was not reported.				
Comments: None				

Abbreviations: ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; VAS, visual analogue scale.

Citation: De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (2010) Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: A systematic review. Rheumatology (UK) 49(6):1063-8.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**7/10**	

STUDY DETAILS				
Reference: De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (2011) Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: A systematic review. Rheumatology (UK) 50(5):911-20.				
Affiliation/source of funds: Conducted on behalf of the Arthritis Research UK working group on complementary and alternative medicines Conflicts of interest: Not reported				
Study design: Systematic review including 3 RCTs		Level of evidence: Level I	Location/setting: Various	
Intervention: Homeopathy		Comparator(s): Paracetamol (1 RCT); Placebo or fenoprofen (1 RCT); Piroxicam gel (1 RCT)		
Sample size: The number of patients enrolled in the RCTs ranged from 36 to 184.				
Population characteristics: Patients with osteoarthritis (OA), specifically – knee OA (1 RCT); hip or knee OA (1 RCT); not specified (1 RCT)				
Length of follow-up: 4 weeks (1 RCT); NR (2 RCTS)		Outcome(s) measured: Reduction in knee pain; pain on movement; pain at rest		
INTERNAL VALIDITY				
Allocation: Random assignment – allocation methods not described (3 RCTs)	Comparison of study groups: Limited patient characteristics provided. All OA patients	Blinding: NR	Treatment/ measurement bias: NR	Follow-up (ITT): NR
Author-assessed quality of included studies: Methods used: Jadad score Quality: Median score 3				
Overall quality assessment Rating: 6/10 according to the AMSTAR criteria Description: Comprehensive literature search (seven databases searched); limited information about patient characteristics (age, sex, disease severity, etc) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was not discussed in detail; publication bias was discussed, although no graphical or statistical analyses were presented.				
RESULTS				
Overall: • **The evidence from the included studies is promising; however it is insufficient to draw any conclusions about the efficacy of homeopathy in OA.**				
Individual study results				
Trial (N) *Quality*[b]	Intervention	Control	Outcome	Results as reported in the systematic review
Shealy 1998 N=65 *Quality not specified*	Homeopathic preparation including *Rhus toxicodendron* 12x, Causticum 12x and Lac Vaccinum 12x)	Paracetamol 2.6g/day	Reduction in knee pain	No difference between homeopathic preparation and paracetamol
Shipley 1983 N=36 *Quality not specified*	*Rhus toxicodendron* 6x	Placebo *or* fenoprofen 600mg three times daily	Pain on movement	Homeopathy less effective than fenoprofen; no

				difference compared to placebo
			Pain at rest	Homeopathy less effective than fenoprofen; no difference compared to placebo
Van Haselen 2000 N=184 *Quality not specified*	Local application of 1g Spiroflor[a] gel three times daily for 4 weeks	1g piroxicam gel (0.5%) applied three times daily for 4 weeks	Level of pain reduction	No difference between the two treatment groups
EXTERNAL VALIDITY				
Generalisability:				
Comments: The information about the individual included trials was limited due to the fact that the SR was not solely focused on homeopathy and instead focused broadly on CAMs, providing limited scope for an in-depth homeopathy analysis.				

Abbreviations: CAM, complementary and alternative medicines; ITT, intention-to-treat; NR, not reported; OA, osteoarthritis; RCT, randomised controlled trial

[a] contains *Symphytum officinale, Rhus toxicodendron* and *Ledum palustre*

[b] Median Jadad score was 3

Citation: De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (2011) Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: A systematic review. Rheumatology (UK) 50(5):911-20.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
	✓	No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**6/10**	

STUDY DETAILS				
Reference: Ernst E, Barnes J (1998) Are homoeopathic remedies effective for delayed-onset muscle soreness: a systematic review of placebo-controlled trials (Structured abstract). Perfusion 11:4-8.				
Affiliation/source of funds: NR Conflicts of interest: NR				
Study design: Systematic review of 3 RCTs, including two designed as pilot studies; 5 controlled trials (CT) (randomisation not clear)		Level of evidence: Level I/III	Location/setting: Various	
Intervention: Homeopathy (3 RCTs; 5 CTs)		Comparator(s): Placebo (3 RCTs; 5 CTs)		
Sample size: The number of patients in the intervention arms ranged from 14 to 36		Sample size: The number of patients in the comparator arms ranged from 6 to 28		
Population characteristics: Healthy women with DOMS (5 CTs); healthy volunteers (either sex) with DOMS (2 RCTs); Oslo Marathon participants with DOMS (1 RCT)				
Length of follow-up: 5-7 days post exercise (5 CTs, 1 RCT); until cessation of soreness (2 RCTs)	Outcome(s) measured: Soreness intensity (rating scale) and duration; maximal isometric muscle strength; blood tests; serum CK concentrations; soreness intensity (VAS) and duration; mean muscle soreness during the 5 post-exercise days; symptom-free days; maximum soreness score; days to no soreness; days of no medication			
INTERNAL VALIDITY				
Allocation: Non-randomised, allocation method not clear (5 CTs). Randomised – allocation methods not clear (3 RCTs)	Comparison of study groups: 5 CTs only included female participants. There was wide variation between the types of exercise used to induce DOMS.	Blinding: Double-blind (5 CTs, 3 RCTs)	Treatment/ measurement bias: Five CTs not randomised	Follow-up (ITT): NR
Author-assessed quality of included studies: Method used: A pre-defined list of criteria (further details not specified) in which a score of ≥55 indicates studies of "higher quality" Quality: 38 (5 CTs); 60 (1 RCT); 85 (2 RCTs).				
Overall quality assessment Rating: 7/10 according to the AMSTAR criteria Description: Comprehensive literature search (four databases searched); limited information about patient characteristics was provided, with the exception of gender and type of exercise used to induce DOMS; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was discussed; neither publication bias nor conflict of interest were discussed.				
RESULTS				
Overall: • The partly positive findings in favour of homeopathy all came from small non-randomised trials and are open to bias • The three randomised trials all report statistically non-significant differences between the verum and placebo groups for all outcome measures • No convincing evidence that homeopathic remedies tested are superior to placebo				
Individual study results				
Trial *Quality*[a]	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Hildebrandt 1983a	*Rhus toxicodendron*	Placebo (n=14)	Soreness intensity	No significant inter-

Quality: 38	D4, 5x10 drops daily for 7 days post exercise (n=14)			group differences
			Soreness duration	No significant inter-group differences
			Maximal isometric muscle strength	Less decrease in muscle strength in homeopathy group compared to placebo; p-value NR
Hildebrandt 1983b *Quality: 38*	*Rhus toxicodendron* D4 (a) 1x50 drops daily, (b) 3x16 drops daily, (c) 5x10 drops daily, (d) 6x8 drops daily, for 7 days post exercise (n=26, 6 per dosing regimen)	Placebo (n=8)	Soreness intensity	NR
			Soreness duration	NR
			Maximal isometric muscle strength	Less decrease in muscle strength in homeopathic groups (a) and (d) compared to placebo; p-value NR
			Serum CK concentrations	NR
Hildebrandt 1983c *Quality: 38*	*Rhus toxicodendron* D4 (a) 1x5 drops daily, (b) 3x5 drops daily, (c) 5x10 drops daily, for 7 days post exercise (n=18, 6 per dosing regimen)	Placebo (n=6)	Soreness intensity	No significant inter-group differences
			Soreness duration	No significant inter-group differences
			Maximal isometric muscle strength	Less decrease in muscle strength in homeopathic groups (b) and (c) compared to placebo (right arm only); p-value NR
Hildebrandt 1983d *Quality: 38*	*Rhus toxicodendron* (a) D2 (b) D3 (c) D4 (d) D5 (e) D6 (f) D8, 3x16 drops daily for 7 days post exercise (n=36, 6 per dosing regimen)	Placebo (n=6)	Soreness intensity	Less soreness in homeopathic group (c) compared with placebo (both arms); p-value NR
			Soreness duration	NR
			Maximal isometric muscle strength	Less decrease in muscle strength in homeopathic group (a) compared with placebo (both arms) and in group (c) compared with placebo (right arm only); p-value NR
			Serum CK concentrations	Lower serum values in homeopathic group (a) compared with placebo; p-value NR
Hildebrandt 1984 *Quality: 38*	*Arnica* (a) D2 (b) D3 (c) D4 (d) D5 (e) D6 (f) D8, 3x16 drops daily for 6 days post	Placebo (n=6)	Soreness intensity	No significant inter-group differences
			Soreness duration	Shorter duration in homeopathic group

	exercise (n=36, 6 per dosing regimen)			(b) compared with placebo (both arms) and in group (c) compared with placebo (left arm only); p-values NR
			Maximal isometric muscle strength	Less decrease in muscle strength in homeopathic group (b) compared with placebo (both arms), and in group (c) compared with placebo (left arm only); p-values NR
			Serum CK concentrations	NR
Jawara 1997 *Quality: 85*	*Arnica Montana* D30, 5 pills twice daily for 5 days starting 1 day prior to the Oslo Marathon (n=18)	Placebo (n=18)	Soreness intensity (VAS)	No significant inter-group differences, but a trend for less soreness in verum compared with placebo group
			Serum CK concentrations	No significant inter-group differences, but a trend for lower serum CK in verum compared with placebo group
Tveilten 1991 *Quality: 60*	*Arnica montana* 30C + *Rhus toxicodendron* 30C one tablet three times daily one day prior to exercise continuing until cessation of soreness (n=25) cessation of soreness (n=25)	Placebo (n=25)	Soreness intensity (VAS)	Intergroup differences did not approach statistical significance (p>0.2), but trend favoured verum
			Soreness duration	Intergroup differences did not approach statistical significance (p>0.2), but trend favoured verum
Vickers 1997 *Quality: 85*	*Arnica Montana* 30C + *Rhus toxicodendron* 30C + *sarcolactic acid* 30C, one tablet three times daily, one day prior to exercise until cessation of soreness (n=29)	Placebo (n=28)	Mean muscle soreness (during the 5 post-exercise days)	No significant inter-group differences, but a trend for less soreness in placebo compared with the verum group
			Symptom free days	No significant inter-group differences
			Maximum soreness score	No significant inter-group differences
			Days to no soreness	No significant inter-group differences

			Days of no medication	No significant inter-group differences
EXTERNAL VALIDITY				
Generalisability: Five CTs did not provide numerical results (figures only). High level of heterogeneity between included studies (particularly regarding homeopathic remedies and administration schedules used, and the type of exercise used to induce DOMS).				
Comments:				

Abbreviations: CK, creatine kinase; CT, controlled trial; DOMS, delayed-onset muscle soreness; ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; VAS, visual analogue scale

[a] Quality was assessed according to a pre-defined list of criteria (further details not specified) in which a score of ≥55 indicated studies of "higher quality"

Citation: Ernst E, Barnes J (1998) Are homoeopathic remedies effective for delayed-onset muscle soreness: a systematic review of placebo-controlled trials (Structured abstract). Perfusion 11:4-8.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**7/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Ernst E, Pittler MH (1998) Efficacy of homeopathic Arnica: A systematic review of placebo- controlled clinical trials. Arch Surg 133(11):1187-90.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, Exeter, England
Conflicts of interest: not reported</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 4 RCTs (Level II) and 4 placebo-controlled trials (Level III-2). The therapeutic conditions covered are:
• Delayed-onset muscle soreness (1 RCT; 1 placebo-controlled trial)
• Postsurgical complications (2 RCTs)
• Acute trauma (1 placebo-controlled trial)
• Bruising (2 placebo-controlled trials)
• Stroke (1 RCT)</td><td>Level of evidence:
Level I/III</td><td colspan="2">Location/setting:
NR (all included studies)</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy regimen specified by authors (all included studies)</td><td colspan="3">Comparator(s)
Placebo (all studies)
1 RCT also had a Metronidazole 400 mg twice daily comparator group (metronidazole was shown to be superior to placebo or arnica)</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 36 to 118. The number of patients enrolled in the placebo-controlled trials ranged from 10 to 42</td></tr>
<tr><td colspan="5">Population characteristics:
Delayed-onset muscle soreness
• Hildebrandt and Eltze, 1984 (placebo-controlled trial): Healthy women for the treatment of delayed-onset muscle soreness
• Tveiten et al, 1991 (RCT): Participants in the Oslo Marathon (Norway) for the treatment of delayed-onset muscle soreness
Postsurgical complications
• Kaziro 1984 (RCT): Patients after extraction of wisdom teeth for the prevention of postsurgical complications
• Pinsent et al, 1984 (RCT): Patients after tooth extraction for the prevention of postsurgical complications
Acute trauma
• Gibson et al, 1991 (placebo-controlled trial): Orthopedic patients for the treatment of acute trauma
Bruising
• Campbell, 1976 (placebo-controlled trial): Healthy volunteers for the treatment of experimentally inflicted mechanical bruising
• Savage and Roe, 1978 (placebo-controlled trial): Healthy volunteers for the treatment of experimentally inflicted mechanical bruising
Stroke
• Livingston, 1991 (RCT): Patients admitted to hospital up to 7 days after acute event for the treatment of stroke</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: 3-5 days
Placebo-controlled trials: 2 days to 3 months</td><td colspan="3">Outcome(s) measured:
Soreness intensity (rating scale) and duration, maximal isometric muscle strength, serum creatine kinase concentrations, pain (visual analogue scale), trismus, edema, wound healing, bleeding, pulse rate, blood pressure, respiratory rate, subjective symptoms, extent of bruising, 3 month mortality</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: The 4 placebo-controlled trials were non-randomised. The 4 RCTs had unclear</td><td>Comparison of study groups:
All of the included studies focused on homeopathy vs placebo in patients with a particular condition.</td><td>Blinding:
All of the included studies were double-blind</td><td>Treatment/ measurement bias:
Unclear in all</td><td>Follow-up (ITT):
Only one of included studies (1 RCT) reported</td></tr>
</table>

concealment of allocation	1 placebo-controlled trial had small baseline differences in disfavour of arnica-treated group	except for one placebo-controlled trial which was single-blind	included studies	loss to follow up. Unclear in all other studies

Author-assessed quality of included studies:
Method used: Jadad score
Jadad score 1 (1 RCT, 1 placebo-controlled trial); Jadad score 2 (1 RCT, 2 placebo-controlled trials); Jadad score 3 (1 placebo-controlled trial); Jadad score 4 (2 RCTs)

Overall quality assessment
Rating: 6/10 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed but key words were not stated. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed using the Jadad score and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were not stated

RESULTS

Overall:

- "Most trials included in this review are methodologically weak. Generally speaking, the more rigorous studies tended to be the ones that yielded negative findings."
- "The claim that homeopathic arnica is efficacious beyond a placebo effect is not supported by rigorous clinical trials."
- "The hypothesis claiming that homeopathic arnica is clinically effective beyond a placebo effect is not based on methodologically sound placebo-controlled trials."

Individual study results

Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Delayed-onset muscle soreness				
Hildebrandt and Eltze, 1984 N=42 *Jadad score 1*	Arnica D2, D3, D4, D5, D6, D8 - 16 drops, 3 times a day for 6 days after exercise n=6 for each of D2, D3, D4, D5, D6, D8	Placebo drops as per verum schedule n=6	Maximal isometric muscle strength	"Less decrease in muscle strength in group B vs placebo (both arms)"[a]
			Soreness intensity (rating scale)	No significant difference
			Soreness duration	"Shorter duration of soreness in group B (both arms) and C (left arm only) vs placebo"[a, b]
Tveiten et al, 1991 N=36 *Jadad score 4*	*Arnica montana* D30 5 pills twice daily for 5 days starting 1 day prior to race n=20	Placebo pills as per verum schedule n=16	Blood tests, including serum creatine kinase concentrations	"No significant intergroup differences but a trend for serum creatine kinase concentrations to be lower with arnica than placebo"
			Soreness intensity (visual analogue scale) and duration	"No significant intergroup differences but a trend for soreness to be lower with arnica than placebo"
			Duration	No significant difference
Postsurgical complications				
Kaziro 1984 N=118	Arnica 200C twice daily for 3 days postoperatively	Group A: Placebo	Pain (visual analogue scale)	No significant difference

Jadad score 2	n=39	(n=38) Group B: Metronidazole 400 mg twice daily (n=41)		
			Trismus	No significant difference
			Edema	No significant difference
			Wound healing	No significant difference
Pinsent et al, 1984 N=59 *Jadad score 4*	Arnica 30C 1 dose 30 minutes preoperatively; 3 doses each 15 minutes postoperatively; 1 dose every 2 hours for 5 doses n=23	Placebo as per verum schedule n=36	Pain	"Less pain with arnica"
			Bleeding	No significant difference
Acute trauma				
Gibson et al, 1991 N=20 *Jadad score 2*	Arninca 30. Frequency and dose of medication not stated n=11	Placebo n=9	Pulse rate	No significant difference
			Blood pressure	No significant difference
			Respiratory rate	No significant difference
			Subjective symptoms	No significant difference
Bruising				
Campbell, 1976 N=13 *Jadad score 1*	Arnica 10M, one tablet before being bruised and 2 after, on the same day, and 2 more tablets on the next day n=NR	Placebo n=NR	Extent of bruising	"Results numerically favoured arnica"
			Subjective symptoms	"Results numerically favoured arnica"
Savage and Roe, 1978 N=10 *Jadad score 2*	Arnica 30C, one tablet before being bruised and 2 after, on the same day, and 2 more tablets on the next day n=NR	Placebo n=NR	Extent of bruising	"Results numerically favoured arnica"
			Subjective symptoms	"Results numerically favoured arnica"
Stroke				
Livingston, 1991 N=40 *Jadad score 3*	Arnica "in M potency" n=20	Placebo n=20	3 month mortality	No significant difference
EXTERNAL VALIDITY				
Generalisability: The age of participants within the included RCTs was not reported. The location of all the included studies was not reported				
Comments: None				

Abbreviations: ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial.

[a] What constitutes groups B and C were not defined by the authors

[b] Lower creatinine kinase concentration on day 6 in group C vs placebo

Citation: Ernst E, Pittler MH (1998) Efficacy of homeopathic Arnica: A systematic review of placebo- controlled clinical trials. Arch Surg 133(11):1187-90.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**6/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Ernst E (2011) Homeopathic Galphimia glauca for hay fever: A systematic review of randomised clinical trials and a critique of a published meta-analysis. Focus Altern Complement Ther 16(3):200-3.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: NR
Conflicts of interest: NR</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 4 RCTs (Level II)</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
NR for all included studies</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy remedy specified by authors but treatment schedules were left to the discretion of the treating physicians (4 RCTs)</td><td colspan="3">Comparator(s):
Placebo (3 RCTs)
1 RCT had two comparator groups: placebo and Galphimia glauca diluted by factor of 10^{-6}</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 121 to 243.</td></tr>
<tr><td colspan="5">Population characteristics:
NR for all of the included studies. Assumed to be patients with hay fever.</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: not specified in 3 RCTs. 4 weeks in 1 RCT</td><td colspan="3">Outcome(s) measured:
Symptom rating scales (not validated) self-assessed by the patient and verified by the physician; Adverse events</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: Concealment of allocation was unclear in all of the included studies</td><td>Comparison of study groups:
All of the RCTs focused on homeopathy vs placebo or diluted homeopathic agent</td><td>Blinding:
All of the RCTs were double blind</td><td>Treatment/ measurement bias:
Unclear in all included studies</td><td>Follow-up (ITT):
Loss to follow up was unclear in all included studies.
“Numerous dropouts/withdrawals” mentioned.
No ITT analysis</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: Jadad score
2 RCTs had a Jadad score of 4; 2 RCTs had a Jadad score of 5</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 5/10 according to the AMSTAR criteria
Description: A priori design provided. No mention of duplicate study selection and data extraction. Literature search was performed on MEDLINE and EMBASE databases. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided but no population characteristics were given. Scientific quality of the included studies was assessed using the Jadad score and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were not stated.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
• “Three RCTs reported significant result in favour of GG over placebo, while one study failed to yield significant inter-group differences. No serious adverse effects were reported in any of the trials”.
• “In conclusion, three of the four currently available placebo-controlled RCTs of homeopathic GG suggest this therapy is an effective symptomatic treatment for hay fever. There are, however, important caveats. Most essentially, independent replication would be required before GG can be considered for the routine treatment of hay fever”.</td></tr>
<tr><td colspan="5">Individual study results</td></tr>
</table>

Trial (N) *Quality*	Intervention (n)	Control group:	Outcome	Results as reported in the systematic review
Wiesenauer, 1983 N=121 *Jadad score 5*	*Galphimia glauca*-D4; dosage individualised; duration of 39 days on average n=NR	Placebo n=NR	Symptom rating scales (improvement by end of treatment)	Statistically significant difference (P=NR) Improvement by end of treatment in intervention group [81% (95% CI 65-92)] and comparator group [57% (95% CI 39-74)]
			Adverse events	Adverse events were noted only in the comparator group
Wiesenauer, 1985 N=213 *Jadad score 5*	*Galphimia glauca* - D6; dosage individualised; duration of 5 weeks on average n=NR	2 groups: Placebo; *Galphimia glauca* diluted by factor of 10^{-6} n=NR	Symptom rating scales (improvement by end of treatment)	No significant difference. Improvement by end of treatment in intervention group [80% ocular, 78% nasal], diluted homeopathy remedy group [66% ocular, 51% nasal], placebo group [65% ocular, 58% nasal].
			Adverse events	No adverse events were noted
Wiesenauer, 1990 N=243 *Jadad score 4*	*Galphimia glauca*-C2; dosage individualised; duration of 33 days on average n=NR	Placebo n=NR	Symptom rating scales (improvement by end of treatment)	Statistically significant difference (P=NR) Improvement by end of treatment in intervention group [88% ocular, 76% nasal] and comparator group [60% ocular, 67% nasal].
			Adverse events	No information regarding adverse events
Wiesenauer, 1995 N=164 *Jadad score 4*	*Galphimia glauca*-D4; dosage individualised; duration of 4 weeks n=NR	Placebo n=NR	Symptom rating scales (improvement by end of treatment)	Differences between groups were statistically significant only for ocular symptoms. Improvement by end of treatment in intervention group [89% ocular, 80% nasal] and comparator group [63% ocular, 69% nasal].
			Adverse events	No adverse events were reported in intervention group.
EXTERNAL VALIDITY				
Generalisability: Age of participants in the included studies were not reported in the article. Location of the included studies was not reported.				

Comments: All four of the RCTs were conducted by the same German research group.

Abbreviations: ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial.

Citation: Ernst E (2011) Homeopathic Galphimia glauca for hay fever: A systematic review of randomised clinical trials and a critique of a published meta-analysis. Focus Altern Complement Ther 16(3):200-3.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
	✓	No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**5/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Ernst E (2012) Homeopathy for eczema: A systematic review of controlled clinical trials. Br J Dermatol 166(6):1170-2.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: None
Conflicts of interest: None declared</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 1 RCT (Level II) and 2 comparative cohort studies (Level III-2)</td><td>Level of evidence:
Level I/III</td><td colspan="2">Location/setting:
NR for all included studies</td></tr>
<tr><td colspan="2">Intervention:
Individualised homeopathy (1 RCT)
Homeopathy – method unclear (2 comparative cohort studies)</td><td colspan="3">Comparator(s):
Placebo (1 RCT)
Conventional treatment (2 comparative cohort studies)</td></tr>
<tr><td colspan="5">Sample size: 24 patients were enrolled in the RCT. The two comparative cohort studies enrolled 118 and 135 patients</td></tr>
<tr><td colspan="5">Population characteristics:
• Kell et al, 2008 (comparative cohort study): Children with eczema
• Witt et al, 2009 (comparative cohort study): Children with atopic eczema
• Siebenwirth et al, 2009 (RCT): Patients with atopic eczema</td></tr>
<tr><td colspan="2">Length of follow-up:
NR in all of the studies</td><td colspan="3">Outcome(s) measured:
Symptom scores; Quality of life</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
The cohort studies were non-randomised. Concealment of allocation was unclear in the RCT</td><td>Comparison of study groups:
The cohort studies compared homeopathy vs conventional treatment in eczema patients. The RCT compared homeopathy vs placebo in eczema patients</td><td>Blinding:
The RCT was double-blind. Blinding in the cohort studies was unclear</td><td>Treatment/ measurement bias:
Unclear in all included studies</td><td>Follow-up (ITT):
Unclear in all included studies</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: Jadad score
The 2 cohort studies had a Jadad score of 1. The RCT had a Jadad score of 3. “All were methodologically weak”</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 6/10 according to the AMSTAR criteria
Description: A priori design provided. No duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. List of included and excluded studies were not provided. Characteristics of the included studies were provided but no patient demographic data. Scientific quality of the included studies was assessed using the Jadad score and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were stated</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">• Kell et al, 2008 - Concluded that “both therapy groups improved similarly regarding perception of eczema symptoms and disease related quality of life.”
• Witt et al, 2009 - Concluded that “homeopathic treatment was not superior to conventional treatment for children with mild eczema.”
• Siebenwirth et al, 2009 - Concluded that “individualised homeopathic remedies did not prove to be superior to placebo.”

Overall:
• “The evidence from controlled clinical trials therefore fails to show that homeopathy is an efficacious treatment for eczema.”
• “In conclusion, the available data do not demonstrate homeopathic remedies to be efficacious as a treatment of eczema.”</td></tr>
</table>

Individual study results				
Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Kell et al, 2008 N=118 *Jadad score 1*	Treatment by homeopaths (not specified) n=NR	Conventional treatment (not specified, mainly corticosteroids and antihistamines) n=NR	Symptom scores	No significant difference
			Quality of life	No significant difference
Witt et al, 2009 N=135 *Jadad score 1*	Treatment by homeopaths (not specified) n=NR	Conventional treatment (not specified, mainly corticosteroids and antihistamines) n=NR	Symptom scores	No significant difference
			Quality of life	No significant difference
Siebenwirth et al, 2009 N=24 *Jadad score 3*	Individualised homeopathic treatment for 32 weeks n=NR	Placebo n=NR	NR	"A nonsignificant trend favoured placebo over homeopathy"
EXTERNAL VALIDITY				
Generalisability: Age specific information on the patients in the included studies was not provided. Two studies featured children. The location of the included studies was not reported				
Comments: None				

Abbreviations: NR, not reported; RCT, randomised controlled trial.

Citation: Ernst E (2012) Homeopathy for eczema: A systematic review of controlled clinical trials. Br J Dermatol 166(6):1170-2.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
	✓	No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**6/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Ernst E (2011) Homeopathy for insomnia and sleep-related disorders: A systematic review of randomised controlled trials. Focus Altern Complement Ther 16(3):195-9.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: NR
Conflicts of interest: NR</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 6 RCTs (Level II)</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
Portugal (1 RCT); France (1 RCT); South Africa (2 RCTs); United States of America (1 RCT); Germany (1 RCT)</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy regimen specified by authors: 4 RCTs
Individualised homeopathy: 2 RCTs</td><td colspan="3">Comparator(s):
Placebo (all included studies)</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 29 to 96.</td></tr>
<tr><td colspan="5">Population characteristics:
• Carlini et al 1987; Caildella et al 2001; Kolia-Adam et al 2008; Naude et al 2010; Wolf 1992 (5 RCTs): NR. Assumed to be patients with insomnia and sleep-related disorders
• La Pine et al, 2006 (RCT): Study was conducted on nurses doing shift work, not on patients with insomnia</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: ranged from 1 week to 4 weeks</td><td colspan="3">Outcome(s) measured:
Sleep duration; Sleep quality; Evaluation by clinician; Improvement on clinical rating scale; Sleep pattern; Sleep quality; Fatigue; Sleep diary; Sleep latency; Percentage of patients reporting improvement; Night awakenings</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: Concealment of allocation was unclear in all included studies.</td><td>Comparison of study groups: All included studies focused on homeopathy vs placebo. Patient population was not specified in 5 RCTs. 1 RCT was not conducted on patients with insomnia</td><td>Blinding:
All of the included studies were double-blind</td><td>Treatment/ measurement bias:
Unclear in all included studies</td><td>Follow-up (ITT):
Loss to follow up was reported in 3 RCTs and unclear in 3 RCTs. No ITT analysis in any of the included studies</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: Cochrane criteria.
4 RCTs were of poor quality; 2 RCTs were of moderate quality.</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 6/10 according to the AMSTAR criteria
Description: A priori design provided. No mention of duplicate study selection and data extraction. Comprehensive literature search was performed. The status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided but no population characteristics were given. Scientific quality of the included studies was assessed using the Cochrane criteria and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were not stated.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
• “In conclusion, the notion that homeopathic remedies are effective for the treatment of insomnia and sleep-related disorders is not supported by the best available evidence. It is recommended that future trials of homeopathy and insomnia be conducted using adequate and rigorous study designs. Until consistently positive evidence emerges, proponents of homeopathy should abstain from making such therapeutic claims”.</td></tr>
</table>

Individual study results				
Trial (N) *Quality*[a]	Intervention	Control	Outcome	Results as reported in the systematic review
Carlini et al 1987 N=44 *Poor quality*	Individualised homeopathy for 45 days	Placebo	Sleep duration	No significant difference
			Sleep quality	No significant difference
			Evaluation by clinician	No significant difference
Cialdella et al 2001 N=96 *Poor quality*	Homeogene or Sedatif PC for 1 month	Placebo	Improvement on clinical rating scale	No significant difference
Kolia-Adam et al 2008 N=30 *Poor quality*	*Coffea cruda* 200C for 1 month	Placebo	Sleep duration	No significant difference
			Sleep pattern	No significant difference
La Pine et al 2006 N=34 *Moderate quality*	No-Shift-Lag for 1 week	Placebo	Sleep quality	No significant difference
			Fatigue	No significant difference
Naude et al 2010 N=30 *Moderate quality*	Individualised homeopathy for 4 weeks	Placebo	Sleep diary	"Change in total hours of sleep per week favoured homeopathy"
Wolf 1992 N=29 *Poor quality*	Requiesan for 1 month	Placebo	Sleep duration	No significant difference
			Sleep quality	No significant difference
			Sleep latency	No significant difference
			Percentage of patients reporting improvement, night awakenings	No significant difference
EXTERNAL VALIDITY				
Generalisability: Age of participants in the included studies were not reported in the article. None of the included studies were conducted in Australia.				
Comments: None				

Abbreviations: ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial.

[a] Quality (risk of bias) was assessed using the Cochrane criteria

Citation: Ernst E (2011) Homeopathy for insomnia and sleep-related disorders: A systematic review of randomised controlled trials. Focus Altern Complement Ther 16(3):195-9.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
	✓	No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**6/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Heirs M, Dean ME (2009) Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane Database Syst Rev.</td></tr>
<tr><td colspan="5">Affiliation/source of funds:
• University of York, UK
• Department of Health, UK
Conflicts of interest: None to report</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 3 RCTs[a] and one quasi-randomised controlled trial (CT)</td><td>Level of evidence:
Level I/III</td><td colspan="2">Location/setting:
Switzerland (1 RCT); US (1 RCT, 1 CT); South Africa (1 RCT)

Private homeopathic clinic (2 RCTs); Screened/treated in child's foster home or facility (1 CT); NR (1 RCT)</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy (2 RCTs, 1 CT); Homeopathy with or without Ritalin (1 RCT)</td><td colspan="3">Comparator(s):
Placebo (2 RCTs, 1 CT); Placebo with or without Ritalin (1 RCT)</td></tr>
<tr><td colspan="5">Sample size: The number of participants enrolled in the included RCTs ranged from 20 to 62.</td></tr>
<tr><td colspan="5">Population characteristics:
Children with:
• ADHD confirmed by neuropsychological examination. Those who entered the cross-over phase were aged 7-15 years (mean 10 years), whose symptoms had improved by 50% under homeopathic treatment. No other ADHD medication could be used for the duration of the trial (1 RCT)
• ADHD confirmed using the computer Diagnostic Interview Schedule for Children tool. Mean age: 9 years. Nine participants (n=5 active, n=4 placebo) were already taking stimulant medication but still displaying symptoms (1 RCT)
• ADHD confirmed by psychological testing. All participants lived in foster homes, in care or under the supervision of a social worker. Mean age: 10 years. 35% Black; 47% Hispanic; 18% Caucasian (1 CT)
• Previously diagnosed ADHD (no confirmation), aged between 7-10 years. 18 boys, 2 girls. Half of the participants (n=10) were already taking Ritalin (1 RCT)</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: range – 2 months to 18 weeks
CT: 2 months</td><td colspan="3">Outcome(s) measured:
Baseline: Conners' Global Index-Parent form (CGI-P); Questionnaire of Change of Behaviour (QCB); VLMT (auditory learning test); sub-tests of WISC (Wechsler intelligence test); K-ABC (Kaufman Assessment Battery for Children); TAP (Test Assessment battery for Attention Performance); Conners' Parents Rating Scale (CPRS), CGI-P, Conners' Global Index-Teach (CGI-T), Continuous Performance Test (CPT); Stimulant Side Effect Checklist; Clinical Global Impression (Clinicians); validated five-point scale of 'change in hyperactivity' (spanning -2 'much worse' to 0 'no change' to +2 'much better', as reported by parent/carer; Childrens' Checking Task to assess sustained attention</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
Participants allocated according to computer generated randomisation sequence (3 RCTs); participants were quasi-randomised using alternate allocation (CT)</td><td>Comparison of study groups:
Significant differences between the studies in terms of the gender and ethnicity of participants. Some studies specifically excluded participants who were on other medications, while another allowed concurrent treatment with Ritalin</td><td>Blinding:
Triple-blind (1 RCT); double-blind (2 RCTs); single-blind (patient/carer) (CT)</td><td>Treatment/ measurement bias:
The CT used an unpublished 5-point rating scale with high risk of</td><td>Follow-up (ITT):
ITT analysis (2 RCTs); 2/22 (9%) excluded from analysis due to lack of compliance (n=1) and upon</td></tr>
</table>

			treatment superiority; the three RCTs used well-known, validated outcome scales (eg. Conners' Rating Scales)	advice from their GP (n=1) (1 RCT); 3 participants missing from analysis after they were withdrawn from active arm due to changes to their stimulant medication (CT)

Author assessed quality of included studies:
Method used: Quality assessed according to 4 items (listed below)

- Was sequence generation adequate? (Yes – 3 RCTs; No – CT)
- Was allocation adequately concealed? (Yes – 2 RCTs; No – CT; Unclear – 1 RCT)
- Were all outcomes blinded? (Yes – 3 RCTs; Unclear – CT)
- Was incomplete outcome data addressed? (Yes – 1 RCT; Unclear – 1 RCT; No – 1 RCT, CT)

Overall quality assessment
Rating: 10/11 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. Status of publication was used as an inclusion criterion. List of included and excluded studies was provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. Pooled results of findings in a meta-analysis. The likelihood of publication bias was not assessed. Conflicts of interest were stated.

RESULTS

Overall:

- **"Overall this review found no evidence that homeopathy has a significant impact on the overall severity, core symptoms or related outcomes of children diagnosed with Attention Deficit Hyperactivity Disorder"**
- Significant heterogeneity exists between the three trials included in the meta-analysis in terms of how 'homeopathic treatment' was operationalised and implemented as well as the effects (one used a formula of medicines given without individualisation to patients over a relatively short period of time; one used a form of individualised homeopathy similar to how 'classical' homeopathy is used in practice with freedom to vary the medicines as well as potency (strength) and frequency, although critics have suggested that the treatment period of 18 weeks was too short to show benefit from homeopathy hence the negative findings)
- However, "a trial of individualised homeopathy with minimised non-specific effects found a significant benefit from homeopathy" (Frei et al 2005)
- **"There is insufficient evidence to draw robust conclusions about the effectiveness of any particular form of homeopathy for ADHD at present given that only three randomised controlled trials have been carried out, and all were relatively small in size"**
- **"There is at present insufficient evidence to recommend the use of homeopathy for children diagnosed with ADHD"**

Individual study results

Trial *Quality*	Intervention (n)	Comparator (n)	Outcome:	Results as reported in the systematic review
Frei et al 2005 *Quality not specified*	Individual homeopathic medicine – prescribed according to Hahnemann and Bönninghausen,	Placebo (n=31)	Overall symptoms (CGI-P)	Significant benefit of verum homeopathy over placebo in the cross-over phase of the study. Generic inverse weighted

	administered as daily liquid doses (LM potencies) (n=31)			average treatment effect: -1.67 (95% CI -3.32, -0.02)
			Inattention and impulsivity (measured by TAP)	Insufficient data to calculate effect size
Jacobs et al 2005 *Quality not specified*	Individualised homeopathic medicine – prescribed according to the Bombay or Sankaran method (with option to vary prescription at 6 and 12 week follow-up) (n=21)	Placebo (n=22)	Overall symptoms (CGI-P)	No evidence for effectiveness of verum homeopathy over placebo. SMD 0.13 (95% CI -0.47, 0.73)
			CPRS-R	No evidence of effectiveness of verum homeopathy over placebo. SMD 0.17 (95% CI 0.43, 0.77)
			Hyperactivity subscale from CPRS-R	No evidence of effectiveness of homeopathy on hyperactivity symptoms. SMD 0.21 (95% CI -0.39, 0.81)
			CPRS-R domain of inattention	No evidence of effectiveness was found. SMD 0.39 (95% CI -0.21, 1.00)
			Restlessness/ impulsivity (from the CPRS-R)	No significant evidence of effectiveness. SMD 0.02 (95% CI -0.57, 0.62)
			Conduct/oppositional behaviour	No evidence of effectiveness. SMD 0.10 (95% CI -0.50, 0.70)
			Emotional Lability domain (from the CPRS-R)	No evidence of effectiveness. SMD 0.21 (95% CI -0.39, 0.81)
			Global total on the CGI-T	No significant differences. SMD 0.41 (95% CI -0.20, 1.01)
			Restless/Impulsive behaviour (sub-domain of CGI-T)	No significant differences. SMD 0.39 (95% CI -0.21, 1.00)
			Emotional Lability (sub-domain of CGI-	No significant differences. SMD 0.41

			T)	(95% CI -0.19, 1.02)
			Inattention (measured by the Conners' CPT)	No significant difference. SMD -0.12 (95% CI -0.72, 0.48)
			Impulsivity (measured by the CPT)	No evidence of effectiveness. SMD -0.07 (95% CI -0.67, 0.53)
Lamont 1997 *Quality not specified*	Individualised homeopathic medicine – prescribed following a consultation using classical homeopathic prescribing and the RADAR repertory software. Administered as 6 x 200c pills daily for up to 5 days. Ten days after the prescription progress was followed-up, with the option of changing the medicine on two further occasions (n=23)	Placebo (n=20)	Change in hyperactivity over 10 days (measured by a five point rating scale completed by parents)	Effectiveness was found. SMD -0.65 (95% CI -1.27, -0.03)
Strauss 2000 *Quality not specified*	Formula homeopathic combination medicine[b] – ten drops, three times daily for two months, with (n=5) or without Ritalin (n=5)	Placebo, with (n=5) or without Ritalin (n=5)	CRS (older version which included a domain termed the Hyperactivity Index but has been renamed the ADHD Index in later revisions)	No evidence of effectiveness of homeopathy on ADHD Index score as rated by parents. SMD -0.17 (95% CI -1.05, 0.71)
			Restlessness/ impulsivity (from the CRS)	No evidence of effectiveness. SMD -0.14 (95% CI -1.02, 0.74)
			Anxiety (based on a domain within the older CRS)	Non-significant difference in levels of anxiety. SMD -0.55 (95% CI -1.45, 0.34)
			Conduct/oppositional behaviour	No evidence of effectiveness. SMD 0.26 (95% CI -1.14, 0.63)
			Inattention (converted by the systematic review author from 'successful attention'	No significant difference. SMD -0.53 (95% CI -1.42, 0.37)

			as measured by the CCT in Strauss 2000)	

Meta-analysis results				
Homeopathy versus Placebo (Parent Ratings)				
Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
CGI-P	2		Mean Difference (Fixed, 95% CI)	-1.56 [-3.18, 0.06]
ADHD Index	2	63	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.43, 0.56]
Hyperactivity:	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
Randomised only	1	43	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.39, 0.81]
Quasi and fully randomised	2	86	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-1.06, 0.63]
Inattention	1	43	Std. Mean Difference (IV, Fixed, 95% CI)	0.39 [-0.21, 1.00]
Restless/Impulsive	2	63	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.52, 0.46]
Oppositional/Conduct	2	63	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.51, 0.48]
Emotional Lability	1	43	Std. Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.39, 0.81]
Anxiety	1	20	Std. Mean Difference (IV, Fixed, 95% CI)	-0.55 [-1.45, 0.34]
Global Index Scores	1	43	Std. Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.47, 0.73]
Homeopathy versus Placebo (Teacher Ratings)				
Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
Global Index Total	1	43	Std. Mean Difference (IV, Fixed, 95% CI)	0.41 [-0.20, 1.01]
Restless/Impulsive	1	43	Std. Mean Difference (IV, Fixed, 95% CI)	0.39 [-0.21, 1.00]
Emotional Lability	1	43	Std. Mean Difference (IV, Fixed, 95% CI)	0.41 [-0.19, 1.02]
Homeopathy versus Placebo (Child completed tests)				
Outcome or subgroup	No. of studies	No. of participants	Statistical method	Effect size
Inattention	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
Original figures	2	63	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.74, 0.25]
Adjusted figures	2	62	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.71, 0.29]
Impulsivity	1	43	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.67, 0.53]
EXTERNAL VALIDITY				
Generalisability:				
Comments: Quasi-randomised trials were included in the review but not in the meta-analysis. Authors acknowledge that the cross-over study design of Frei 2005 may have possible led to a regression to the mean (Bland 1994) in the first phase, or a carry-over effect (Elbourne 2002) in either phase one or two, but that sufficient evidence is not available to investigate either of those potential factors. The meta-analysis has not taken into account the type of homeopathy due to the lack of studies available – most of the pooling possible was between Strauss (formula approach) and Jacobs (individualised homeopathy). However "it was felt by the reviewers that pooling was still appropriate since overall all of the studies could be interpreted as addressing the ongoing controversy of whether homeopathic dilutions have any effect over a placebo dose". "There are a number of factors that could be taken into account in future trials. Good quality observational studies documenting how homeopaths in the country of an intended trial actually practice, including time to see benefit and adverse events or side effects, are crucial for the development of good quality trials (McCarney 2008). Future trials should ideally take this information into account in the design phase, while recognising that homeopathy, particularly individualised homeopathy, is a package of care which potentially contains multiple active ingredients (Thompson 2006).The latter point relates to an ongoing debate as to the suitability of the placebo-controlled trial for testing homeopathy, which is exacerbated when ethics committees refuse to permit a wait-list condition (e.g. Jacobs 2005) to explore the non-specific effects"				

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CCT, Childrens' Checking Task; CGI-P, Conners' Global Index rated by parents; CGI-T, Conners' Global Index – Teacher form; CPRS, Conners' Parent Rating Scale; CPRS-R, Conners'

Parent Rating Scale – Revised; CPT, Continuous Performance Test; CRS, Conners' Rating Scale; SMD, standard mean difference; TAP, Test battery for Attention Performance; UK, United Kingdom

[a] 1 RCT was preceded by a screening phase in which 'responders' were identified. The RCT then included only those who were responsive to homeopathy in the screening phase

[b] containing selenium in 10X, 15X, 30X, 200X with potassium phosphate in 2X, 10X, 30X, 200X. This combination is sold commercially to improve concentration, memory and alertness

[c] No information available on the development or validation of this measure

Citation: Heirs M, Dean ME (2007) Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane Database Syst Rev.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	✓	Yes
		No
		Can't answer
		Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**10/11**	

STUDY DETAILS				
Reference: Holdcraft LC, Assefi N, Buchwald D (2003) Complementary and alternative medicine in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 17(4):667-83.				
Affiliation/source of funds: NR Conflicts of interest: NR				
Study design: Systematic review of 1 RCT		Level of evidence: Level I		Location/setting: NR
Intervention: Homeopathy		Comparator(s): Placebo		
Sample size: Included trial recruited 30 participants				
Population characteristics: Fibromyalgia patients				
Length of follow-up: NR		Outcome(s) measured: TPC, sleep or pain VAS		
INTERNAL VALIDITY				
Allocation: Randomised – method of allocation not clear	Comparison of study groups: Limited patient characteristics provided. All FM patients.	Blinding: Double-blind	Treatment/ measurement bias: No wash-out period between active and placebo interventions (cross-over trial)	Follow-up (ITT): NR
Author-assessed quality of included studies: Method used: CONSORT – rated on a scale of 0 (low) to 22 (high) Quality of included trial: 10				
Overall quality assessment Rating: 5/10 according to the AMSTAR criteria Description: Comprehensive literature search (six databases searched); limited information about patient characteristics (beyond indication) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trial was discussed, but the likelihood of publication bias was not; the authors stated that the sources of funding had no role in data collection or interpretation (but did not specifically identify that source).				
RESULTS				
Overall: • **There is limited evidence to support the use of homeopathy for FM due to the low quality of the RCT**				
Individual study results				
Trial (N) *Quality*[a]	Intervention	Control	Outcome	Results as reported in the systematic review
Fisher 1989 N=30 *Quality: 10*	*Rhus toxicodendron* (poison ivy)	Placebo	TPC	Mean number of tender points was reduced by 25% in active group. Significant improvement compared to placebo ($p<0.05$)
			Pain and sleep (VAS)	Significant improvement in active compared to placebo

				group (p<0.05)
EXTERNAL VALIDITY				
Generalisability:				
Comments: Results limited by the fact that sleep and pain scores were not reported separately and also by the fact that there was no wash-out period between the active and placebo interventions.				

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; FM, fibromyalgia; NR, not reported; RCT, randomised controlled trial; TPC, tender point count; VAS, visual analogue scale

[a] Quality was assessed using the CONSORT criteria. Studies were rated from 0 (low quality) to 22 (high quality)

Citation: Holdcraft LC, Assefi N, Buchwald D (2003) Complementary and alternative medicine in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 17(4):667-83.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
	✓	No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**5/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Huang T, Shu X, Huang YS, Cheuk DK (2011) Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 12:CD005230.</td></tr>
<tr><td colspan="5">Affiliation/source of funds:
• Chief Scientist Office, Scottish Executive Health Department, United Kingdom
• National Health Service Executive Research and Development Program, United Kingdom
• Chinese Cochrane Centre, China
• Chinese Evidence-Based Medicine Centre, China
Conflicts of interest: From the previous version of the review, one of the authors (Jonathan HC Evans) has received reimbursement for attending a conference, fees for lecturing and a consultancy fee which was paid into a research fund from Ferring Pharmaceuticals, manufacturers of desmopressin</td></tr>
<tr><td colspan="2">Study design:
NA</td><td>Level of evidence:
NA</td><td colspan="2">Location/setting: NA</td></tr>
<tr><td colspan="2">Intervention: NA</td><td colspan="3">Comparator(s): NA</td></tr>
<tr><td colspan="5">Sample size: NA</td></tr>
<tr><td colspan="5">Population characteristics: NA</td></tr>
<tr><td colspan="2">Length of follow-up: NA</td><td colspan="3">Outcome(s) measured: NA</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: NA</td><td>Comparison of study groups: NA</td><td>Blinding: NA</td><td>Treatment/ measurement bias: NA</td><td>Follow-up (ITT): NA</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies: NA</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 5/5 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search was performed. The status of publication was used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were stated</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
No trials were found which addressed the comparison of homeopathy versus no treatment or placebo or another treatment for nocturnal enuresis in children</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisability: NA</td></tr>
<tr><td colspan="5">Comments: None</td></tr>
</table>

Abbreviations: NA, not applicable; NR, not reported; RCT, randomised controlled trial.

Citation: Huang T, Shu X, Huang YS, Cheuk DK (2011) Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 12:CD005230.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer

	✓	Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.		Yes
		No
		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**5/5**	

<table>
<tr><th colspan="3">STUDY DETAILS</th></tr>
<tr><td colspan="3">Reference: Kassab S, Cummings M, Berkovitz S, van HR, Fisher P (2011) Homeopathic medicines for adverse effects of cancer treatments. Cochrane Database Syst Rev(2):CD004845.</td></tr>
<tr><td colspan="3">Affiliation/source of funds: Support was given from the Royal London Homeopathic Hospital, UK and the Knowledge and Research Center for Alternative Medicine, Denmark.
Conflicts of interest:
Peter Fisher has received fees from homeopathic manufactures for lectures and seminars. Sosie Kassab is Director of Complementary Cancer Services at the Royal London Homoeopathic Hospital and uses homeopathic medicines for patients with cancer alongside their conventional care. Robbert van Haselen was Deputy Director of Research at the Royal London Homoeopathic Hospital when an application for funding for this Cochrane Review was made from ViFAB. He had a major input into the development of the protocol which was published in 2004. He left the hospital in 2005 and took up his post as Director of Research for Heel in Germany in 2006 (the company that makes Traumeel S, one of the interventions included in this review). Prior to his leaving, we had run some of the searches and identified some potential studies but had not gone through the process of formally selecting studies for inclusion into the review. He had no input into the selection of included studies, data extraction, quality assessment or interpretation of the analysis. On finally approving the publication, he did not make any recommendations for change to the implications for clinical practice, research or to the conclusions, but commented on it critically for intellectual content.</td></tr>
<tr><td>Study design:
Systematic review of 6 RCTs</td><td>Level of evidence:
Level I</td><td>Location/setting:
France (1 RCT); Italy (1 RCT); USA (1 RCT); Israel – Schneider Children's Medical Center (1 RCT); UK – local oncology centres and surgical breast units (1 RCT); Germany – University hospital women's clinic (1 RCT)</td></tr>
<tr><td>Intervention:
Homeopathy (5 RCTs); Homeopathy + conventional antiemetics on Day 1 if symptomatic (1 RCT)</td><td colspan="2">Comparator(s):
Placebo (5 RCTs); Sambucus nigra D3 (1 RCT)</td></tr>
<tr><td colspan="3">Sample size: The number of patients enrolled in the RCTs ranged from 29 to 254.</td></tr>
<tr><td colspan="3">Population characteristics:
• Women (mean age: 52.7 years, range: 28.3 to 70 years) who had undergone conservative surgery for breast cancer and were being treated with radiotherapy (Balzarini, 2000)
• Women with a history of carcinoma in situ or Stage I to III breast cancer who had completed all surgery, chemotherapy and radiotherapy (women taking Tamoxifen were also included), who had hot flushes for at least one month, with an average of at least three hot flushes per day in the week prior to beginning treatment. Mean age: 55.5 years (Jacobs, 2005)
• Patients aged 3-25 years suffering from malignant disease who had undergone allogeneic or autologous stem cell transplantation (Oberbaum, 2001)
• Women with breast cancer (mean age; range: 54.41 years; 7.61 years) undergoing intravenous chemotherapy (Thompson, 2005)
• Women treated for breast cancer, who had more than three hot flushes per day, did not have metastatic disease, were no on any other treatment for hot flushes, did not have any severe concurrent illnesses and who were not undergoing, or about the receive, any adjuvant chemotherapy. Mean age: 52.7 years (Bourgois, 1984)
• Women aged 28-67 years undergoing chemotherapy for breast cancer (Daub, 2005)</td></tr>
<tr><td colspan="2">Length of follow-up:
Range: 20 days to 1 year</td><td>Outcome(s) measured:
Skin reactions to radiotherapy (during radiotherapy and during recovery), measured by: skin colour, heat to touch, oedema, hyperpigmentation (four scores combined to calculate the Index of</td></tr>
</table>

	Total Severity); Hot Flush Severity Score (frequency times severity of hot flushes); total number of hot flushes; Kupperman Menopausal Index (KMI); quality of life (SF-36); FSH level before and after treatment; WHO grading for muscositis (a five point scale – AUC for stomatitis symptoms, time to worsening of stomatitis symptoms, patient-reported pain, dryness and dysphagia); pain (measured by VAS); self-assessed satisfaction questionnaire; the occurrence, duration and reasons for interruption of radiotherapy or of study compound; MYMOP (where a change of 0.8 was considered to be clinically relevant); Menopausal Symptom Questionnaire; EORTC QLQ C30; HADS; FAQ; GHHOS; pain caused by injection or haematoma graded by patient (on a vertical line: 0=no pain, 160=intense pain); venous tone assessed by the number of haematomas; venous accessibility; percentage of patients who did not require additional conventional medication for nausea and vomiting related to chemotherapy; intensity of nausea questionnaire; quality of life; side effects			
INTERNAL VALIDITY				
Allocation: All randomised; allocation concealment was clearly described in four RCTs and alluded to in two RCTs	Comparison of study groups: Of the eight included RCTs: 1 studied adverse effects of radiotherapy; 2 studied adverse effects of chemotherapy; 1 studied adverse effects of venous canulation in patients undergoing chemotherapy; 2 studied menopausal symptoms due to oestrogen withdrawal or hormonal therapy as part of breast cancer treatment	Blinding: Triple-blind (1 RCT); Double-blind (4 RCTs); Single-blind (1 RCT); Unclear (1 RCT)	Treatment/ measurement bias: All outcomes described in methods were reported in all studies, suggesting that they were free of reporting bias	Follow-up (ITT): No withdrawals or dropouts and ITT analysis (1 RCT); ITT analysis – 15 to 34% attrition (2 RCTs); Dropouts described but not included in the analysis (2 RCTs); Dropouts selectively included/excluded from analyses (1 RCT)
Author assessed quality of included trials: Method used: the Delphi List and the Cochrane Collaboration's tool for assessing risk of bias (measures of selection bias, performance and detection bias, attrition bias, reporting bias and other bias) Quality: Low risk of bias (3 RCTs); Unclear risk of bias (2 RCTs); High risk of bias (1 RCT)				
Overall quality assessment Rating: 9/10 according to the AMSTAR criteria Description: Comprehensive literature search (fifteen databases searched); the details of both included, excluded and ongoing trials were provided; extensive details were provided about patient characteristics; no meta-analysis completed – the results of individual included studies were discussed and the authors provided a narrative review; scientific quality of included trials was considered when drawing conclusions; the likelihood of publication bias was not discussed.				
RESULTS				
Overall: • In general there were mixed findings or unclear risk of bias: two studies reported positive results for skin reactions with radiotherapy but the studies had an unclear risk of bias • One study with low risk of bias demonstrated benefit from Traumeel S for chemotherapy-induced stomatitis, however two others found negative results. Two high quality studies found no evidence for the efficacy of homeopathic medicines over placebo in the treatment of menopausal symptoms • **Overall there is preliminary data to support the efficacy of Taumeel S mouthwash in the treatment of**				

chemotherapy-induced stomatitis, but there is no evidence to support the efficacy of homeopathic medicines for other adverse effects of cancer treatments.				
Individual study results				
Trial (N) *Quality*[a]	Intervention	Control	Outcomes	Results as reported in the systematic review
Balzarini 2000 N=66 *Unclear risk of bias*	Belladonna 7c – three granules twice daily and X-ray 15c three granules once daily	Placebo	Total severity of skin reactions *during radiotherapy* (based on skin colour, heat to touch, hyperpigmentation and oedema)	No significant difference between groups
			Total severity of skin reactions *during recovery* (based on skin colour, heat to touch, hyperpigmentation and oedema)	Statistically significant reduction in homeopathy-treated patients (p=0.05)
Jacobs 2005 N=83 *Low risk of bias*	Individualised homeopathy with unrestricted remedy choice and unrestricted ability to change remedy (single medicine given once monthly or bimonthly); or Hyland's Menopause[b] (given three times a day)	Placebo	Hot flush severity score	Positive trend towards an improvement in the single remedy group during the first three months of the study, however the trend was not significant (p=0.1)
			General health score (SF-36) at 1 year	Statistically significant improvement in both homeopathy groups (p<0.05)
			Hot flush severity score (post hoc subgroup analysis defined by use of tamoxifen)	Highly statistically significant increase in the combination homeopathic group (subgroup of patients not receiving tamoxifen)
Oberbaum 2001 N=32 *Low risk of bias*	TraumeelS®[c] – supplied as 2.2ml ampoules used as a mouthwash for a minimum of 30 seconds, five times per day, alongside standard mouthcare	Placebo – supplied as 2.2ml ampoules used as a mouthwash for a minimum of 30 seconds, five times per day, alongside standard mouthcare	AUC for stomatitis symptoms	Homeopathy group: 10.4; Placebo group: 24.3. Wilcoxon rank-sum score: 167.5; expected score 232.5; p<0.01)
			Time to worsening of symptoms	Log-rank test indicated that there was a statistically significant difference between the two groups (chi-square test, 13.4 with 1

				degree of freedom; p<0.001)
			Median time to worsening in those patients whose symptoms wosened	Homeopathy group: 4.7 days; Placebo group: 4.0 days. Significance not reported.
			Patient-reported score	Reduction in all three symptoms (pain, dryness, dysphagia) in the Traumeel S group compared to placebo. Significance not reported
Thompson 2005 N=53 *Low risk of bias*	Individualised homeopathy – unrestricted remedy choice and unrestricted ability to change remedy	Placebo	Symptoms and mood disturbances	Clinically relevant improvements for both groups. Inter-group differences not reported
			MYMOP activity	No evidence of a difference between groups (adjusted difference: -0.4, 95% CI -0.9, 0.1, p=0.13)
Bourgois 1984 N=29 *High risk of bias*	Homepathic Arnica 5c – three granules four times a day for three days before and three days after treatment, for two chemotherapy cycles	Placebo – three granules four times a day for three days before and three days after treatment, for two chemotherapy cycles	Improvements from baseline (based on pain produced by the injection or haematoma(s), venous tone, and venous accessibility)	No significant inter-group differences
Daub 2005 N=65 *Unclear risk of bias*	Vomitusheel S[d] given as a suppository and Gastricumeel[e] given as oral tablets (starting on day 2, if symptomatic – conventional antiemetics were used for the first day)	Sambucus nigra D3 oral tablets[f]	Percentage of patients requiring additional conventional treatment for nausea/vomiting	No significant difference between groups. Intervention group: 68.2%; control group: 59.1% (p=0.6)
EXTERNAL VALIDITY				
Generalisability: Most included studies were small and the study populations were heterogenous. Only two studies examined the treatment for the same conditions and even then, 'individualised homeopathy' is a very broad and varied intervention. Each of the studies also measured very different outcomes.				
Comments: The review identified a number of relevant ongoing studies.				

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; FAQ, Final assessment questionnaire; FSH, follicle stimulating hormone; GHHOS, Glasgow Homeopathic Hospital Outcome Scale; HADS, Hospital Anxiety and Depression Scale; KMI, Kupperman Menopausal Index; QLQ, Quality of Life Questionnaire; RTOG, Radiation Therapy Oncology Group; SF-36, Short Form 36

[a] Quality was assessed using the Delphi List and the Cochrane Collaboration's tool for assessing risk of bias (measures of selection bias, performance and detection bias, attrition bias, reporting bias and other bias)

[b] Hyland's Menopause is a proprietary combination homeopathic medicine of Amyl Nitrate 3x, Sanguinaria Canadensis 3x and Lachesis 12x.
[c] TraumeelS is a proprietary complex homeopathic medicine. Each 2.2ml ampoule contains: Arnica montana D2 (2.2mg), calendula officianalis D2 (2.2mg), Achillea millefolium D3 (2.2mg), Matricharia chamomilla D2 (2.2mg), Symphytum officinale D6 (2.2mg), Atropa belladonna D2 (2.2mg), Aconitum napelus D2 (1.32mg), Bellis perenis D2 (1.1mg), Hypericum perfoliatum D2 (0.66mg), Echinacea angustifolia D2 (2.2mg), Echinacea purpurea D2 (2.2mg), Hammamelis virginica D1 (0.22mg), Mercurius solubilis D1 (1.1mg), and Hepar sulphuris D6 (2.2mg).
[d] Vomitushell S is a proprietary complex homeopathic medicine containing Ipecacuanha D2 (1.1mg), Aesthusea D2 (1.1mg), Nux vomica D2 (1.1mg), Apomorphium hydrochloricum D4 (1.65mg), Colchicum D4 (2.75mg), Ignatia D4 (3.3mg)
[e] Gastricumeel is a proprietary complex homeopathic medicine containing Argentum nitricum D6 (30mg), Acidum arsenicosum D6 (30mg), Pulsatilla D4 (60mg), Nux vomica D4 (60mg), Carbo vegetablis D6 (60mg), Antimonium crudum D6 (60mg)
[f] The 'placebo' was another homeopathic medicine that the authors chose because "no antiemetic properties had been described".

Citation: Kassab S, Cummings M, Berkovitz S, van HR, Fisher P (2011) Homeopathic medicines for adverse effects of cancer treatments. Cochrane Database Syst Rev(2):CD004845.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**9/10**	

STUDY DETAILS

Reference:

- Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, Jonas WB (1997) Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 350(9081):834-43.
- Linde K (1998) Erratum. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials (The Lancet (1997) Sept 20 (834)). Lancet 351(9097):220.

Affiliation/source of funds: Partial support from the Carl and Veronica Carstens Foundation (Essen, Germany)
Conflicts of interest: Not reported

Study design:	Level of evidence:	Location/setting:
Systematic review of 89 RCTs (Level II). The therapeutic conditions covered are: • **Allergy** (7 RCTs) • **Dermatology** (9 RCTs) • **Gastroenterology** (9 RCTs) • **Musculoskeletal complaints** (6 RCTs) • **Neurology** (7 RCTs) • **Obstetrics and gynaecology** (10 RCTs) • **Upper respiratory tract, asthma and ear, nose and throat** (15 RCTs) • **Rheumatology** (7 RCTs) • **Surgery and anaesthesiology** (12 RCTs) • **Miscellaneous** (7 RCTs)	Level I	NR (all included studies)

Intervention:	Comparator(s):
Homeopathy regimen specified by authors (78 RCTs) Individualised homeopathy (11 RCTs)	Placebo (all included studies)

Sample size: The number of patients enrolled in the RCTs ranged from 13 to 1270.

Population characteristics:

Allergy

- Reilly 1994 (1 RCT): Patients with allergic asthma
- Reilly 1985; Reilly 1986; Wiesenauer 1983; Wiesenauer 1985; Wiesenauer 1990; Wiesenauer 1995 (6 RCTs): Patients with pollinosis

Dermatology

- Labrecquet 1992 (1 RCT): Patients with warts
- Leaman 1989 (1 RCT): Patients with minor burns
- Mossinger 1980 (1 RCT): Patients with pyodermia
- Paterson NR; Paterson NR; Paterson NR; Paterson NR (4 RCTs): Patients with skin lesions
- Schwab NR; Schwab NR (2 RCTs): Patients with dermatoses

Gastroenterology

- Bignamini 1991 (1 RCT): Patients with anal fissure
- Jacobs 1993; Jacobs 1994 (2 RCTs): Patients with diarrhoea
- Mossinger NR; Mossinger NR; Ritter 1966 (3 RCTs): Patients with gastritis
- Mossinger 1984 (1 RCT): Patients with cholecystopathia
- Rahlfs 1979; Rahlfs 1976 (2 RCTs): Patients with irritable bowel

Musculoskeletal complaints

- Bohmer 1992; Zell 1988 (2 RCTs): Patients with sprains
- Thiel 1991 (1 RCT): Patients with haemarthrosis
- Mossinger NR; Mossinger NR; Mossinger NR (3 RCTs): Patients with cramps

Neurology

- Albertini 1984 (1 RCT): Patients with dental neuralgia

- Brigo 1991 (1 RCT): Patients with migraine
- Dexpert 1987; Ponti 1986 (2 RCTs): Patients with seasickness
- Master 1987 (1 RCT): Patients with aphasia
- Savage 1977; Savage 1978 (2 RCTs): Patients with stroke

Obstetrics and gynaecology

- Bekkering 1993 (1 RCT): Patients with menopause
- Carey 1986 (1 RCT): Patients with vaginal discharge
- Chapman 1994; Lepaisant 1994 (2 RCTs): Patients with premenstrual syndrome
- Coudert 1981; Dorfman 1987; Hofmeyr 1990 (3 RCTs): Patients going through childbirth
- Gauthier 1983 (1 RCT): Patients with menopausal complications
- Kubista 1986 (1 RCT): Patients with mastodynia
- Ustianowski 1974 (1 RCT): Patients with cystitis

Upper respiratory tract, asthma, ears, nose and throat

- Bordes 1986 (1 RCT): Patients with a cough
- Casanova 1992; Ferley 1989; Hourst 1981; Lecocq 1985 (4 RCTs): Patients with upper respiratory infection
- Davies 1971; Ferley 1987; Hellmann 1992; Nollevaux 1994 (4 RCTs): For the prevention of upper respiratory infection
- de Lange 1994 (1 RCT): For recurrent, upper respiratory infection
- Mossinger 1976 (1 RCT): Patients with pharyngitis
- Mossinger 1982 (1 RCT): Patients with running nose
- Mossinger 1985 (1 RCT): Patients with otitis media
- Weiser 1994 (1 RCT): Patients with chronic sinusitis
- Freitas 1995 (1 RCT): Patients with asthma

Rheumatology

- Andrade 1991; Gibson 1980; Kohler 1991; Wiesenauer 1991 (4 RCTs): Patients with rheumatoid arthritis
- Shipley 1983 (1 RCT): Patients with osteoarthritis
- Fisher 1989 (1 RCT): Patients with fibrositis
- Casanova 1981 (1 RCT): Patients with myalgia

Surgery and anaesthesiology

- Alibeu 1990 (1 RCT): Patients with agitation
- Aulagnier 1985; Chevrel 1984; Dorfman 1992; Estrangin 1983; GRECHO 1987; Valero 1981 (6 RCTs): Patients with postoperative ileus
- Kaziro 1984; Lokken 1995; Michaud 1981 (3 RCTs): Patients with tooth extraction
- Kennedy 1971 (1 RCT); Preventing complications
- Valero 1981 (1 RCT): Preventing postoperative infections

Miscellaneous

- Bourgois 1984; Dorfman 1988 (2 RCTs): Patients with haematomas
- Campbell 1976 (1 RCT): Patients with bruises
- Ernst 1990 (1 RCT): Patients with varicosis
- Hariveau 1987 (1 RCT): Patients with cramps
- Mokkapatti 1992 (1 RCT): Patients with preventative conjunctivitis
- Werk 1994 (1 RCT): Patients who are overweight

Length of follow-up: NR (all included studies)	Outcome(s) measured: **Allergy:** VAS improvement (mm); Global assessment patient; Improvement ocular symptoms **Dermatology:** Disappearance of warts; Pain; Days to healing (days); Depth of lesion; Predicted reactions on remedy **Gastroenterology:** Improvement; Duration of diarrhoea; Global assessment, physician; Global assessment, patient **Musculoskeletal complaints:** Global assessment, patient; Joint movement; Global assessment, physician **Neurology:** Global assessment, patient; Global assessment, physician; Survival

	Obstetrics and gynaecology: Symptom score; Global assessment, physician; Labour pains; Global assessment, patient; Perineal pain **Upper respiratory tract, asthma and ear, nose and throat:** Global assessment, patient; Fever on third day; Patients with infection; Patients recovered within 48 hours; Complaints; Duration; Symptoms; Global assessment, physician; Severity score **Rheumatology:** Global assessment, physician; Global assessment, patient; Predefined responder criteria; Treatment preference **Surgery and anaesthesiology:** Physician's assessment; Global assessment, patient; Time to first stool; Patients without pain; Time to flatulence; Pain; Complications; Treatment preference; Oedema; Infections. **Miscellaneous:** Pain score; Treatment preference; Pain reduction; Global assessment; Patients with infection; Body mass index

INTERNAL VALIDITY

Allocation: Method of random sequence allocation not specified for all included studies	Comparison of study groups: All included studies focused on homeopathy vs placebo in patients with a particular condition	Blinding: Unclear (all included studies)	Treatment/ measurement bias: Unclear (all included studies)	Follow-up (ITT): Unclear (all included studies)

Author-assessed quality of included studies:
Overall, there were 26 "high" quality studies, 40 with a Jadad score ≥3 and 34 with internal validity >5.

Publication bias:
"The general non-parametric selection model applied to the 89 studies confirmed that there was statistically significant publication bias and suggested the bias was primarily due to under-reporting of studies with statistically insignificant effects and with negative effect".

Overall quality assessment
Rating: 9/11 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. The status of publication was used as an inclusion criterion (a number of thesis were included in the final list of included studies). List of included and excluded studies were provided, however they were not complete and full references of the some of the included studies were missing. Characteristics of the included studies were provided but patient demographics were not given. Scientific quality of the included studies was assessed using the Jadad score and appropriately reported and considered in formulating conclusions. Pooled results of findings and the results were reported as odds ratios. The likelihood of publication bias was assessed. Conflicts of interest were not stated.

RESULTS

Overall:

- "The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition".

Individual study results

Trial (N) *Quality*[a]	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Allergy				
Reilly 1994 N=28 *Quality: 100/93*	Individual nosode C30 n=NR	Placebo n=NR	VAS improvement (mm)*	Odds ratio favoured homeopathy
Reilly 1985 N=39	Pollen C30 n=NR	Placebo n=NR	Global assessment patient	Odds ratio favoured

Quality: 60/50				homeopathy
Reilly 1986 N=162 *Quality: 100/93*	Pollen C30 n=NR	Placebo n=NR	VAS improvement (mm)*	Odds ratio favoured homeopathy
Wiesenauer 1983 N=121 *Quality: 80/79*	Galphimia D4 n=NR	Placebo n=NR	Improvement ocular symptoms	Odds ratio favoured homeopathy
Wiesenauer 1985 N=142 *Quality: 80/79*	Galphimia D6 n=NR	Placebo n=NR	Improvement ocular symptoms	Odds ratio showed no difference between homeopathy and placebo
Wiesenauer 1990 N=243 *Quality: 60/86*	Galphimia C2 n=NR	Placebo n=NR	Improvement ocular symptoms	Odds ratio favoured homeopathy
Wiesenauer 1995 N=164 *Quality: 60/79*	Galphimia D4 n=NR	Placebo n=NR	Improvement ocular symptoms	Odds ratio favoured homeopathy
Dermatology				
Labrecquet 1992 N=174 *Quality: 80/100*	Thuya C30, Ant C5, Ac.nitr.C7 n=NR	Placebo n=NR	Disappearance of warts	Odds ratio showed no difference between homeopathy and placebo
Leaman 1989 N=34 *Quality: 40/50*	Cantharis C200 n=NR	Placebo n=NR	Pain (area under curve)*	Odds ratio showed no difference between homeopathy and placebo
Mossinger 1980 N=144 *Quality: 40/36*	Hepar sulfuris D4 n=NR	Placebo n=NR	Days to healing*	Odds ratio showed no difference between homeopathy and placebo
Paterson NR N=40 *Quality: 80/64*	Mustard gas C30 n=NR	Placebo n=NR	Depth of lesion	Odds ratio favoured homeopathy
Paterson NR N=169 *Quality: 40/57*	Individual treatment n=NR	Placebo n=NR	Depth of lesion	Odds ratio showed no difference between homeopathy and placebo
Paterson NR N=22 *Quality: 40/57*	Rhus tox C30 n=NR	Placebo n=NR	Depth of lesion	Odds ratio showed no difference between homeopathy and placebo
Paterson NR N=39 *Quality: 40/57*	Mustard gas C30 n=NR	Placebo n=NR	Depth of lesion	Odds ratio favoured homeopathy
Schwab NR	(only patients	Placebo	Predicted reactions	Odds ratio showed

N=13 *Quality: 60/71*	fitting) Sulphur n=NR	n=NR	on remedy	no difference between homeopathy and placebo
Schwab NR N=16 *Quality: 40/71*	(only patients fitting) Sulphur n=NR	Placebo n=NR	Predicted reactions on remedy	Odds ratio favoured homeopathy
Gastroenterology				
Bignamini 1991 N=31 *Quality: 40/64*	Acidum nitricum C9 n=NR	Placebo n=NR	Improvement	Odds ratio favoured homeopathy
Jacobs 1993 N=34 *Quality: 60/64*	Individual treatment in C30 n=NR	Placebo n=NR	Duration of diarrhoea (days)*	Odds ratio showed no difference between homeopathy and placebo
Jacobs 1994 N=92 *Quality: 100/86*	Individual treatment in C30 n=NR	Placebo n=NR	Duration of diarrhoea (days)*	Odds ratio favoured homeopathy
Mossinger NR N=53 *Quality: 20/29*	Nux vomica D4 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Mossinger NR N=16 *Quality: 20/29*	Nux vomica D30 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Ritter 1966 N=147 *Quality: 40/50*	Nux vomica D4 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio favoured homeopathy
Mossinger 1984 N=14 *Quality: 0/14*	Absinthium D2 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio favoured homeopathy
Rahlfs 1979 N=119 *Quality: 40/79*	Asa foetida D3 n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Rahlfs 1976 N=72 *Quality: 40/79*	Asa foetida D1 n=NR	Placebo n=NR	Global assessment, patient	Odds ratio showed no difference between homeopathy and placebo
Musculoskeletal complaints				
Bohmer 1992 N=102 *Quality: 100/100*	Traumeel (complex) n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Zell 1988 N=73 *Quality: 100/100*	Traumeel (complex) n=NR	Placebo n=NR	Joint movement	Odds ratio favoured homeopathy

Thiel 1991 N=80 *Quality: 40/79*	Traumeel (complex) n=NR	Placebo n=NR	Joint movement	Odds ratio favoured homeopathy
Mossinger NR N=47 *Quality: 20/29*	Cuprum D30 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Mossinger NR N=34 *Quality: 20/29*	Cuprum D4 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Mossinger NR N=48 *Quality: 20/29*	Cuprum D200 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Neurology				
Albertini 1984 N=60 *Quality: 20/36*	Arnica C7, Hypericum C15 n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Brigo 1991 N=60 *Quality: 40/79*	Individual treatment in C30 n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Dexpert 1987 N=55 *Quality: 20/29*	Cocculine (complex) n=NR	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Ponti 1986 N=93 *Quality: 20/50*	Nux C2, Cocculus C2, Tab C2 n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Master 1987 N=36 *Quality: 40/29*	Individual treatment n=NR	Placebo n=NR	Global assessment, physician	Odds ratio favoured homeopathy
Savage 1977 N=40 *Quality: 60/64*	Arnica C30 n=NR	Placebo n=NR	Survival	Odds ratio showed no difference between homeopathy and placebo
Savage 1978 N=40 *Quality: 60/79*	Arnica M n=NR	Placebo n=NR	Survival	Odds ratio showed no difference between homeopathy and placebo
Obstetrics and gynaecology				

Bekkering 1993 N=5 *Quality: 60/57*	Famosan (complex) n=NR	Placebo n=NR	Symptom score*	Odds ratio showed no difference between homeopathy and placebo
Carey 1986 N=40 *Quality: 40/57*	Candida C30 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Chapman 1994 N=10 *Quality: 80/7*	Individual treatment n=N	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Coudert 1981 N=34 *Quality: 40/64*	Caulophyllum C5 n=NR	Placebo n=NR	Labour pains	Odds ratio favoured homeopathy
Dorfman 1987 N=93 Quality: 60/71	Complex n=NR	Placebo n=NR	Labour pains	Odds ratio favoured homeopathy
Gauthier 1983 N=24 *Quality: 60/50*	Lachesis C30 n=NR	Placebo n=NR	Global assessment, patient	Odds ratio showed no difference between homeopathy and placebo
Hofmeyr 1990 N=122 *Quality: 100/100*	Arnica D6 (D30) n=NR	Placebo n=NR	Perineal pain	Odds ratio showed no difference between homeopathy and placebo
Kubista 1986 N=119 *Quality: 40/57*	Mastodynon (complex) n=NR	Placebo n=NR	Global assessment, physician	Odds ratio favoured homeopathy
Lepaisant 1994 N=45 *Quality: 60/64*	Folliculinum C9 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio favoured homeopathy
Ustianowski 1974 N=200 *Quality: 20/29*	Staphisagria C30 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio favoured homeopathy
Upper respiratory tract, asthma, ears, nose and throat				
Bordes 1986 N=60 *Quality: 40/57*	Drosetux (complex) n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Casanova 1992 N=300 *Quality: 40/57*	Oscillococcinum n=NR	Placebo n=NR	Fever on third day (°C)*	Odds ratio favoured homeopathy
Davies 1971	'Common cold'	Placebo	Patients with	Odds ratio showed

N=36 *Quality: 40/29*	tablets n=NR	n=NR	infection**	no difference between homeopathy and placebo
de Lange 1994 N=175 *Quality: 100/100*	Individual treatment n=NR	Placebo n=NR	Global assessment, patient	Odds ratio showed no difference between homeopathy and placebo
Ferley 1987 N=1270 *Quality: 60/79*	L52 (complex) n=NR	Placebo n=NR	Patients with infection**	Odds ratio showed no difference between homeopathy and placebo
Ferley 1989 N=487 *Quality: 60/79*	Oscillococcinum n=NR	Placebo n=NR	Patients recovered within 48 hours	Odds ratio favoured homeopathy
Hellmann 1992 N=102 *Quality: 40/43*	Engystol (complex) n=NR	Placebo n=NR	Patients with infection**	Odds ratio showed no difference between homeopathy and placebo
Hourst 1981 N=41 *Quality: 40/71*	Thuya C9+2 other remedies n=NR	Placebo n=NR	Complaints	Odds ratio showed no difference between homeopathy and placebo
Lecocq 1985 N=60 *Quality: 40/50*	L52 (complex) n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Mossinger 1976 N=118 *Quality: 40/50*	Phytolacca D2 n=NR	Placebo n=NR	Duration (days)*	Odds ratio showed no difference between homeopathy and placebo
Mossinger 1982 N=106 *Quality: 20/43*	Euphorbium D3 n=NR	Placebo n=NR	Symptoms	Odds ratio showed no difference between homeopathy and placebo
Mossinger 1985 N=44 *Quality: 20/50*	Pulsatilla D2 n=NR	Placebo n=NR	Global assessment, physician	Odds ratio showed no difference between homeopathy and placebo
Nollevaux 1994 N=200 *Quality: 20/43*	Mucococcinum 200K n=NR	Placebo n=NR	Patients with infection**	Odds ratio favoured homeopathy
Weiser 1994 N=116	Euphorbium comp (complex)	Placebo n=NR	Severity score*	Odds ratio showed no difference

Quality: 100/79	n=NR			between homeopathy and placebo
Freitas 1995 N=64 *Quality: 80/79*	Blatta orientalis C6 n=NR	Placebo n=NR	Severity score*	Odds ratio showed no difference between homeopathy and placebo
Rheumatology				
Andrade 1991 N=44 *Quality: 80/79*	Individual treatment n=NR	Placebo n=NR	Global assessment physician	Odds ratio showed no difference between homeopathy and placebo
Gibson 1980 N=46 *Quality: 60/64*	Individual treatment n=NR	Placebo n=NR	Global assessment	Odds ratio showed no difference between homeopathy and placebo
Kohler 1991 N=176 *Quality: 60/43*	Rheumaselect (complex) n=NR	Placebo n=NR	Predefined responder criteria	Odds ratio favoured homeopathy
Wiesenauer 1991 N=176 *Quality: 80/79*	Rheumaselect (complex) n=NR	Placebo n=NR	Predefined responder criteria	Odds ratio favoured homeopathy
Shipley 1983 N=36 *Quality: 60/71*	Rhus tox. D6 n=NR	Placebo n=NR	Treatment preference	Odds ratio showed no difference between homeopathy and placebo
Fisher 1989 N=30 *Quality: 60/71*	Rhus tox. C6 n=NR	Placebo n=NR	Global assessment	Odds ratio favoured homeopathy
Casanova 1981 N=60 *Quality: 20/29*	Urathone (complex) n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Surgery and anaesthesiology				
Alibeu 1990 N=50 *Quality: 40/57*	Aconite C4 n=NR	Placebo n=NR	Physician's assessment	Odds ratio favoured homeopathy
Aulagnier 1985 N=200 *Quality: 40/64*	Opium C9, Raph. C9, Arnica C9 n=NR	Placebo n=NR	Global assessment, patient	Odds ratio favoured homeopathy
Chevrel 1984 N=96 *Quality: 40/71*	Opium C15 n=NR	Placebo n=NR	Time to first stool (hours)*	Odds ratio favoured homeopathy
Dorfman 1992 N=80 *Quality: 40/36*	Complex n=NR	Placebo n=NR	Patients without pain	Odds ratio favoured homeopathy
Estrangin 1983	Arnica C7, China	Placebo	Time to flatulence	Odds ratio showed

N=97 *Quality: 40/43*	C7, Pyrog C5 n=NR	n=NR	<2 days	no difference between homeopathy and placebo
GRECHO 1987 N=450 *Quality: 80/86*	Opium C15 (+C15, Raph C5) n=NR	Placebo n=NR	Time to first stool (hours)*	Odds ratio showed no difference between homeopathy and placebo
Kaziro 1984 N=77 *Quality: 60/50*	Arnica C200 n=NR	Placebo n=NR	Pain	Odds ratio showed no difference between homeopathy and placebo
Kennedy 197 N=128 *Quality: 60/57*	Arnica C200 n=NR	Placebo n=NR	Complications**	Odds ratio showed no difference between homeopathy and placebo
Lokken 1995; N=24 *Quality: 100/86*	Individual treatment in D30 n=NR	Placebo n=NR	Treatment preference	Odds ratio showed no difference between homeopathy and placebo
Michaud 1981 N=49 *Quality: 0/14*	Apis C7, Arnica C15 n=NR	Placebo n=NR	Oedema	Odds ratio favoured homeopathy
Valero 1981 N=161 *Quality: 80/57*	Pyrogenium C7 n=NR	Placebo n=NR	Infections**	Odds ratio showed no difference between homeopathy and placebo
Valero 1981 N=102 *Quality: 80/64*	Raphanus C7 n=NR	Placebo n=NR	Time to first stool (hours)*	Odds ratio showed no difference between homeopathy and placebo
Miscellaneous				
Bourgois 1984 N=29 *Quality: 40/36*	Arnica C5 n=NR	Placebo n=NR	Pain score*	Odds ratio favoured homeopathy
Dorfman 1988 N=39 *Quality: 20/43*	Arnica C5 n=NR	Placebo n=NR	Pain	Odds ratio favoured homeopathy
Campbell 1976 N=46 *Quality: 40/36*	Arnica C30 n=NR	Placebo n=NR	Treatment preference	Odds ratio showed no difference between homeopathy and placebo
Ernst 1990 N=59	Poikiven (complex) n=NR	Placebo n=NR	Pain reduction	Odds ratio showed no difference

Quality: 40/71				between homeopathy and placebo
Hariveau 1987 N=68 *Quality: 20/43*	Cuprum C15 n=NR	Placebo n=NR	Global assessment	Odds ratio favoured homeopathy
Mokkapatti 1992 N=85 *Quality: 40/43*	Euphrasia C30 n=NR	Placebo n=NR	Patients with infection**	Odds ratio showed no difference between homeopathy and placebo
Werk 1994 N=108 *Quality: 100/57*	Helianthus tuberosus D1 n=NR	Placebo n=NR	Body mass index <26	Odds ratio favoured homeopathy
Pooled analysis of included studies				
Outcome:	No. studies included	Odds ratio (95% CI)	Favours homeopathy/placebo/no effect	
All studies	89	2.45 (2.05-2.93)	Favours homeopathy	
High quality studies	26	1.66 (1.33-2.08)	Favours homeopathy	
Adequate concealment	34	1.93 (1.51-2.47)	Favours homeopathy	
Double-blinding stated	81	2.17 (1.83-2.57)	Favours homeopathy	
Adequate follow up	28	3.18 (2.14-4.73)	Favours homeopathy	
MEDLINE-listed studies	23	1.70 (1.31-2.20)	Favours homeopathy	
Predefined main outcome	21	2.27 (1.67-3.18)	Favours homeopathy	
Corrected for publication bias	89	1.78 (1.03-3.10)	Favours homeopathy	
Worst case scenario***	5	1.97 (1.04-3.75)	Favours homeopathy	
High-potencies only	31	2.66 (1.83-3.87)	Favours homeopathy	
High/medium potencies	51	2.77 (2.09-3.67)	Favours homeopathy	
Classical homeopathy	13	2.91 (1.57-5.37)	Favours homeopathy	
Clinical homeopathy	49	2.00 (1.60-2.51)	Favours homeopathy	
Isopathy	7	5.04 (2.24-11.32)	Favours homeopathy	
Complex homeopathy	20	2.94 (2.12-4.08)	Favours homeopathy	
EXTERNAL VALIDITY				
Generalisability:				
Comments: A full reference was not provided for some of the included studies.				

Abbreviations: NR, not reported; RCT, randomised controlled trial; VAS, visual analogue score

[a] Expressed as Jadad/IV score: actual number of quality criteria met x 100/maximum possible score

* Trials with continuous outcomes (converted to odds ratios)

** For prevention trials, presented odds ratio = 1/actual odds ratio

*** MEDLINE only, high quality studies with predefined outcome measures, medium and high dilutions only, n=5

Citation: • Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, Jonas WB (1997) Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 350(9081):834-43. • Linde K (1998) Erratum. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials (The Lancet (1997) Sept 20 (834)). Lancet 351(9097):220.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
	✓	Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	✓	Yes
		No
		Can't answer
		Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**9/11**	

<table>
<tr><th colspan="3">STUDY DETAILS</th></tr>
<tr><td colspan="3">Reference: Linde K, Melchart D (1998) Randomized controlled trials of individualized homeopathy: a state-of-the-art review. J Altern Complement Med 4(4):371-88.</td></tr>
<tr><td colspan="3">Affiliation/source of funds: The review was partly supported by a grant from the Carl and Veronica Carstens Foundation
Conflicts of interest: Not reported</td></tr>
<tr><td>Study design:
Systematic review of 31 RCTs and quasi-randomised controlled trials[a]. The therapeutic areas included in the systematic review are:
• Headache
• Diarrhoea
• Rheumatology
• Infectious diseases
• Premenstrual Syndrome
• Various conditions</td><td>Level of evidence:
Level I/III</td><td>Location/setting:
UK (5 studies); US (3 studies); Australia (2 studies); Netherlands (2 studies); Brazil (2 studies); Mexico (2 studies); Norway (2 studies); Germany (2 studies); Italy (1 study); Nepal (1 study); Peru (1 study); Ghana (1 study); Israel (1 study); Venezuela (1 study); South Africa (1 study); India (1 study); NR (1 study)

Trials were conducted in a broad range of settings including homeopathic clinics, rheumatology centres and hospitals (outpatients).</td></tr>
<tr><td>Intervention:
Homeopathy (31 studies)</td><td colspan="2">Comparator(s):
Placebo (27 studies); Chloroquine (1 study); Salazopyrine and ASA or placebo (1 study); Dicyclomine hydrochloride, faecal bulking agents, diet advice (1 study); Salicylate or placebo (1 study)</td></tr>
<tr><td colspan="3">Sample size:
The number of patients enrolled in the RCTs ranged from 10 to 175. The number of patients analysed ranged from 10 to 155.

The number of patients enrolled in the pseudo-randomised studies ranged from 29 to 195. The number of patients analysed ranged from 26 to 60.</td></tr>
<tr><td colspan="3">Population characteristics:
Patients with:
• Migraine
• Chronic headaches
• Childhood diarrhoea
• Rheumatoid arthritis
• Fibrositis
• Recurrent upper respiratory tract infection
• Cholera
• Amebiasis and giardiasis
• Malaria attack
• PMS
• Postviral fatigue syndrome
• Heroin detoxification
• Insomnia
• Mild traumatic brain injury
• Proctocolitis
• Common warts on hands</td></tr>
</table>

<table>
<tr><td colspan="5">• Various conditions, including 18 mental health and 4 rheumatologic conditions
• Attention deficit
• Allergic asthma
• Irritable bowel syndrome
• Pain after oral surgery
• Broca's aphasia in stroke patients
• Acne vulgaris
• Dermatoses and the remedy picture of sulfur</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: range – 1 week to 12 months
Pseudo-randomised studies: range – 16 days (per cross-over phase) to 12 months</td><td colspan="3">Outcome(s) measured:
NR</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
6 RCTs randomised by independent third party; 6 RCTs randomised by coded drugs; 13 RCTs randomised with no details of allocation method; 3 CTs quasi-randomised using alternate allocation; 3 CTs provided no clear description of either randomised or method of allocation</td><td>Comparison of study groups:
1 RCT (Whitmarsh et al 1997) acknowledged differences between groups at baseline (although details were not provided); study group differences were not reported for the remaining studies.</td><td>Blinding:
Double-blind (24 RCTs, 5 CTs); Single-blind (1 CT); No blinding (1 RCT)</td><td>Treatment/ measurement bias:
6 RCTs had good methodological quality, low risk of bias; 6 RCTs were unlikely to have major flaws; 5 RCTs and 3 CTs had minor or moderate problems; 4 RCTs, 3 CTs were either not assessable or had major flaws</td><td>Follow-up (ITT):
No drop-outs or withdrawals and/or ITT analysis (2 RCTs); significant loss to follow-up of 25% (1 RCT); extremely high dropout rate (1 RCT, 1 CT); NR (21 RCTs, 5 CTs)</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Methods used: Jaded score (max. 5 points), Internal validity score (max. 6 points)
RCTs (Jadad score): 1 RCT scored 1; 3 RCTs scored 2; 8 RCTs scored 3; 5 RCTs scored 4; 4 RCTs scored 5; 4 RCTs were NR[b]
RCTs (Internal validity score): 1 RCT scored 1.5; 5 RCTs scored 3; 1 RCT scored 3.5; 3 RCTs scored 4; 3 RCTs scored 4.5; 5 RCTs scored 5; 1 RCT scored 5.5; 2 RCTs scored 6; 4 RCTs were NR[b]

CTs (Jadad score): 2 CTs scored 1; 2 CTs scored 2; 2 CTs scored 3
CTs (Internal validity score): 2 CTs scored 1; 2 CTs scored 2; 1 CT scored 3.5; 1 CT scored 4</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 8/11 according to the AMSTAR criteria
Description: Comprehensive literature search; data extraction by only one reviewer; sufficient information about patient characteristics was provided; meta-analysis conducted to pool trial data; scientific quality of included trial was discussed, but the likelihood of publication bias was not; the authors acknowledged the source of funding.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
• A meta-analysis showed an overall trend in favour of homeopathy. The rate ratio was 1.62 (95% CI 1.17 to 2.23) and the odds ratio was 2.62[c]
• The pooled rate ratio of the methodologically best studies was clearly smaller and not statistically</td></tr>
</table>

significant (1.12, 95% CI 0.87 to 1.44)[c] • Similarly, the poor rate ratio of the six studies published in MEDLINE-listed journals was not significantly different from placebo (1.22, 95% CI 0.94 to 1.56)[c]				
Individual study results				
Trial (N) *Quality* [d]	Intervention	Control	Outcome	Results as reported in the systematic review
Migraine				
Brigo 1991 N=60 *Quality: 3,5*	Eight homeopathic remedies (patients were included provided that the similimum was among the eight) in C30, four doses in 2-week intervals	Placebo	Number of patients assessed globally as improved	Intervention group: 24/30 (80%); Control group: 4/30 (13%); p<0.001
			Intensity of attacks (VAS)	Intervention group: 2.9; Control group: 7.8. Significance of inter-group differences not reported
			Frequency of attacks/month	Intervention group: 1.8; Control group: 7.9. Significance of inter-group differences not reported
Straumsheim et al 1997 N=73 *Quality: 3,5*	Individual similimum (if possible constitutional) chosen from 60 available remedies in D30, D200, or 1M and individual dosage	Placebo	Number of patients assessed globally as improved	Intervention group: 8/35 (23%); Control group: 5/33 (15%). Significance of inter-group differences not reported
			Attack frequency	Similar decrease in both treatment groups
			Medication use	Similar decrease in both treatment groups
Whitmarsh et al 1997 N=63 *Quality: 4,4*	Eleven homeopathic remedies (patients were included provided that the similimum was among those) in C30, two tablets, twice weekly	Placebo	Number of patients assessed globally as improved	No statistically significant inter-group differences. Intervention group: 11/32 (34%); Control group: 5/31 (16%)
Chronic headaches				
Walach et al 1997 N=98 *Quality: 5,6*	Completely free individualised homeopathy treatment	Placebo	Number of patients assessed globally as improved	Slight trend in favour of placebo. Intervention group: 25/61 (41%); Control group: 19/37 (51%). Significance of inter-group differences not reported
			Headache frequency	Slight decrease in both groups

			Medication use	Slight decrease in both groups
Childhood diarrhoea				
Jacobs et al 1993 N=34 *Quality: 3,3*	Fully individualised computer-assisted (RADAR) choice of remedy, taken as C30 twice daily for 3 days	Placebo	Duration of diarrhoea	Positive trends, but no significant inter-group differences. Intervention group: 2.4 days; Control group: 3.0 days; p=0.28
Jacobs et al 1994 N=92 *Quality: 5,5*	Fully individualised, computer-assisted (RADAR) choice of remedy, taken as C30 after each unformed stool	Placebo	Duration of diarrhoea	Significant difference between groups. Intervention group: 3.0 days; Control group: 3.8 days; p<0.05
			Days to first formed stool	"Homeopathy significantly better" – no p-value reported
			Diarrhoea score	"Homeopathy significantly better" – no p-value reported
Jacobs et al 1997 N=126 *Quality: NR[b]*	Fully individualised, computer-assisted (RADAR) choice of remedy, taken as C30 after each unformed stool	Placebo	Duration of diarrhoea	No significant inter-group differences. Intervention group: 3.5 days; Control group: 4.2 days; p=0.065
Rheumatoid arthritis				
Andrade et al 1991 N=44 *Quality: 4,5*	Individual "constitutional" and "local" medications chosen by one expert homeopath, taken as C5 to C30, monthly changes possible	Placebo	Number of patients assessed globally as improved	No significant difference between groups. Intervention group: 10/17 (59%); Control group: 7/16 (44%).
			Improved morning stiffness	No significant difference between groups. Intervention group: 21%; Control group: 33%.
			Improved grip strength	No significant difference between groups. Intervention group: 0.5%; Control group: 11%.
			Daily prednisone dose (mg)	No significant difference between groups. Intervention group: -2.2; Control group: -1.9.
Gibson et al 1978	Individualised	Salicylate or placebo	Unclear	Results not reported

N=195 *Quality: 2,1*	homeopathy			in systematic review due to significant dropout rate and poor methodological quality
Gibson et al 1980 N=46 *Quality: 3,3.5*	Individualised homeopathy	Placebo	'Much better' improvement	Intervention group: 4/23 (17%); Control group: 0/24 (0%). Significance of inter-group differences not reported
			At least 'slightly better' improvement	Intervention group: 19/23 (83%); Control group: 5/24 (22%)
			Unclear	"Homeopathy significantly better than placebo"
Fibrositis				
Fisher et al 1989 N=30 *Quality: 3,4.5*	*Rhus tox* C6 (only patients in whom this was the similimum were included), two tablets, three times daily for one month	Placebo	Number of patients assessed globally as improved	Intervention group: 11/30 (37%); Control group: 4/30 (13%). Statistical significance of results has been questioned.
Recurrent upper respiratory tract infection				
de Lange et al 1994 N=175 *Quality: 5,6*	Constitutional and acute individual similimum as necessary (changes possible, dosage and potency variable)	Placebo	Number of patients assessed globally as improved	Intervention group: 48/88 (55%); Control group: 44/87 (51%). "Trends in favour of homeopathy"
			Difference in daily symptom score	Difference between groups: 0.41 (95% CI 0.02, 0.83)
Cholera				
Gaucher 1994 N=NR *Quality: 2,3*	Most indicated remedy chosen from 8 preselected options	Placebo	NR	No significant differences
Amebiasis and giardiasis				
Solanki and Gandhi 1995 N=34 *Quality: 3,3*	Individual similimum	Placebo	Number cured	"Better response in homeopathy group". Intervention group: 11/19 (58%); Control group: 2/15 (13%). Significance of inter-group differences not reported
Malaria				
van Erp and Brands 1996 N=74 *Quality: 2,3*	Individual similimum	Chloroquine	Number of patients assessed globally as improved	Similar response in both groups. Intervention group: 25/30 (83%); Control

				group: 18/25 (72%). Significance of inter-group differences not reported
Premenstrual syndrome				
Chapman et al 1994 N=10 *Quality: 4,5*	Individual similimum given in 3 doses at 12 hour intervals, repeated or new remedy at follow-up	Placebo	Number of patients assessed globally as improved	Similar response in both groups. Intervention group: 2/5 (40%); Control group: 3/5 (60%). Significance of inter-group differences not reported
Yakir et al 1994 N=23 *Quality: NR[b]*	Individual similimum	Placebo	Number of patients assessed globally as improved	Greater improvement in homeopathy group. Intervention group: 75%; Control group: 25%. Significance of inter-group differences not reported
Postviral fatigue syndrome				
Awdry 1996 N=64 *Quality: 3,4*	Individual similimum	Placebo	Number of patients assessed globally as improved	Intervention group: 13/32 (41%); Control group: 1/32 (3%). Significance of inter-group differences not reported. "Homeopathy superior regarding sleep, fatigue, disability, mood"
Heroin detoxification				
Bakshi 1990 N=60 *Quality: 1,2*	Individual similimum	Placebo	Unclear	"Homeopathy superior to placebo"
Insomnia				
Carlini et al 1987 N=44 *Quality: 3,4.5*	Individual similimum in potencies C6 to C200	Placebo	Unclear	"No difference between groups"
Mild traumatic brain injury				
Chapman et al 1997 N=50 *Quality:NR[b]*	Best fitting from 18 predefined remedies	Placebo	Unclear	"Homeopathy significantly superior"
Proctocolitis				
Janssen et al 1992 N=20 *Quality: 4,3.5*	Individual similimum once in C30, C200 or C100	Salazopyrine and ASA or placebo	Unclear	"Hard to interpret – but conventional therapy seemed most effective"
Common warts				
Kainz et al 1996	Best fitting similimum	Placebo	At least 50% size	Intervention group:

N=77 *Quality: 4,4*	out of predefined set of 10 constitutional remedies in D12 (once a day) and D30 (once every other day)		reduction	9/33 (27%); comparator group: 7/34 (21%) Rate ratio (95% CI): 1.29 (0.55, 3.00)
Various conditions				
Kuzeff 1998 N=36 *Quality: 3,4.5*	Individualised similimum (method according to Sankaran) in C30 or higher; patients were admitted only if an appropriate similimum had been identified (four sessions)	Placebo	Unclear	"Trend in favour of homeopathy"
Attention deficit				
Lamont 1997 N=45 *Quality: 2,2*	Individual similimum in C200 daily up to 5 days, computer-assisted (RADAR)	Placebo	Mean response score	Response scores in homeopathy group significantly better (mean scores 1.00 vs 0.35; t=2.16; p<0.05
Allergic asthma				
Lara-Marquez et al 1997 N=19 *Quality: NR[b]*	Individualised similimum	Placebo	Unclear	"Homeopathy better than placebo"
Irritable bowel syndrome				
Lecoyte et al 1993 N=23 *Quality: 1,1.5*	Individualised similimum	Dicyclomine hydrochloride, faecal bulking agents, diet advice	Unclear	"Similar improvements in both groups"
Pain after oral surgery				
Lökken et al 1994 N=24 *Quality: 5,5.5*	Best-fitting similimum from 6 predefined remedies in D30 given according to a fixed scheme (highly repetitive)	Placebo	Treatment preference (cross-over design)	"No significant differences". 11 patients preferred homeopathy; 13 preferred placebo. Rate ratio (95% CI): 0.85 (0.48, 1.50)
			Pain	"Pain similar in both groups"
			Bleeding	"Bleeding similar in both groups"
			Swelling	"Less swelling in homeopathy group" (p-value not reported)
Broca's aphasia in stroke patients				
Master 1987 N=36 *Quality: 1,1*	Individualised similimum	Placebo	Number of patients assessed globally as improved	Intervention group: 22/24 (92%); Control group: 3/12 (25%)

Acne vulgaris					
McDavid 1994 N=30 *Quality: 2,3*	Individualised similimum	Placebo	Number of patients assessed globally as improved	No significant difference between treatment groups. Intervention group: 9/15 (60%); Control group: 11/15 (73%)	
Dermatoses					
Schwab 1990 N=29 *Quality: 3,4*	Sulphur C30, C200, C1000 (serial application)	Placebo	"Reaction score" (including therapeutic response, aggravation, etc)	12 patients reacted during a treatment phase and none during a placebo phase. Significance of results unclear	
Meta-analysis					
Outcome	No. of included trials	Rate ratio	95% CI	Odds ratio	Significance/direction of effect
Overall meta-analysis	19	1.62	1.17, 2.23	2.62	Significantly favours homeopathy
High quality studies	6	1.12	0.87, 1.44	NR	No statistically significant difference between groups
Studies published in MEDLINE	NR	1.22	0.94, 1.56	NR	No statistically significant difference between groups
EXTERNAL VALIDITY					
Generalisability: Difficult to generalise the overall effect to every clinical condition					
Comments: Insufficient reporting meant that some of the included trials could not be properly assessed for reliability/validity. Other trials were hardly interpretable due to low recruitment of participants. Findings were also limited in many cases by crude outcome measurements. For these reasons, only 19 of the included trials were included in the quantitative analysis. The review's knowledge and experience of homeopathy are insufficient to judge the "homeopathic" quality of the included trials.					

Abbreviations: CI, confidence interval; CT, controlled trial; ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial

[a] Includes quasi-randomised trials with alternate allocation or where the randomisation process was unclear

[b] Studies excluded from quality assessment as they were available as abstracts only

[c] Values >1 indicate results in favour of homeopathy, <1 in favour of placebo. If the 95% confidence interval does not fall below 1 the result is statistically significant.

[d] Jadad score (out of 5); internal validity score (out of 6).

Citation: Linde K, Melchart D (1998) Randomized controlled trials of individualized homeopathy: a state-of-the-art review. J Altern Complement Med 4(4):371-88.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
	✓	No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	✓	Yes
		No
		Can't answer
		Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**8/11**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Long L, Ernst E (2001) Homeopathic remedies for the treatment of osteoarthritis: a systematic review. Br Homeopath J 90(1):37-43.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: NR
Conflicts of interest: NR</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 4 RCTs</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
Germany/Austria (1 RCT); England (2 RCTs); NR (1 RCT)</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy</td><td colspan="3">Comparator(s):
Hyalart® (hyaluronic acid) (1 RCT); paracetamol (1 RCT); fenoprofen or placebo (1 RCT); piroxicam gel (1 RCT)</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 36 to 184.</td></tr>
<tr><td colspan="5">Population characteristics:
3 RCTs enrolled patients with knee osteoarthritis (OA); 1 RCT enrolled patients with knee or hip OA</td></tr>
<tr><td colspan="2">Length of follow-up:
Range: 4 to 6 weeks</td><td colspan="3">Outcome(s) measured:
Subjective pain during active movement (VAS); pain during the night; duration of morning stiffness; functional ability; tolerance; average pain (VAS); pain at rest, pain on movement, night pain using both 10cm VAS and four point pain scores; pain on walking (VAS); joint tenderness (single-joint Ritchie index)</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
Random assignment– no allocation methods described (4 RCTs)</td><td>Comparison of study groups:
Limited patient characteristics provided. All OA patients.</td><td>Blinding:
Double-blind (3 RCTs); patient-blind (1 RCT)</td><td>Treatment/ measurement bias:
Measurement methods were generally standardised and validated across the 4 RCTs</td><td>Follow-up (ITT):
Populations used for analyses not clear in any of the 4 RCTs. However, one study suggests ITT was not used.</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: Jadad score
Quality: 3 RCTs scored 3; 1 RCT scored 4</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 6/10 according to the AMSTAR criteria
Description: Comprehensive literature search (six databases searched); limited information about patient characteristics (age, sex, disease severity, etc) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was considered when drawing conclusions; publication bias and conflict of interest were not discussed.</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
Two of the four included trials present positive evidence for the effectiveness of combination homeopathic preparations in comparison to conventional medications
A third concluded that Rhus toxicodendron was significantly inferior to conventional medication, while the fourth demonstrated that homeopathic gel was at least as effective as conventional NSAID gel.
Overall, there appears to be a positive trend towards the effectiveness of combination homeopathic</td></tr>
</table>

preparations; however, the authors acknowledged the small number of RCTs from which their conclusions are drawn.				
Individual study results				
Trial (N) *Quality*	Intervention	Control	Outcome	Results as reported in the systematic review
Nahler 1998 N=121 *Jadad score 3*	Two 2mL intra-articular Zeel®[a] injections per week	One 2mL intra-articular Hyalart® (hyaluronic acid) injection per week	Pain during the night	No significant difference between treatment groups (p=0.3077)
			Number of patients with undesirable adverse effects	Significance of inter-group differences not reported (intervention group: n=6; control group: n=13)
			Subjective reduction in arthritic pain during active movement, measured by standardised VAS	No significant differences between the two treatments (p=0.4298)
			Duration of morning stiffness	No significant difference between treatment groups (p=0.9211)
			Final assessment by physician and patient	No significant difference between treatment groups (p-value NR)
			Tolerance, measured by VAS	No significant difference between treatment groups
Shealy 1998 N=65 *Jadad score 3*	Oral administration of 10 drops of a homeopathic preparation (*Rhus toxicodendron, Causticum* and *Lac Vaccinum*) and placebo capsules four times daily	Paracetamol capsules four times daily (daily dose of 2600mg) and liquid placebo	Percentage of patients achieving clinically useful pain reduction (40% or greater), measured daily by VAS	Non-significant difference between treatment groups (55% of patients receiving homeopathy and 38% of those receiving paracetamol)
Shipley 1983 N=36 *Jadad score 4*	Five drops of *Rhus toxicodendron* (6x:1/1000000 dilution) three times daily and placebo capsules	Oral administration of two fenoprofen capsules (each 300mg) three times daily and placebo drops; or placebo drops and placebo capsules	Pain at rest (measured by both 10cm VAS and four point pain scores)	No significant difference between homeopathy and placebo; fenoprofen produced highly significant pain relief compared with homeopathy and placebo
			Pain on movement (measured by both 10cm VAS and four	No significant difference between homeopathy and

			point pain scores)	placebo; fenoprofen produced highly significant pain relief compared with homeopathy and placebo
			Night pain (measured by both 10cm VAS and four point pain scores)	No significant difference between homeopathy and placebo; fenoprofen produced highly significant pain relief compared with homeopathy and placebo
Van Haselen & Fisher 2000 N=184 *Jadad score 3*	Topical application of 1g SRL®[b] gel to the knee three times daily	Topical application of 1g 0.05% piroxicam gel to the knee three times daily	Mean pain reduction	16.5mm (s.d. 24.6) VAS in the intervention group (n=86); 8.1mm (s.d. 25.7) in the comparator group. Difference between treatment groups was 8.4mm (95% CI 0.8, 15.9), adjusted for pain at baseline was 6.8mm (95% CI -0.3, -13.8)
			Joint tenderness (measured by the single-joint Ritchie index)	No significant difference between treatment groups (p=0.78)
EXTERNAL VALIDITY				
Generalisability: The standardised homeopathic treatments used in the four RCTs may not represent common homeopathic practice				
Comments: The four RCTs had a relatively short duration compared to other homeopathic trials in the literature (often > 23 weeks). The cross-over trial had no wash-out periods between treatments (Shipley 1983).				

Abbreviations: ITT, intention-to-treat; OA, osteoarthritis; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial; VAS, visual analogue scale

[a] A combination homeopathic preparation composed of *Rhus toxicodendron, Arnica Montana, Solanum dulcamara, Sanguinaria Canadensis,* and *Sulphur*.

[b] Contains *Symphytum officinale* (comfrey), *Rhus toxicodendron* (poison ivy) and *Ledurn palustre* (marsh-tea).

Citation: Long L, Ernst E (2001) Homeopathic remedies for the treatment of osteoarthritis: a systematic review. Br Homeopath J 90(1):37-43.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**6/10**	

STUDY DETAILS				
Reference: Loo SK, Tang WY (2009) Warts (non-genital). Clin Evid (Online) 2009.				
Affiliation/source of funds: NR Conflicts of interest: both authors declare that they have no competing interests				
Study design: Systematic review of 2 RCTs (Level II)		Level of evidence: Level I	Location/setting: NR for all included studies	
Intervention: Homeopathy regimen specified by authors (2 RCTs)		Comparator(s): Placebo (2 RCTs)		
Sample size: The number of patients enrolled in the 2 RCTs was 174 and 67				
Population characteristics: NR for both RCTs. Assumed to be patients with non-genital warts				
Length of follow-up: RCTs: ranged from 8-18 weeks		Outcome(s) measured: Proportion of people with wart clearance; Adverse effects		
INTERNAL VALIDITY				
Allocation: Concealment of allocation was unclear in both RCTs	Comparison of study groups: Both RCTs focused on homeopathy vs placebo in patients with non-genital warts	Blinding: Unclear for both RCTs	Treatment/ measurement bias: Unclear for both RCTs	Follow-up (ITT): Unclear for both RCTs
Author-assessed quality of included studies: Method used: GRADE criteria Both RCTs were assessed as low quality				
Overall quality assessment Rating: 6/10 according to the AMSTAR criteria Description: A priori design provided. Unknown if there was duplicate study selection and data extraction. Comprehensive literature search performed. Only published articles were included. No list of included and excluded studies provided. Characteristics of the included studies were provided but population characteristics were not given. Scientific quality of the included studies was assessed using the GRADE approach and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were stated				
RESULTS				
Overall: • "We don't know whether homeopathy increases cure rates compared with placebo, as few high-quality studies have been found." • "We don't know whether homeopathy is more effective at increasing the proportion of people with wart clearance after 8-18 weeks."				
Individual study results				
Trial (N) *Quality*[a]	Intervention	Control	Outcome	Results as reported in the systematic review
Labrecque et al, 1992 N=174 *Low quality*	Oral homeopathy for 6 weeks (Thuya 30CH plus antimony crudum 7CH plus nitricium acidum 7CH)	Placebo	Proportion of people with wart clearance	No significant difference • ARR 4% (95% CI -8-17%) • 16/80 (20%) patients in homeopathy group, and 20/82 (24%) patients in placebo group had wart clearance at 18 weeks

			Adverse effects	No significant difference • RR 0.51 (95% CI 0.10-2.72) • 2/86 (2%) patients in homeopathy group and 4/88 (5%) patients in placebo group experienced adverse effects • Adverse effects included stomach ache, loose stools, fatigue and acne
Kainz et al, 1996 N=67 *Low quality*	Oral homeopathy (individually selected regimen)	Placebo	Proportion of people with wart clearance	No significant difference • RR 4.85 (95% CI 0.60-39.35) • 5/34 (15%) patients in homeopathy group, and 1/33 (3%) patients in placebo group had wart clearance at 8 weeks
EXTERNAL VALIDITY				
Generalisability: Age of participants in the included studies was not reported in the article. Location of included studies was not reported				
Comments: NR				

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; NR, not reported; RR, relative risk.

[a] According to the GRADE criteria.

Citation: Loo SK, Tang WY (2009) Warts (non-genital). Clin Evid (Online) 2009.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**6/10**	

STUDY DETAILS				
Reference: Macfarlane GJ, El-Metwally A, De Silva V, Ernst E, Dowds GL, Moots RJ (2011) Evidence for the efficacy of complementary and alternative medicines in the management of rheumatoid arthritis: A systematic review. Rheumatology (UK) 50(9):1672-83.				
Affiliation/source of funds: This work was supported by Arthritis Research UK (formerly the Arthritis Research Campaign) Conflicts of interest: The authors have declared no conflicts of interest				
Study design: Systematic review of 2 RCTs		Level of evidence: Level I	Location/setting: UK and Brazil	
Intervention: Homeopathy		Comparator(s): Placebo		
Sample size: The two included RCTs recruited 44 and 112 patients				
Population characteristics: Seropositive rheumatoid arthritis (RA) patients on stable treatment (1 RCT); patients with RA according to ARA criteria (1 RCT)				
Length of follow-up: Both studies had a duration of 6 months (one study was a cross-over design in which participants spent 3 months per treatment arm)		Outcome(s) measured: Articular index, ESR, duration of morning stiffness; 15-m walking time; Ritchie articular index; grip strength; functional class; other medications; seromucoids; physician assessment		
INTERNAL VALIDITY				
Allocation: Randomised – method of allocation/ concealment not clear (2 RCTs)	Comparison of study groups: NR	Blinding: NR	Treatment/ measurement bias: NR	Follow-up (ITT): High withdrawal rate – none due to adverse events (only 58 of 112 completed the study) (1 RCT). Analysed population unclear (2 RCTs)
Author-assessed quality of included studies: Method used: Jadad score Quality: Both studies scored 3				
Overall quality assessment Rating: 8/10 according to the AMSTAR criteria Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed (7 databases), and key words provided. Status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were not provided in an aggregated form and only limited characteristics provided in-text. Scientific quality of the included studies was assessed using the Jadad score and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was discussed. The authors acknowledged the source of funding				
RESULTS				
Overall: • **The available evidence does not currently support the use of homeopathy in the management of RA.**				
Individual study results				
Trial (N) *Quality*	Intervention	Control	Outcome	Results as reported in the systematic review
Fisher 2001	Homeopathic	Placebo	Pain	Significantly lower

N=112 *Jadad score 3*	medicines in 6cH or 30cH. The most commonly used were *Rhus toxicodendron* and sulphur			pain scores after placebo therapy
			Articular index	No difference between treatment groups
			ESR	No difference between treatment groups
			Duration of morning stiffness	No difference between treatment groups
Andrade 1991 N=44 *Jadad score 3*	Individualised homeopathy	Placebo	Morning stiffness	No difference between treatment groups
			15-m walking time	No difference between treatment groups
			Ritchie articular index	No difference between treatment groups
			Grip strength	No difference between treatment groups
			Functional class	No difference between treatment groups
			Other medications	No difference between treatment groups
			ESR	No difference between treatment groups
			Seromucoids	No difference between treatment groups
			Physician assessment	No difference between treatment groups
EXTERNAL VALIDITY				
Generalisability:				
Comments: This review was a broad review of complementary medicines for RA and therefore provided limited conclusions specifically about homeopathy. Publication bias is not a huge concern because there is not good evidence of efficacy for any of the compounds reviewed anyway				

Abbreviations: ARA, American Rheumatism Association; ESR, erythrocyte sedimentation rate; ITT, intention-to-treat; NR, not reported; RA, rheumatoid arthritis; RCT, randomised controlled trial

Citation: Macfarlane GJ, El-Metwally A, De Silva V, Ernst E, Dowds GL, Moots RJ (2011) Evidence for the efficacy of complementary and alternative medicines in the management of rheumatoid arthritis: A systematic review. Rheumatology (UK) 50(9):1672-83.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration,		Yes
	✓	No

severity, or other diseases should be reported.		Can't answer
		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**8/10**	

STUDY DETAILS

Reference: Vickers AJ, Smith C (2006) Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes (Review). Cochrane Database Syst Rev(3).

Updated citation: Mathie RT, Frye J, Fisher P. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like illness. Cochrane Database Syst Rev 2012, Issue 12. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub5.

Affiliation/source of funds: NR

Conflicts of interest: All three reviewauthors are research-active in the field of homeopathy, and they aremembers of the International ScientificCommittee for Homeopathic Investigations (ISCHI),whosemembership also includes two employees of Boiron, themanufacturers ofOscillococcinum ®. Progress with the Cochrane Review on Oscillococcinum® was presented briefly at ISCHI meetings in 2010 and 2011. The drafting of this Cochrane Review has been carried out independently of those communications and of the authors' other ongoing research activity. ISCHI has not, and is not, running or sponsoring any research on Oscillococcinum®

Study design:	Level of evidence:	Location/setting:
Systematic review of 6 RCTs (Level II)	Level I	France (3 RCTs); Germany (1 RCT); Russia (2 RCTs)

Intervention:	Comparator(s):
Homeopathy regimen specified by authors (all included studies)	Placebo (all included studies)

Sample size: The number of patients enrolled in the RCTs ranged from 100 to 487

Population characteristics:

- Casanova, 1984: Patients with influenza-like illness onset less than 48 hours previously. Intervention group: average age: 42 years; 19 males and 31 females. Comparator group: average age: 41 years; 26 males and 24 females
- Casanova 1988: Participants complaining of influenza. Intervention group: average age: 44 years; 61 males and 89 females. Comparator group: average age: 38 years; 56 males and 94 females.
- Ferley 1989: Participants in primary care with a complaint of influenza-like illness. Inclusion criteria: age older than 12 years; rectal temperature above 38 °C and at least 2 of headache, stiffness, lumbar and articular pain, shivers. Exclusion criteria: duration more than 24 hours; immune deficiency; local infection; immunisation against influenza; depression; immunostimulant treatment. Intervention group: average age: 34 years; 93 males and 127 females. Comparator group: average age: 35 years; 97 males and 129 females.
- Papp 1998: Patients recruited in primary care or by internal medicine specialists. Inclusion criteria: rectal temperature above 38 °C; muscle pain or headache; one of shivering, cough, spinal pain, nasal irritation, malaise, thoracic pain, periarticular pain. Exclusion criteria: duration more than 24 hours; immune deficiency; local infection; immunisation against influenza; medical need for medication; immunostimulant or immunosuppressive treatment. Use of analgesics, antibiotics or anti-influenza agents in the first 48 hours was a postrandomisation exclusion criterion. Intervention group: average age: 35 years; 95 males and 93 females. Comparator group: average age: 35 years; 96 males and 88 females.
- Selkova 2005a: Professional staff (average age approximately 50 years) in outpatient health clinic with influenza-like symptoms in previous 2 days or have family contact/s displaying influenza-like symptoms
- Selkova 2005b: Students aged 16-22 years at medical school, Kalouga, Russia; not vaccinated against influenza

Length of follow-up:	Outcome(s) measured:
RCTs: range from 3 days to 4 weeks	Participant global assessment of success; Presence of chills, aches, rhinitis, night cough, day cough, fever; Temperature; Proportion of patients who recovered (defined as rectal temperature below 37.5 °C and complete resolution of all 5 symptoms); Number of days to recovery; Number of days to return to work; Use of medication for pain or fever; Use of medication for cough or sore throat; Use of antibiotic medication; Patient judgment of effectiveness of treatment; Whether absence of symptoms after 48 hours (physician-assessed); Time to recovery (patient-assesse); Total symptoms score; Number of participants who fell ill with influenza symptoms

INTERNAL VALIDITY

Allocation: Concealment of allocation adequate in 1 RCT and unclear in 5 RCTs	Comparison of study groups: All included studies focused on homeopathy vs placebo in patients with influenza-like illness	Blinding: Unclear in all included studies	Treatment/ measurement bias: Unclear in all included studies	Follow-up (ITT): Unclear in 5 RCTs. 1 RCT reported "some minor inconsistencies between figures suggest a small amount of missing data"

Author-assessed quality of included studies:
4 RCTs has unclear risk of bias for: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias
1 RCT had unclear risk of bias for: random sequence generation, allocation concealment, blinding of outcome assessment, selective reporting. Low risk of bias for blinding of participants and personnel, incomplete outcome data and other bias.
1 RCT had unclear risk of bias for: blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Low risk of bias for random sequence generation, allocation concealment and blinding of participants and personnel

Overall quality assessment
Rating: 9/11 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. List of included and excluded studies were provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. Pooled results of findings in a meta-analysis. The likelihood of publication bias was not assessed. Conflicts of interest were stated.

RESULTS

Overall:

- "There is insufficient good evidence to enable robust conclusions to be made about Oscillococcinum in the prevention or treatment of influenza and influenza-like illness. Our findings do not rule out the possibility that Oscillococcinum could have a clinically useful treatment effect but, given the low quality of the eligible studies, the evidence is not compelling. There was no evidence of clinically important harms due to Oscillococcinum".

Individual study results

Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Casanova, 1984 N=100 *Quality score not specified*	Oscillococcinum®, 4 doses in over 2 days at 6-hour intervals n=50	Placebo n=50	No fever at 48 hours	Favours homeopathy (RR 1.98; 95% CI 1.34-2.92; P=0.00061)
			No rhinitis at 48 hours	No significant difference (RR 1.33; 95% CI 0.66-2.70)
			No general aches at 48 hours	Favours homeopathy (RR 1.73; 95% CI 1.16-2.59; P=0.0072)
			No night cough at 48 hours	No significant difference (RR 1.44; 95% CI 0.73-2.84)
			No day cough at 48 hours	Favours homeopathy (RR 2.00; 95% CI 1.20-3.31; P=0.0076)
Casanova, 1988 N=300 *Quality score not*	Oscillococcinum® twice a day for 3 to 4 days	Placebo n=150	Temperature at 48 hours	Favours homeopathy (MD -0.50; 95% CI -0.67, -0.33;

specified	n=150			P<0.00001)
Ferley, 1989 N=487 *Quality score not specified*	Oscillococcinum® twice a day for 5 days n=220	Placebo n=226	Absence of symptoms at 48 hours – patient assessment by age (12-29 years; 30+ years)	Favours homeopathy (RR 1.98; 95% CI 1.14-3.43; P-value not reported)
			Absence of symptoms at 48 hours – patient assessment by severity of symptoms (severe; moderate to severe)	Favours homeopathy (RR 1.65; 95% CI 1.02-2.65;P-value not reported)
			Medication used for pain or fever	Favours homeopathy (RR 0.82; 95% CI 0.67-1.00; P=0.048)
			Medication used for cough or coryza	No significant difference (RR 0.96; 95% CI 0.76-1.21)
			Antibiotics used	No significant difference (RR 0.87; 95% CI 0.47-1.62)
Papp, 1998 N=372 *Quality score not specified*	Oscillococcinum® 3 times a day for 3 days n=188	Placebo n=184	Fitness for work at 2 days	No significant difference (RR 1.80; 95% CI 0.99-3.26)
			Fitness for work at 4 days	No significant difference (RR 1.04; 95% CI 0.83-1.30)
			No headache at 48 hours	No significant difference (RR 1.20; 95% CI 0.88-1.63)
			No backache at 48 hours	No significant difference (RR 1.27; 95% CI 1.00-1.61; P=0.05)
			No spinal pain at 48 hours	Favours homeopathy (RR 1.27; 95% CI 1.02-1.58; P=0.030)
			No muscle pain at 48 hours	Favours homeopathy (RR 1.47; 95% CI 1.10-1.97; P=0.010)
			No articular pain at 48 hours	Favours homeopathy (RR 1.40; 95% CI 1.09-1.80; P=0.0090)
			Improvement in symptoms at 48 hours – physician assessment	No significant difference (RR 1.07; 95% CI 0.98-1.18)
			Absence of symptoms at 48 hours – physician assessment	No significant difference (RR 1.28; 95% CI 0.79-2.06)
			Increased use of concomitant medication during trial	Favours homeopathy (RR 0.61; 95% CI 0.40-0.92; P=0.020)
Selkova, 2005a N=100	Oscillococcinum®, prophylactically, once	Placebo n=NR	Number of patients who fell ill with influenza symptoms	NR

Quality score not specified	per week for 4 weeks n=NR			
Selkova, 2005b N=227 *Quality score not specified*	Oscillococcinum®, prophylactically, once per week for 4 weeks n=NR	Placebo n=NR	Number of patients who fell ill with influenza symptoms	NR
Meta-analysis by the systematic review				
Outcome:	Intervention group:	Control group:	RR (95% CI)	P-value • Favours intervention/control/no difference • Substantial/moderate/ mild heterogeneity[a] P=X (I^2=X)
Prevention: Oscillococcinum versus placebo				
Occurrence of influenza-like illness (2 RCTs; N=327)	23/160	44/167	0.48 (0.17-1.34)	• No significant difference (P=0.16) • Moderate heterogeneity (P=0.22; I^2=33%)
Treatment: Oscillococcinum versus placebo				
Absence of symptoms at 48 hours – patient assessment (2 RCTs; N=796) Ferley 1989 Papp 1998	66/395	36/401	1.86 (1.27-2.73)	• Favours homeopathy (P=0.0014) • No significant heterogeneity (P=0.46; I^2=0%)
No chills at 48 hours (2 RCTs; N=418) Casanova 1984 Papp 1998	136/209	108/209	1.30 (1.04-1.63)	• Favours homeopathy (P=0.020) • Moderate heterogeneity (P=0.19; I^2=42%)
Absence of symptoms at 3 days (patient's assessment) (2 RCTs; N=796) Ferley 1989 Papp 1998	136/395	109/401	1.27 (1.03-1.56)	• Favours homeopathy (P=0.020) • No significant heterogeneity (P=0.94; I^2=0%)
Absence of symptoms at 4 days (patient's assessment) (2 RCTs; N=796) Ferley 1989 Papp 1988	223/395	203/401	1.11 (0.98-1.27)	• No significant difference (P=0.10) • No significant heterogeneity (P=0.88; I^2=0%)
Absence of symptoms at 5 days (patient's assessment) (2 RCTs; N=796) Ferley 1989 Papp 1988	277/395	266/401	1.06 (0.96-1.16)	• No significant difference (P=0.25) • No significant heterogeneity (P=0.94; I^2=0%)
EXTERNAL VALIDITY				
Generalisability: Participants within the included studies were of varying ages. None of the included studies were conducted in Australia				

Comments:

Comments about the included studies from Mathie 2012:

- Casanova, 1984: Reported in what appears to be a general medical magazine, very few experimental details given
- Casanova, 1988: Inconsistency between text and Table 3 of the original study paper. The data for day 4 in the table appear to have been transposed. The text values were selected
- Ferley, 1989: Specific outcomes (temperature, symptoms including cough, coryza and fatigue) not reported *per se*
- Papp, 1998 : Some outcomes not clearly reported, including mean time to recovery or return to work

Abbreviations: CI, confidence interval; ITT, intention-to-treat; MD, Mean difference; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, relative risk.

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Citation: Vickers AJ, Smith C (2006) Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes (Review). Cochrane Database Syst Rev(3). Updated citation: Mathie RT, Frye J, Fisher P. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like illness. Cochrane Database Syst Rev 2012, Issue 12. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub5.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration,	✓	Yes
		No

severity, or other diseases should be reported.		Can't answer
		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	✓	Yes
		No
		Can't answer
		Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**9/11**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: McCarney R, Warner J, Fisher P, Van Haselen R (2009) Homeopathy for dementia. Cochrane Database Syst Rev(1):CD003803.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: Funded by the Alzheimer's Society, UK
Conflicts of interest: Authors stated that there were no conflicts of interest</td></tr>
<tr><td colspan="2">Study design:
No studies fulfilled the criteria for inclusion</td><td>Level of evidence: N/A</td><td colspan="2">Location/setting: N/A</td></tr>
<tr><td colspan="2">Intervention: N/A</td><td colspan="3">Comparator(s): N/A</td></tr>
<tr><td colspan="5">Sample size: N/A</td></tr>
<tr><td colspan="5">Population characteristics:
N/A</td></tr>
<tr><td colspan="2">Length of follow-up: N/A</td><td colspan="3">Outcome(s) measured: N/A</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: N/A</td><td>Comparison of study groups: N/A</td><td>Blinding:
N/A</td><td>Treatment/ measurement bias: N/A</td><td>Follow-up (ITT): N/A</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies: N/A</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 5/5 according to the AMSTAR criteria
Description: Comprehensive literature search (seven databases and various registries searched; keywords provided); both published and unpublished studies included; no data extraction – no relevant studies identified; a list of excluded studies was provided</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
"In view of the absence of evidence it is not possible to comment on the use of homeopathy in treating dementia."</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisability: N/A</td></tr>
<tr><td colspan="5">Comments: None</td></tr>
</table>

Abbreviations: N/A, not applicable.

Citation: McCarney R, Warner J, Fisher P, Van Haselen R (2009) Homeopathy for dementia. Cochrane Database Syst Rev(1):CD003803.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
		Can't answer
	✓	Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer

	✓	Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.		Yes
		No
		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**5/5**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: McCarney RW, Linde K, Lasserson TJ. Homeopathy for chronic asthma. Cochrane Database Syst Rev. 2008 Issue 1. Art. No.: CD000353. DOI: 10.1002/14651858.CD000353.pub2.</td></tr>
<tr><td colspan="5">Affiliation/source of funds:
• NHS Research and Development, UK
• Blackie Foundation Trust, UK
• Homoeopathic Trust, UK
• Karl und Veronica Carstens-Stiftung, Germany
• NIAMS Grant No 5 U24-AR-43346-02, USA
• British Homoeopathic Association, UK
Conflicts of interest: None known</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 4 RCTs (Level II) and 2 non-randomised controlled studies (Level III-2)</td><td>Level of evidence:
Level I/III</td><td colspan="2">Location/setting:
Brasil (1 RCT); Poland (2 non-randomised controlled studies); Scotland (1 RCT); NR (2 RCTs)</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy regimen specified by authors (3 RCTs, 2 non-randomised controlled studies);
Individualised homeopathy (1 RCT)</td><td colspan="3">Comparator(s):
Placebo (all included studies).
Participants in the comparator group of Matusiewicz 1995 also received methylxanthines for mucolysis and tetracycline in case of exacerbations.</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 28 to 242. The number of patients enrolled in the non-randomised controlled studies ranged from 40-84.</td></tr>
<tr><td colspan="5">Population characteristics:
• Freitas 1995 (RCT): Children (aged 1-12 years) with “at least 3 bronchospastic episodes with intervals of 3 months or less, or continuous wheeze for at least 3 months”
• Lewith 2002 (RCT): Patients with mild to severe asthma
• Matusiewicz 1995 (non-randomised controlled study): Patients with corticosteroid-dependent bronchial asthma
• Matusiewicz 1999 (non-randomised controlled study): Patients with chronic bronchial asthma
• Reilly 1994 (RCT): Patients aged >16 years with allergic asthma, mostly sensitivity to house-dustmite
• White 2003 (RCT): Patients (aged 5-15 years) with general practitioner’s diagnosis and prescription for either beta-agonist or corticosteroid inhaler in previous 3 months</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: range from 8-52 weeks
Non-randomised controlled studies: range from 6-9 month</td><td colspan="3">Outcome(s) measured:
Frequency, duration and intensity of bronchospastic episodes and a score combining these 3 measures; Lung function; Medication use; Subjective symptoms; Granulocyte function; Immune system functioning; Change of subjective symptoms measured on a 100mm VAS; Quality of life</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: Concealment of allocation was adequate in the RCTs and unclear in the non-randomised controlled studies.</td><td>Comparison of study groups:
2 RCTs and 2 non-randomised controlled studies focused on homeopathy vs placebo in patients with asthma. 2 RCTs had more specific patient inclusion criteria.</td><td>Blinding:
All of the included studies were double-blind</td><td>Treatment/ measurement bias:
Unclear in all included studies</td><td>Follow-up (ITT):
All of the RCTs reported on the number of dropouts or withdrawals from the study. Loss to follow up is unclear in the two non-randomised</td></tr>
</table>

				controlled studies

Author-assessed quality of included studies:
Method used: Jadad scores reflecting the points awarded for the three component domains in the order of: randomisation (0,1 or 2), blinding (0, 1 or 2) and withdrawals (0 or 1).
Quality: 2 RCTs scored 1-2-1; 2 RCTs scored 2-2-1; 1 non-randomised controlled study scored 0-1-0; 1 non-randomised controlled study scored 1-1-0

Overall quality assessment
Rating: 9/11 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. List of included and excluded studies were provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. Pooled results of findings in a meta-analysis. The likelihood of publication bias was not assessed. Conflicts of interest were stated.

RESULTS

Overall:

- "There is not enough evidence to reliably assess the possible role of homeopathy in asthma. As well as randomised trials, there is a need for observational data to document the different methods of homeopathic prescribing and how patients respond. This will help to establish to what extent people respond to a 'package of care' rather than the homeopathic intervention alone".
- "The currently available evidence is insufficient to assess reliably the possible role of homeopathy in the treatment of asthma. Whilst the scientific rationale behind homeopathy remains unproven, non-specific benefits associated with a 'holistic' package of care may exist. The effect of homeopathy on asthma has yet to be proven in a randomised study. However, the varied quality of the studies precludes us from extrapolating any effects observed to the general population level".

Individual study results

Trial (N) *Quality*[a]	Intervention	Control	Outcome	Results as reported in the systematic review
Freitas 1995 N=69 *Jadad score 1-2-1*	Blatta officinalis C6, 2 globules 3 times per day for 6 months	Placebo	Intensity of exacerbations	No significant difference between treatment groups
			Frequency of exacerbations	No significant difference between treatment groups
			Duration of exacerbations	No significant difference between treatment groups
Lewith 2002 N=242 *Jadad score 2-2-1*	Isopathy (30C house dust mite), 3 doses orally in 24 hours	Placebo	Lung function	No significant difference
			Medication use	No significant difference in bronchodilator usage after treatment of at 15 week follow-up
			Subjective symptoms	No adverse events reported
Matusiewicz 1995 N=40 *Jadad score 0-1-0*	1 ampoule Engystol N (a complex remedy consisting of the homeopathic remedies Vincetoxin D6/D10/	Placebo. In addition, patients received methylxanthines for mucolysis and tetracycline in	PEF	Significant difference between homeopathy and control in favour of homeopathy (no p value reported). PEF increased from 200ml to 330ml in

	D30, Sulfur D4/D10) injected subcutaneously at intervals of 5 to 7 days. In addition, patients received methylxanthines for mucolysis and tetracycline in case of exacerbations	case of exacerbations.		the treatment group and decreased from 210ml to 190ml in the placebo group
			FEV	There was a 'clear difference' between treatment and control. FEV litres improved from 1.7 at baseline to 2.4 after treatment in the homeopathy group; placebo group changed from 1.9 to 1.8 litres, no SDs reported.
			FVC	There was a 'clear difference' between treatment and control (treatment group: +1.3 litres versus control group: 0 litres); no p values reported
			Medication use	There was a 'clear difference' between treatment and control in terms of oral steroid use (3mg per day in the treatment group versus 7mg in the control group). No SD or p values reported
Matusiewicz 1999 N=84 *Jadad score 1-1-0*	1 ampoule of Asthma H (a complex remedy consisting of 14 homeopathic potencies of D3, D4, D5 and D6) injected subcutaneously at intervals of 5 to 7 days	Placebo	Medication use	"Significant effect"
			Immune functioning	"Significant effect"
			Global ratings	"Significant effect"
			Number of infections	"Significant effect"
			FVC	No significant differences (2.7 litres, SD: 0.91 in treatment group; 2.74 litres, SD: 0.7 in the control group)
			Medication use	Study reported "inhaled triamcinolone usage with treatment leading to a significant reduction

				(baseline 4.73mg versus 2.3mg in the treatment group; p<0.01; and 4.38mg versus 4.51mg in the control group; p>0.01.
Reilly 1994 N=28 *Jadad score 1-2-1*	Homeopathic preparation of the individual allergens in potency C30 (30 dilution steps 1:100) prepared in a water-alcohol solution and impregnated on lactose/sucrose globules (placebo impregnated with diluent only). Treatment consisted of 3 doses of globules within 24 hours (once).	Placebo	Severity symptoms quantified by a 100mm VAS	Highly significant difference between treatment groups (p=0.003). Improvement of 7.2mm (SD: 10.6mm) in the treatment group; deterioration by 7.8mm (SD: 10.8mm) in the placebo group.
			PEFR	No significant difference between groups
			FVC	Significant difference between the medians of the groups (0.36 litres; 95% CI 0.03 to 0.73; p value 0.03)
White 2003 N=93 *Jadad score 2-2-1*	Any number of individualised homeopathy prescriptions.	Placebo	Days off school (measured as a change from the previous month; increased, no change, or reduced)	No statistically significant differences between the treatment groups
			Lung function (PEF)	No significant difference between treatment groups in terms of improvement
			Quality of life	No significant difference between treatment and control
			Medication use	No significant difference in terms of use of inhaler
			Global assessment of change	No significant difference between treatment groups
			Adverse events	No significant intergroup differences reported
Meta-analysis by the systematic review				
Outcome:	Intervention group:	Control group:	Measure of effect/effect size (95% CI):	P-value • Favours intervention/control/no difference • Substantial/moderate/ mild heterogeneity[b]

				P=X (I^2=X)
Individualised homeopathy versus placebo				
Reduction in the number of days absent from school (1 RCT; N=NR)	2/43	4/46	Odds ratio 0.51 (0.09-2.95)	• Effect size: not estimable • Heterogeneity: NR
Improvement by ≥15% (1 RCT; N=NR)	12/43	17/46	Odds ratio 0.66 (0.27-1.62)	• Effect size: not estimable • Heterogeneity: NR
Use of inhalers (reduced) (1 RCT; N=NR)	18/43	18/46	Odds ratio 1.12 (0.48-2.61)	• Effect size: not estimable • Heterogeneity: NR
Formula homeopathy versus placebo				
Symptoms in adults (1 RCT; N=NR)	Mean(SD): 2.73(1.88) N=122	Mean(SD): 2.68(1.97) N=120	Mean difference 0.03 (-0.23 to 0.28)	• Effect size: not estimable • Heterogeneity: NR
Symptoms (change scores) (1 RCT; N=NR)	Mean(SD): -7(10.6) N=11	Mean(SD): 7.8(10.8) N=13	Mean difference: -14.80 (-23.39 to -6.21)	• Effect size: not estimable • Heterogeneity: NR
PEF (morning) in adults (1 RCT (A), 1 non-randomised controlled study (B); N=NR)	Mean(SD): A: 399(55.23); N=122 B: 330(0); N=20	Mean(SD): A: 399(54.77); N=120 B: 190(0); N=20	Mean difference A: 0.0 (-13.86 to 13.86) B: 0.0 (0.0-0.0)	• Effect size: not estimable • Heterogeneity: NR
FEV1 (1 RCT, 2 non-randomised controlled studies; N=366)	Mean(SD): NR N=203	Mean(SD): NR N=163	Mean difference: -0.06 (-0.17 to 0.04)	• No significant difference (P=0.24) • No significant heterogeneity: P=0.68 (I^2=0%)
FVC (1 non-randomised controlled study; N=NR)	Mean(SD): 2.7(0.91) N=61	Mean(SD): 2.74(0.7) N=23	Mean difference: -0.04 (-0.41 to 0.33)	• Effect size: not estimable • Heterogeneity: NR
Steroid usage (1 RCT; N=NR)	Mean(SD): 2.3(2.71) N=61	Mean(SD): 4.51(1.9) N=23	Mean difference: -2.21 (-3.24 to -1.18)	• Effect size: not estimable • Heterogeneity: NR
Bronchodilator usage (1 RCT; N=NR)	Mean(SD): 3.89(1.21) N=122	Mean(SD): 3.5(2.19) N=120	Mean difference: 0.39 (-0.06 to 0.84)	• Effect size: not estimable • Heterogeneity: NR
EXTERNAL VALIDITY				
Generalisability: Participants within the included studies were of varying ages. None of the included studies were conducted in Australia				
Comments: Comments about the included studies from McCarney 2008: • Freitas 1995: characterisation of the patient sample insufficient: is it really asthma? • Lewith 2002: insufficient reporting • Matusiewicz 1995: insufficient reporting • Matusiewicz 1999: small but rigorous study • White 2003: starting lung function not much different to healthy individuals (PEF 100.4 and 96.9 % predicted) so unclear as to whether much change could occur and doubt over whether the quality of life measure was sensitive enough to change. 13 adverse events reported in the homeopathy group and 10 in the placebo (no serious)				

Abbreviations: CI, confidence interval; FEV1, Forced expiratory volume in 1 second; PEF, Peak expiratory flow; NR, not reported; RCT, randomised controlled trial; SD, standard deviation; UK, United Kingdom; VAS, visual analogue scale

[a] Jadad scores reflect the points awarded for the three component domains in the order of: randomisation (0,1 or 2), blinding (0, 1 or 2) and withdrawals (0 or 1).
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Citation: McCarney RW, Linde K, Lasserson TJ. Homeopathy for chronic asthma. Cochrane Database Syst Rev. 2008 Issue 1. Art. No.: CD000353. DOI: 10.1002/14651858.CD000353.pub2.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	✓	Yes
		No
		Can't answer
		Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**9/11**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Milazzo S, Russell N, Ernst E (2006) Efficacy of homeopathic therapy in cancer treatment. Eur J Cancer 42(3):282-9.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: NR
Conflicts of interest: No conflict of interest stated</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 5 RCTs and 1 non-randomised, controlled trial (1 CT)</td><td>Level of evidence:
Level I/III</td><td colspan="2">Location/setting:
Various</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy (5 RCTs, 1 CT)</td><td colspan="3">Comparator(s):
Placebo (5 RCTs); Randomly chosen controls from the same age group with similar stages of cancer, who received no treatments for stomatitis (1 CT)</td></tr>
<tr><td colspan="5">Population characteristics:
• Cancer patients undergoing radiation therapy (1 RCT)
• Children and teenagers with leukemia (1 CT)
• Breast cancer patients undergoing radio-therapy (1 RCT)
• Patients aged 3-25 years with blood malignant cancer who underwent allogeneic or autologous stem-cell transplantation (1 RCT)
• Breast cancer survivors (1 RCT)
• Breast cancer survivors with oestrogen withdrawal symptoms. No more than three hot flushes per day, without metastatic disease, no concurrent treatment for hot flushes, no severe concurrent illness, and not undergoing chemotherapy (1 RCT)</td></tr>
<tr><td colspan="2">Length of follow-up:
Range: 10 weeks to 1 year (not reported in 1 RCT and the case-control study)</td><td colspan="3">Condition investigated; outcome(s) measured:
Radiation reaction; degree of reaction according to an 18-point radiation reaction profile (0-5: minimal; 6-10: moderate but tolerable; >11: severe); chemotherapy-induced stomatitis (mouth sores); opiate requirements for pain; duration of symptoms; quality of life; radiodermatitis; skin heat; hyperpigmentation; erytherma; oedema; total severity of symptoms; adverse events; time to worsening of symptoms; oral pain; menopausal symptoms; hot flush frequency and severity (Kupperman Menopausal Index); quality of life (measured according to EORTC QLQ-C30, plus Breast module; SF-36); estrogen withdrawal symptoms; MYMOP Activity score; MYMOP Profile score</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
Randomisation methods not described</td><td>Comparison of study groups:
Significant heterogeneity between trials –
• Child vs adult populations
• Underlying condition (e.g. breast cancer, leukemia, etc)
• Symptoms associated with cancer treatments (radiodermatitis, chemotherapy-induced stomatitis).</td><td>Blinding:
Triple-blind (1 RCT); double-blind (3 RCTs); unclear (1 RCT, 1 CT)</td><td>Treatment/ measurement bias:
NR</td><td>Follow-up (ITT):
NR</td></tr>
<tr><td colspan="5">Author assessed quality of included trials:
Method used: Jadad score
Quality: 1 CT scored 0; 1 RCT scored 1; 2 RCTs scored 4; 2 RCTs scored 5</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 7/10
Description: Comprehensive literature search (five databases searched); study provided information about patient</td></tr>
</table>

characteristics (age, patient condition, etc); no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was described briefly; publication bias was not discussed.

RESULTS

Overall:

- Five out of six trials yielded positive results (for chemotherapy induced stomatitis, radiodermatitis and general adverse events from radiotherapy).
- Insufficient evidence to support clinical efficacy of homeopathic therapy in cancer care.
- Only four of the six studies provided statistical features in their results sections.
- **Of the six trials included in the review, only two reported statistically significant positive results of their primary outcome, one of which only reached significance at certain time points.**
- **The main limitation of our systematic review is the lack and sometimes poor quality of the primary data.**

Individual study results

Trial *Quality*	Intervention (n):	Control (n):	Outcome:	Results as reported in the systematic review:
Oberbaum 1998 *Jadad score 0*	TraumeelS®[a] (n=20)	Randomly chosen controls from the same age group with similar stages of cancer, who received no treatments for stomatitis (n=7)	Symptom duration	Statistical difference between groups not reported. Homeopathy group: 6 days; controls: 13 days
			Use of opiates	Non-significant trend suggesting less patients in the intervention group required opiates compared to the control group (p=0.09)
Balzarini 2000 *Jadad score 4*	Belladonna 7cH (three granules, twice a day) and X-ray 15cH (once a day) (n=29)	Placebo (n=32)	Hyperpigmentation	Significantly less hyperpigmentation in the homeopathy treated group at Week 5 (p=0.050), although the difference was no longer statistically significant by the end of the 10-week follow-up (p=0.060)
			Skin heat	Significant decrease in the homeopathy-treated group compared to placebo at Week 8 (p=0.011). However the benefit was transient as the difference was no longer significant at the 10-week follow-up (p=0.250)
			Total severity score	More favourable in the intervention group during radiotherapy and recovery. Statistically significant in recovery only (p=0.05)
			Frequency of oedema	Higher frequency in the intervention group - statistically significant difference at Weeks 5 and 6 (p=0.025)
			Adverse event – hot flushes, perspiration and migraine	Statistical difference between groups not reported. Homeopathy group: n=1; placebo group: n=0
Oberbaum 2001 *Jadad score 4*	TraumeelS®[a] (n=15)	Placebo (n=15)	Mean AUC (severity and duration of stomatitis)	Statistically significant difference between groups. Homeopathy: 10.4; Placebo: 24.3; p<0.01

			Mean time to worsening of symptoms	Statistically significant difference between groups favouring homeopathy. Homeopathy group: 6.9 days; placebo group: 4.3 days; p<0.001
			Median time to worsening of symptoms	Homeopathy group: 4.7 days; placebo group: 4.0 days. P-value not specified
			Severity score (subgroup analysis of patients aged less than 15)	Significant difference between treatment groups favouring homeopathy. Homeopathy group: 11; placebo group: 25.9; p<0.01
			Oral pain and discomfort	Patients in the intervention group showed a reduction (no p-values provided)
			Dryness of mouth and tongue	Patients in the intervention group showed a reduction (no p-values provided)
			Difficulty to swallow	Patients in the intervention group showed a reduction (no p-values provided)
			Dysphagia	Patients in the intervention group showed a reduction (no p-values provided)
			Adverse events: (i) Graft vs. host disease (ii) Sepsis (iii) GI complications (iv) VOD (v) Pneumonitis	In homeopathy and placebo groups respectively: (i) n=3, n=6 (ii) n=3, n=8 (iii) n=0, n=5 (iv) n=4, n=0 (v) n=4, n=0
Jacobs 2005 *Jadad score 5*	Verum single remedy[b] plus placebo, or a verum combination medicine (Hyland's menopause)[c] (n=30) plus a verum single remedy (n=26)	Placebo (n=27)	General health score	Significant improvement in both homeopathy groups compared to placebo (p<0.03, combination; p=0.02, single)
			Hot flush severity score (subgroup not receiving tamoxifen)	Statistically significantly higher in combination group than single remedy (p<0.001; 95% CI -51.9 to 15.0). Statistically significantly higher in combination homeopathy group than placebo (p=0.01; 95% CI 6.2 to 47.1)
			Total number of hot flushes (subgroup not receiving tamoxifen)	Statistically significantly higher in combination group than single remedy (p=0.002). Statistically significantly higher in combination homeopathy group than placebo (p=0.006)
			Headaches	Statistically significant increase in headaches in the combination

				group (p=0.03)
Thompson 2005 *Jadad score 5*	71 different remedies (tablets, liquid, or granules) (n=28)	Placebo (n=25)	MYMOP activity score	No significant difference between treatment groups (p=0.17; 95% CI -1.0 to 0.2)
			MYMOP overall profile score	No significant difference between treatment groups (p=0.13; 95% CI -0.9 to 0.1)
EXTERNAL VALIDITY				
Generalisability:				
Comments:				

Abbreviations: AUC, area under the curve; EORTC, The European Organization for Research and Treatment of Cancer; GI, gastrointestinal; VOD, venous occlusive disease

[a] Traumeel® is a homeopathic preparation containing: arnica 2X, calendula 2X, millefolium 3X, chamomilla 3X, symphytum 6X, belladonna 2X ana 0.1ml, aconitum 2X 0.06ml, bellis perennis 2X 0.05ml, hypericum 2X 0.03ml, echinacea angustifolia 2X, echniacea purpurea 2X ana 0.025ml, hamamelis 1X 0.01, mercurius sol. 6X 0.05g, and hepar sulfuris 6X 0.1g.

[b] Single remedies consist of 35 different homeopathic medications, mainly: sepia, calcarea carbonica, sulphur, lachesis, and kali carbinicum

[c] 'Hyland's menopause' contains: amyl nitrate, sanguinaria canadensis, and lachesis

Citation:
Milazzo S, Russell N, Ernst E (2006) Efficacy of homeopathic therapy in cancer treatment. Eur J Cancer 42(3):282-9.

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No

	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable

11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**7/10**	

STUDY DETAILS				
Reference: Mills E, Wu P, Ernst E (2005) Complementary therapies for the treatment of HIV: In search of the evidence. Int J STD AIDS 16(6):395-402.				
Affiliation/source of funds: NR Conflicts of interest: NR				
Study design: Systematic review of 2 RCTs		Level of evidence: Level I	Location/setting: India (1 RCT); NR (1 RCT)	
Intervention: Homeopathy		Comparator(s): Placebo		
Sample size: The number of patients enrolled in the RCTs was 12 and 100				
Population characteristics: HIV-positive patients				
Length of follow-up:		Outcome(s) measured: CD4 cell count; weight; body fat; distress		
INTERNAL VALIDITY				
Allocation: Random allocation; 50 in each strata (asymptomatic; persistent generalised lymphadenopathy) – method of allocation not clear (1 RCT); randomised – method of allocation not reported (1 RCT)	Comparison of study groups: NR	Blinding: Double-blinded (1 RCT); non-blinded (1 RCT)	Treatment/ measurement bias: NR	Follow-up (ITT): Withdrawals ranged from 20% to 58%
Author-assessed quality of included studies: Authors stated that both studies were burdened with serious methodological flaws due to small sample sizes and poor patient retention				
Overall quality assessment Rating: 8/10 according to the AMSTAR criteria Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed but key words were not stated. Unpublished studies were not included. No list of included and excluded studies provided. Limited but sufficient characteristics of the included studies were provided. Scientific quality of the included studies was assessed, however the tool used for assessment was unclear. No pooled results of findings. The likelihood of publication bias was assessed. Conflicts of interest were not stated				
RESULTS				
Overall: • **There is no good quality evidence to support the use of homeopathy in the HIV community**				
Individual study results				
Trial (N) *Quality*	Intervention:	Control:	Outcome:	Results as reported in the systematic review:
Rastogi 1999 N=100 *Quality not specified*	Homeopathy – not specific	Placebo	CD4 cell count	Significant difference in cell count before and after treatment in the PGL group. No change in placebo and asymptomatic

				HIV group
Struwe 1993 N=12 *Quality not specified*	Dronabinol (delta-9-tetrahydrocannabinol)	Placebo	Body fat	Significantly increase body fat (1%, p=0.04) in the treatment group compared with the controlled group
EXTERNAL VALIDITY				
Generalisability:				
Comments: It appears that no standardised/validated tool was used to assess the quality of included trials. However, the authors chose to include published RCTs and stated that the possible sources of bias were assessed for each study. The authors of the review have concerns about the conduct of the Rastogi 1999 trial – and stated that there are potential fatal flaws related to ethical concerns. Struwe 1993 was a small trial with large dropouts in both groups (n=7; 58%)				

Abbreviations: HIV, human immunodeficiency virus; ITT, intention-to-treat; NR, not reported; PGL, persistent generalised lymphadenopathy; RCT, randomised controlled trial

Citation: Mills E, Wu P, Ernst E (2005) Complementary therapies for the treatment of HIV: In search of the evidence. Int J STD AIDS 16(6):395-402.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**8/10**	

<table>
<tr><th colspan="6">STUDY DETAILS</th></tr>
<tr><td colspan="6">Reference: Myers CD, White BA, Heft MW (2002) A review of complementary and alternative medicine use for treating chronic facial pain. J Am Dent Assoc 133(9):1189-96.</td></tr>
<tr><td colspan="6">Affiliation/source of funds: Support for this research was provided to Dr Myers from a National Institute of Dental and Craniofacial Research grant
Conflicts of interest:
• Dr. Myers is a research scientist, Pediatric Pain Program, University of California Los Angeles School of Medicine
• Dr. White is a senior investigator, Kaiser Permanente Center for Health Research, Portland, Ore
• Dr. Heft is a professor and the associate chair, Department of Oral and Maxillofacial Surgery and Diagnostic Sciences, University of Florida</td></tr>
<tr><td colspan="3">Study design: N/A</td><td>Level of evidence: N/A</td><td colspan="2">Location/setting: N/A</td></tr>
<tr><td colspan="3">Intervention:
N/A</td><td colspan="3">Comparator(s):
N/A</td></tr>
<tr><td colspan="6">Sample size:
N/A</td></tr>
<tr><td colspan="6">Population characteristics:
N/A</td></tr>
<tr><td colspan="3">Length of follow-up: N/A</td><td colspan="3">Outcome(s) measured: N/A</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: N/A</td><td colspan="2">Comparison of study groups: N/A</td><td>Blinding: N/A</td><td>Treatment/ measurement bias: N/A</td><td>Follow-up (ITT): N/A</td></tr>
<tr><td colspan="6">Author-assessed quality of included studies:
N/A</td></tr>
<tr><td colspan="6">Overall quality assessment
Rating: 3/5 according to the AMSTAR criteria
Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search was performed. Unclear if the status of publication was used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were stated</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td colspan="6">Overall:
• The authors did not locate any randomised clinical trials that tested the effects of homeopathy</td></tr>
<tr><td>Outcome:</td><td>Intervention group:</td><td>Control group:</td><td>Measure of effect/effect size:</td><td>Benefits (NNT):</td><td>95% CI:</td></tr>
<tr><td>N/A</td><td>N/A</td><td>N/A</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability: N/A</td></tr>
<tr><td colspan="6">Comments: Only acupuncture, biofeedback and relaxation trials identified</td></tr>
</table>

Abbreviiations: N/A, not applicable.

Citation: Myers CD, White BA, Heft MW (2002) A review of complementary and alternative medicine use for treating chronic facial pain. J Am Dent Assoc 133(9):1189-96.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer

	✓	Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.		Yes
		No
		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**3/5**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: National Collaborating Centre for Women's and Children's Health (UK). Diarrhoea and Vomiting Caused by Gastroenteritis: Diagnosis, Assessment and Management in Children Younger than 5 Years. London: RCOG Press; 2009 Apr. (NICE Clinical Guidelines, No. 84.)</td></tr>
<tr><td colspan="5">Affiliation/source of funds: National Institute for Health and Clinical Excellence
Conflicts of interest: Not reported</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 1 RCT (Level II)</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
Municipal acute care clinic in Honduras (1 RCT)</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy regimen specified by the authors (1 RCT)</td><td colspan="3">Comparator(s):
Placebo (1 RCT)</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the one RCT was 292.</td></tr>
<tr><td colspan="5">Population characteristics:
• Jacobs 1996 (RCT): Children aged between 5 months and 6 years who had acute diarrhoea (defined as the passage of three or more unformed stools in the previous 24 hours) that was confirmed visually by study staff</td></tr>
<tr><td colspan="2">Length of follow-up:
7 days after the initial visit (1 RCT)</td><td colspan="3">Outcome(s) measured:
Duration of diarrhoea; Mean rate of unformed stool passage per day during follow up; Total number of unformed stools during follow up</td></tr>
<tr><th colspan="5">INTERNAL VALIDITY</th></tr>
<tr><td>Allocation:
Randomisation by sequential assignment of children to pre-randomised and coded vials of intervention or placebo.</td><td>Comparison of study groups:
Homeopathy vs placebo in children with acute diarrhoea.</td><td>Blinding:
Double-blind (1 RCT)</td><td>Treatment/ measurement bias:
Unclear. Not specified by authors</td><td>Follow-up (ITT):
Loss to follow up was reported.</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
• Jacobs 2006: EL=1+. This score was defined as a “well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias”.</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 5/10 according to the AMSTAR criteria
Description: A priori design provided. Unclear how many people performed study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. The conflict of interest was not stated.</td></tr>
<tr><th colspan="5">RESULTS</th></tr>
<tr><td colspan="5">Overall:
• “Evidence from an RCT examining the effects of a combined homeopathy tablet compared with placebo found that there were no differences in effect on duration of diarrhoea, mean rate of unformed stool passage per day during follow-up or total number of unformed stools during follow-up in young children. [EL = 1+]”
• “The Guidelines Development Group considered that the clinical trials assessing homeopathy had significant methodological limitations. Moreover, there was a lack of consistency in the evidence. Therefore, no recommendation was made for the use of homeopathy.”</td></tr>
<tr><th colspan="5">Individual study results</th></tr>
</table>

Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Jacobs 2006 N=292 *SIGN EL 1+*	Homeopathic combination therapy tablets (Arsenicum album, Calcarea carbonica, chamomilla, podophyllum and sulphur – in a liquid homeopathic dilution in the 30C potency) n=131	Placebo n=134	Duration of diarrhoea	No significant difference
			Mean rate of unformed stool passage per day during follow up	No significant difference
			Total number of unformed stools during follow up	No significant difference
EXTERNAL VALIDITY				
Generalisability: The once RCT examined was performed on children aged 5 months to 6 years. The trial was conducted in Honduras.				
Comments: None.				

Abbreviations: EL, evidence level; RCT, randomised controlled trial; SIGN, Scottish Intercollegiate Guidelines Network

Citation: National Collaborating Centre for Women's and Children's Health (UK). Diarrhoea and Vomiting Caused by Gastroenteritis: Diagnosis, Assessment and Management in Children Younger than 5 Years. London: RCOG Press; 2009 Apr. (NICE Clinical Guidelines, No. 84.)		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be	✓	Yes
		No

relevant.		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**5/10**	

STUDY DETAILS				
Reference: National Collaborating Centre for Women's and Children's Health (UK). Surgical management of otitis media with effusion in children. London: RCOG Press; 2008 Feb. (NICE Clinical Guidelines, No. 60.)				
Affiliation/source of funds: National Institute for Health and Clinical Excellence Conflicts of interest were reported in detail in Appendix A of the guidelines				
Study design: Systematic review of 1 RCT (Level II)		Level of evidence: Level I	Location/setting: United Kingdom (1 RCT)	
Intervention: Homeopathy – method unclear (1 RCT)		Comparator(s): Placebo (1 RCT)		
Sample size: The number of patients enrolled in the one RCT was 33				
Population characteristics: • Harrison 1999 (RCT): Children aged 18 months to 8 years with a positive diagnosis of otitis media with effusion by the patient's general practitioner, hearing loss >20 dB and an abnormal tympanogram				
Length of follow-up: 1 year (1 RCT)		Outcome(s) measured: Audiometry; Tympanometry		
INTERNAL VALIDITY				
Allocation: Process of randomisation not described. No concealment of allocation	Comparison of study groups: Homeopathy vs placebo in patients with glue ear	Blinding: No blinding of participants	Treatment/ measurement bias: Unclear. Not specified by authors	Follow-up (ITT): Results given without ITT analysis.
Author-assessed quality of included studies: • Harrison 1999: [EL=1-]. Defined as "meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias"				
Overall quality assessment Rating: 6/10 according to the AMSTAR criteria Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search performed. The status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. The conflicts of interest were stated				
RESULTS				
Overall: • "Results from a pilot trial show some improvement in tympanogram in children treated with homeopathy after 12 months of follow-up compared with standard care, but there was no benefit for the other outcomes." • Homeopathy is not recommended for the management of otitis media with effusion				
Individual study results				
Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Harrison 1999 N=33 *SIGN EL=1-*	Homeopathy n=17	Standard care (watchful waiting) n=16	Audiometric improvement (hearing loss <20 dB)	No significant difference
			Improvement in tympanograms	Significant difference in favour of homeopathy 76.4% versus 31.3%; P=0.01

EXTERNAL VALIDITY
Generalisability: The one included study was performed on children aged 18 months to 8 years in the United Kingdom
Comments: Children in the two groups had similar age ranges but there was a significant difference with regard to their initial hearing loss. NICE (2009) also included the results of a systematic review and meta-analysis (Jacobs et al, 2003) in their evaluation. Jacobs et al (2003) included the results of three RCTs (Jacobs, 1993; Jacobs, 1994; Jacobs 2000), however this systematic review had been excluded for the purposes of this evidence evaluation as the included studies were not identified by systematic methods.

Abbreviations: EL, evidence level; ITT, intention-to-treat; RCT, randomised controlled trial; SIGN, Scottish Intercollegiate Guidelines Network.

Citation: National Collaborating Centre for Women's and Children's Health (UK). Surgical management of otitis media with effusion in children. London: RCOG Press; 2008 Feb. (NICE Clinical Guidelines, No. 60.)		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be	✓	Yes
		No

relevant.		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**6/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: National Collaborating Centre for Women's and Children's Health (UK). Constipation in children and young people: diagnosis and management of idiopathic childhood constipation in primary and secondary care. London: RCOG Press; 2010. (NICE Clinical Guidelines, No. 99.)</td></tr>
<tr><td colspan="5">Affiliation/source of funds: National Institute for Health and Clinical Excellence
Conflicts of interest were reported by all members of the Guidelines Development Group. Refer to Appendix 2 of the guidelines for details</td></tr>
<tr><td colspan="2">Study design:
NA</td><td>Level of evidence:
NA</td><td colspan="2">Location/setting:
NA</td></tr>
<tr><td colspan="2">Intervention: NA</td><td colspan="3">Comparator(s): NA</td></tr>
<tr><td colspan="5">Sample size: NA</td></tr>
<tr><td colspan="5">Population characteristics: NA</td></tr>
<tr><td colspan="2">Length of follow-up: NA</td><td colspan="3">Outcome(s) measured: NA</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: NA</td><td>Comparison of study groups: NA</td><td>Blinding: NA</td><td>Treatment/ measurement bias: NA</td><td>Follow-up (ITT): NA</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies: NA</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 3/5 according to the AMSTAR criteria
Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search was performed. Unclear if the status of publication was used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were stated</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
• “No published evidence was found on the effectiveness of the following complimentary therapies for ongoing treatment and/or maintenance in children with chronic idiopathic constipation: homeopathy.”</td></tr>
<tr><td>Trial (N)</td><td>Intervention (n)</td><td>Control (n)</td><td>Outcome</td><td>Results</td></tr>
<tr><td colspan="5">NA</td></tr>
<tr><td colspan="5">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="5">Generalisability: NA</td></tr>
<tr><td colspan="5">Comments: None</td></tr>
</table>

Abbrevations: NA, not applicable.

Citation: National Collaborating Centre for Women's and Children's Health (UK). Constipation in children and young people: diagnosis and management of idiopathic childhood constipation in primary and secondary care. London: RCOG Press; 2010. (NICE Clinical Guidelines, No. 99.)		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer
	✓	Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be		Yes
		No

relevant.		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**3/5**	

STUDY DETAILS				
Reference: National Collaborating Centre for Acute Care (UK). Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension. London: National Collaborating Centre for Acute Care; 2009 April. (NICE Clinical Guidelines, No. 85).				
Affiliation/source of funds: National Institute for Health and Clinical Excellence Conflicts of interest are reported in detail in Appendix 2 of the guidelines				
Study design: NA		Level of evidence: NA	Location/setting: NA	
Intervention: NA		Comparator(s): NA		
Sample size: NA				
Population characteristics: NA				
Length of follow-up: NA		Outcome(s) measured: NA		
INTERNAL VALIDITY				
Allocation: NA	Comparison of study groups: NA	Blinding: NA	Treatment/ measurement bias: NA	Follow-up (ITT): NA
Author-assessed quality of included studies: NA				
Overall quality assessment Rating: 3/5 according to the AMSTAR criteria Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search was performed. The status of publication was not used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were stated				
RESULTS				
Overall: • "No studies meeting the inclusion criteria for any of the treatments mentioned above (including homeopathy) were identified."				
Trial (N)	Intervention (n)	Control (n)	Outcome	Results
NA				
EXTERNAL VALIDITY				
Generalisability: NA				
Comments: None				

Abbrevations: NA, not applicable.

Citation: National Collaborating Centre for Acute Care (UK). Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension. London: National Collaborating Centre for Acute Care; 2009 April. (NICE Clinical Guidelines, No. 85.)		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer
	✓	Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be		Yes
		No

relevant.		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**3/5**	

<table>
<tr><th colspan="6">STUDY DETAILS</th></tr>
<tr><td colspan="6">Reference: National Collaborating Centre for Nursing and Supportive Care (UK). Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. London: Royal College of Nursing; 2008 Feb. (NICE Clinical Guidelines, No. 61.)</td></tr>
<tr><td colspan="6">Affiliation/source of funds: National Institute for Health and Clinical Excellence
Conflicts of interest were reported by all members of the Guidelines Development Group. Refer to Appendix K of the guidelines for details</td></tr>
<tr><td colspan="3">Study design: NA</td><td>Level of evidence: NA</td><td colspan="2">Location/setting: NA</td></tr>
<tr><td colspan="3">Intervention: NA</td><td colspan="3">Comparator(s): NA</td></tr>
<tr><td colspan="6">Sample size: NA</td></tr>
<tr><td colspan="6">Population characteristics: Patients with irritable bowel syndrome</td></tr>
<tr><td colspan="3">Length of follow-up: NA</td><td colspan="3">Outcome(s) measured: NA</td></tr>
<tr><td colspan="6">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: NA</td><td colspan="2">Comparison of study groups: NA</td><td>Blinding: NA</td><td>Treatment/ measurement bias: NA</td><td>Follow-up (ITT): NA</td></tr>
<tr><td colspan="6">Author-assessed quality of included studies: NA</td></tr>
<tr><td colspan="6">Overall quality assessment
Rating: 3/5 according to the AMSTAR criteria
Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search was performed. The status of publication was not used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were stated.</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td colspan="6">Overall:
• “An initial search identified two trials using homeopathy for irritable bowel syndrome, both conducted about 30 years ago and reported in German. No trials have been done since. Only randomised trials were to be considered for this review and the absence of further studies suggested no need to carry out a full review.”</td></tr>
<tr><td>Trial (N)</td><td>Intervention (n)</td><td>Control (n)</td><td>Outcome</td><td colspan="2">Results</td></tr>
<tr><td colspan="6">NA</td></tr>
<tr><td colspan="6">EXTERNAL VALIDITY</td></tr>
<tr><td colspan="6">Generalisability: NA</td></tr>
<tr><td colspan="6">Comments: None</td></tr>
</table>

Abbrevations: NA, not applicable.

Citation: National Collaborating Centre for Nursing and Supportive Care (UK). Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. London: Royal College of Nursing; 2008 Feb. (NICE Clinical Guidelines, No. 61.)		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer
	✓	Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be		Yes
		No

relevant.		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**3/5**	

STUDY DETAILS				
Reference: National Collaborating Centre for Mental Health (UK). Borderline personality disorder: treatment and management. Leicester: British Psychological Society; 2009. (NICE Clinical Guidelines, No. 78.)				
Affiliation/source of funds: National Institute for Health and Clinical Excellence Conflicts of interest were reported by all members of the Guidelines Development Group. Refer to Appendix 2 of the guidelines for details.				
Study design: Systematic review of any primary research design (Level II, Level III-2)		Level of evidence: Level I/III	Location/setting: NA	
Intervention: NA		Comparator(s): NA		
Sample size: NA				
Population characteristics: Patients with borderline personality disorder				
Length of follow-up: NA		Outcome(s) measured: NA		
INTERNAL VALIDITY				
Allocation: NA	Comparison of study groups: NA	Blinding: NA	Treatment/ measurement bias: NA	Follow-up (ITT): NA
Author-assessed quality of included studies: NA				
Overall quality assessment Rating: 3/5 according to the AMSTAR criteria Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search was performed. The status of publication was not used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were stated				
RESULTS				
Overall: • "No studies were found from the search undertaken. The Guideline Development Group's special advisor knew of no studies on the use of complementary therapies (including homeopathy) in people with a personality disorder, other than those on the use of omega-3 fatty acids already identified." • "There is no evidence on the use of complementary therapies as a treatment in people with a personality disorder, therefore no recommendations could be made."				
Trial (N)	Intervention (n)	Control (n)	Outcome	Results
NA				
EXTERNAL VALIDITY				
Generalisability: NA				
Comments: None				

Abbrevations: NA, not applicable

Citation: National Collaborating Centre for Mental Health (UK). Borderline personality disorder: treatment and management. Leicester: British Psychological Society; 2009. (NICE Clinical Guidelines, No. 78.)		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer
	✓	Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.		Yes
		No
		Can't answer

	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**3/5**	

STUDY DETAILS				
Reference: National Clinical Guideline Centre (UK). The management of lower urinary tract symptoms in men. London: Royal College of Physicians; 2010. (NICE Clinical Guidelines, No. 97.)				
Affiliation/source of funds: National Institute for Health and Clinical Excellence Conflicts of interest were reported in detail by members of the Guidelines Development Group. Refer to Appendix B of the guidelines for full details				
Study design: NA		Level of evidence: NA	Location/setting: NA	
Intervention: NA		Comparator(s): NA		
Sample size: NA				
Population characteristics: NA				
Length of follow-up: NA		Outcome(s) measured: NA		
INTERNAL VALIDITY				
Allocation: NA	Comparison of study groups: NA	Blinding: NA	Treatment/ measurement bias: NA	Follow-up (ITT): NA
Author-assessed quality of included studies: NA				
Overall quality assessment Rating: 3/5 according to the AMSTAR criteria Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search was performed. The status of publication was not used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were stated				
RESULTS				
Overall: • "No clinical studies were identified".				
Trial (N)	Intervention (n)	Control (n)	Outcome	Results
NA				
EXTERNAL VALIDITY				
Generalisability: NA				
Comments: None				

Abbrevations: NA, not applicable.

Citation: National Collaborating Centre for Acute Care (UK). Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension. London: National Collaborating Centre for Acute Care; 2009 April. (NICE Clinical Guidelines, No. 85.)		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer
	✓	Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be		Yes
		No

relevant.		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**3/5**	

STUDY DETAILS				
Reference: Oladapo OT, Fawole B. Treatments for suppression of lactation. Cochrane Database Syst Rev. 2012, Issue 9. Art. No.: CD005937. DOI: 10.1002/14651858.CD005937.pub3.				
Affiliation/source of funds: • UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction-HRP, Switzerland • The Effective Health Care Alliance Programme (EHCAP) of the Liverpool School of Tropical Medicine, funded by the Department for International Health, UK Conflicts of interest: "none known"				
Study design: Systematic review of 1 RCT (Level II)		Level of evidence: Level I	Location/setting: France (1 RCT)	
Intervention: Homeopathy regimen specified by authors (1 RCT)		Comparator(s): Placebo (1 RCT)		
Sample size: 71 patients were enrolled in the RCT				
Population characteristics: • Berrebi 2001 (RCT): Postpartum women who elected not to breastfeed				
Length of follow-up: RCT: 10 days		Outcome(s) measured: Milk secretion, breast engorgement and breast pain. Outcome assessment recorded on visual analogue scale		
INTERNAL VALIDITY				
Allocation: Unclear. Method for random sequence allocation not stated	Comparison of study groups: Homeopathy vs placebo in postpartum women who elected not to breastfeed	Blinding: Double-blind	Treatment/ measurement bias: Unclear. Not specified by authors	Follow-up (ITT): No missing outcome data
Author-assessed quality of included studies: "Overall, the risk of bias for most reports was uncertain as they contained little methodological description" Unclear risk of bias for random sequence generation, allocation concealment, blinding for lactation and adverse events, selective reporting and other bias. Low risk of bias for incomplete outcome data for lactation and adverse events				
Overall quality assessment Rating: 8/10 according to the AMSTAR criteria Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. Only published articles were included. List of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were stated				
RESULTS				
Overall • "This review did not show sufficient evidence to indicate if other pharmacologic agents (includes homeopathic preparation) are useful in suppressing the symptoms of lactation postpartum, as they are all based on individual small trials."				
Individual study results				
Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Berrebi 2001	Five homeopathic	Placebo. All	Milk secretion,	"Berrebi 2001 (71

N=71 *Quality not specified*	pills twice daily for 10 days. All patients received an anti-inflammatory treatment (naproxine-Apranax) for 5 days n=36	patients received an anti-inflammatory treatment (naproxine-Apranax) for 5 days n=35	breast engorgement and breast pain. Outcome assessment recorded on visual analogue scale	women) suggested a lower risk of treatment failure when homeopathic preparation (with anti-inflammatory and analgesic properties) was compared with placebo on days two and four postpartum"
EXTERNAL VALIDITY				
Generalisability: Age of the participants within the included study was not specified. The one included RCT was not conducted in Australia				
Comments: None				

Abbreviations: RCT, randomised controlled trial.

Citation: Oladapo OT, Fawole B. Treatments for suppression of lactation. Cochrane Database Syst Rev. 2012, Issue 9. Art. No.: CD005937. DOI: 10.1002/14651858.CD005937.pub3.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**8/10**	

STUDY DETAILS				
Reference: Owen JM, Green BN (2004) Homeopathic treatment of headaches: a systematic review of the literature. J Chiropr Med 3(2):45-52.				
Affiliation/source of funds: NR Conflicts of interest: NR				
Study design: Systematic review of 4 RCTs		Level of evidence: Level I	Location/setting: Various	
Intervention: Homeopathy		Comparator(s): Placebo		
Sample size: The number of patients enrolled in the RCTs ranged from 60 to 98.				
Population characteristics: Patients with: chronic headaches (1 RCT); migraines (3 RCTs)				
Length of follow-up: RCTs: range – 3 to 4 months		Outcome(s) measured: Frequency, intensity, and severity of headaches/migraine; duration and level of medication necessary for attacks		
INTERNAL VALIDITY				
Allocation: One RCT described the randomisation procedure (details not provided in SR); 2 RCTs partially described the randomisation procedure; 1 RCT did not report the method of allocation	Comparison of study groups: NR	Blinding: Double-blind (3 RCTs); NR (1 RCT	Treatment/ measurement bias: Enthusiasm of homeopath may have effect on treatment efficacy	Follow-up (ITT): ITT analysis conducted (4 RCTs)
Author-assessed quality of included trials: Method used: 20-item methodological assessment tool Quality: 4 RCTs: 64.3%, 57.1%, 38.5%, 25.0%				
Overall quality assessment Rating: 6/10 according to the AMSTAR criteria Description: A comprehensive literature search was conducted; limited information was provided about patient characteristics (age, sex, disease severity, etc); no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was considered when drawing conclusions; publication bias was discussed and thought to have had minimal impact on review.				
RESULTS				
Overall: • There is insufficient evidence to support or refute the use of homeopathy for managing tension type, cervicogenic, or migraine headache – this is partially due to flaws in design • **The present review indicates that it is still unclear whether homeopathy acts as a placebo or an effective intervention**				
Individual study results				
Trial (N) *Quality*	Intervention:	Control:	Outcome:	Results as reported in the systematic review:
Walach 1997 N=98	Individualised homeopathy	Placebo	Frequency of chronic headache	Reduction in both homeopathic and

Quality: 64.3%				placebo groups, no significant differences reported between groups
			Intensity of headache	Reduction in both homeopathic and placebo groups, no significant differences reported between groups
			Severity of headache	Reduction in both homeopathic and placebo groups, no significant differences reported between groups
			Level of medication used	Reduction in both homeopathic and placebo groups, no significant differences reported between groups
Straumsheim 1997 N=73 *Quality: 57.1%*	Individualised homeopathy	Placebo	Frequency of migraine	Reduction in both homeopathic and placebo groups, no significant differences reported between groups
			Intensity of migraine	Reduction in both homeopathic and placebo groups, no significant differences reported between groups
			Severity of migraine	Reduction in both homeopathic and placebo groups, no significant differences reported between groups
			Level of medication used	Reduction in both homeopathic and placebo groups, no significant differences reported between groups
Brigo 1991 N=60 *Quality: 38.5%*	Single dose 30c/4x in two weeks	Placebo	Frequency of migraine	Homeopathy superior to placebo (p-value NR)
			Intensity of migraine	Homeopathy superior to placebo (p-value NR)

			Severity of migraine	Homeopathy superior to placebo (p-value NR)
			Level of medication used	Homeopathy superior to placebo (p-value NR)
Whitmarsh 1997 N=60 *Quality: 25.0%*	Individualised homeopathy	Placebo	Frequency of migraine	"Chance difference. Both groups improved"
			Intensity of migraine	"Chance difference. Both groups improved"
			Severity of migraine	"Chance difference. Both groups improved"
			Level of medication used	"Chance difference. Both groups improved"
EXTERNAL VALIDITY				
Generalisability:				
Comments:				

Abbreviations: ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial; SF-36, Short Form-36; SR, systematic review.

Citation: Owen JM, Green BN (2004) Homeopathic treatment of headaches: a systematic review of the literature. J Chiropr Med 3(2):45-52.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**6/10**	

STUDY DETAILS				
Reference: Passalacqua G, Bousquet PJ, Carlsen KH, Kemp J, Lockey RF, Niggemann B, Pawankar R, Price D, Bousquet J (2006) ARIA update: I--Systematic review of complementary and alternative medicine for rhinitis and asthma. J Allergy Clin Immunol 117(5):1054-62.				
Affiliation/source of funds: NR Conflicts of interest: NR				
Study design: Systematic review of 10 RCTs		Level of evidence: Level I	Location/setting: Various	
Intervention: Homeopathy (9 RCTs); Homeopathy plus drugs (1 RCT)		Comparator(s): Placebo (7 RCTs); Placebo plus drugs or conventional dilution (2 RCTs); Active comparator (1 RCT)		
Sample size: The number of patients enrolled in the RCTs ranged from 28 to 242.				
Population characteristics: Asthma patients (3 RCTs); Seasonal allergic rhinitis (4 RCTs); Perennial allergic rhinitis (1 RCT); Pollen-induced rhinitis (1 RCT)				
Length of follow-up: NR		Outcome(s) measured: Improvement in asthma (VAS); PEF; pulmonary function; histamine challenge; FEV; use of β_2-agonists; asthma score; asthma-related QoL; missing days; PNIF		
INTERNAL VALIDITY				
Allocation: NR	Comparison of study groups: Asthma patients (3 RCTs); three different types of rhinitis patients (7 RCTs)	Blinding: Double-blind (8 RCTs); 2 RCTs NR	Treatment/ measurement bias: NR	Follow-up (ITT): No. of patients enrolled vs completed was reported. Type of analysis used not reported.
Author-assessed quality of included studies: Method used: Jadad score Quality: 2 RCTs scored 4; 8 RCTs scored 5				
Overall quality assessment Rating: 4/10 according to the AMSTAR criteria Description: No a priori design provided. Duplicate study selection and data extraction unclear. Comprehensive literature search of two databases was performed and key words were stated. The status of publication was used as an inclusion criterion (ie. only English studies were included). No list of included and excluded studies provided. Limited characteristics of the included studies were provided and no patient characteristics. Scientific quality of the included studies was assessed using the Jadad score and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were not stated.				
RESULTS				
Overall: • Three well-conducted trials showed no or marginal effects in asthmatic patients • Some positive results were found with homeopathy and rhinitis in good-quality trials, but an equal number of negative studies counterbalanced the positive ones. • **It is not possible to provide evidence-based recommendations for the use of homeopathy to treat allergic rhinitis**				
Individual study results				
Trial (N)	Intervention	Control	Outcome	Results as reported in

Quality				the systematic review:
Asthma				
Reilly 1994 N=28 *Jadad score 4*	30c dilution of allergens	Placebo	Asthma VAS	Significant improvement (no p-value)
			PEF	No change
			Pulmonary function	No change
			Histamine challenge	No change
Lewith 2002 N=242 *Jadad score 5*	Dust mite homeopathy	Placebo	FEV	No difference between active and placebo groups
			PEF	No difference between active and placebo groups
			Asthma symptoms	No difference between active and placebo groups
			Use of β_2-agonists	No difference between active and placebo groups
			Asthma score	No difference between active and placebo groups
White 2003 N=93 *Jadad score 5*	Individual homeopathy plus drugs	Placebo plus drugs	Asthma-related QoL	No difference between active and placebo groups
			PEF	No difference between active and placebo groups
			Use of β_2-agonists	No difference between active and placebo groups
			Missing days	No difference between active and placebo groups
Rhinitis				
Aabel 2000 N=70 *Jadad score 5*	Birch 30c	Placebo	Rhinitis symptoms	No effect on symptoms
Aabel 2000 N=80 *Jadad score 5*	Birch 30c	Placebo	Rhinitis symptoms	No effect on symptoms
Reilly 1986 N=158 *Jadad score 5*	30c dilution grass pollen	Placebo	Symptom score	Decrease (presumably in homeopathy group?) No mention of placebo or between-group differences
			VAS	Decrease (presumably in homeopathy group?)

				No mention of placebo or between-group differences
			Use of antihistamines	Decrease (presumably in homeopathy group?) No mention of placebo or between-group differences
Taylor 2000 N=51 *Jadad score 5*	30c dilution of various allergens	Placebo	VAS	No difference between groups
			Symptom score	No difference between groups
			PNIF morning and evenings	Increase (presumably in homeopathy group?) No mention of placebo or between-group differences
Weiser 1999 N=147 *Jadad score 5*	Nasal *Luffa compositum Heel*	Nasal cromone	Rhinitis symptoms	Homeopathy = nasal cromone
Kim 2005 N=40 *Jadad score 5*	Homeopathic grass, trees, weeds mix	Placebo	3 QoL questionnaires	Significant improvement in active group (compared to placebo or baseline?)
Wiesenauer and Gaus 1985 N=164 *Jadad score 4*	*Galphimia* homeopathic dilution	Conventional dilution/placebo	NR	No significant difference between active and placebo treatments
EXTERNAL VALIDITY				
Generalisability:				
Comments:				

Abbreviations: FEV, forced expiratory volume; ITT, intention-to-treat; NR, not reported; PEF, peak expiratory flow; PNIF, peak nasal inspiratory flow; QoL, quality of life; RCT, randomised controlled trial; VAS, visual analogue scale

Citation: Passalacqua G, Bousquet PJ, Carlsen KH, Kemp J, Lockey RF, Niggemann B, Pawankar R, Price D, Bousquet J (2006) ARIA update: I--Systematic review of complementary and alternative medicine for rhinitis and asthma. J Allergy Clin Immunol 117(5):1054-62.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.		Yes
	✓	No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**4/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Perry R, Terry R, Ernst E (2010) A systematic review of homoeopathy for the treatment of fibromyalgia. Clin Rheumatol 29(5):457-64.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: Grants from The Laing Foundation, Schwabe, Pilkington and GSK
Conflicts of interest: There are no conflicts of interest to declare</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 4 RCTs</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
Various</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy (4 RCTs)</td><td colspan="3">Comparator(s):
Placebo (4 RCTs)</td></tr>
<tr><td colspan="2">Sample size:
Number of patients in the intervention arm(s) ranged from 12 to 30.</td><td colspan="3">Sample size:
Number of patients in the comparator arm(s) ranged from 12 to 32.</td></tr>
<tr><td colspan="5">Population characteristics:
Fibromyalgia patients (all studies)</td></tr>
<tr><td colspan="2">Length of follow-up:
Range: 2 months (1 month per treatment) to 22 weeks</td><td colspan="3">Outcome(s) measured:
Tender point count (TPC); analgesic consumption; improvements in sleep and pain (measured by a combined VAS); tender point pain (TPP) on palpation; fibromyalgia (FM) scores; global health rating; McGill Pain Questionnaire (MPQ); Profile of Mood States (POMS) for depression and anger-hostility; Fibromyalgia Impact Questionnaire (FIQ); McGill pain, affective and sensory scores; European Quality of Life Scale (EuroQol), Measure Yourself Medical Outcome Profile (MYMOP), Hospital Anxiety and Depression Scale (HADS)</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
Computer generated (2 RCTs); NR (2 RCTs)</td><td>Comparison of study groups:
Groups similar at baseline (1 RCT); Groups differed at baseline – active group had a higher TPC and used more anti-histamine and expectory drugs (1 RCT); Limited patient characteristics – all fibromyalgia patients (1 RCT); N/A – repeated measures study design (1 RCT)</td><td>Blinding:
Double-blind (1 RCT); NR (3 RCTs)</td><td>Treatment/ measurement bias: All studies used validated assessment tools or standardised measures of pain to evaluate outcomes</td><td>Follow-up (ITT):
ITT analysis used in 3 RCTs; NR (1 RCT).

No dropouts/ withdrawals (1 RCT); 14.5% withdrawals/ dropouts (1 RCT)</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: Jadad score
Quality: 1 RCT score 2; 2 RCTs scored 3; 1 RCT scored 4</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 8/10 according to the AMSTAR criteria
Description: Comprehensive literature search (six databases searched); limited information about patient characteristics (age, sex, disease severity, etc) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was considered when drawing conclusions; publication bias discussed; sources of support and conflicts of interest were reported</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
</table>

Overall: • **The effectiveness of homeopathy as a symptomatic treatment for FM remains unproven (mainly due to the limited number of RCTs and the relatively poor scientific quality of the existing trials)**				
Individual study results				
Trial: *Quality*	Intervention (n)	Comparator (n)	Outcome:	Results as reported in the systematic review:
Fisher 1986 *Jadad score 3*	One of three homeopathic remedies (*Rhus toxicodendron* (n=5), *Arnica Montana* (n=5), or *Bryonia* (n=2)) in 6c potency twice a day	Placebo – twice a day (n=12)	Pain	No significant difference between intervention groups and placebo (p=0.19). Significant difference between intervention and placebo groups at 2 and 3 months when those with 'poorly indicated' homeopathic remedies were removed, leaving only those with 'optimal fit' (p<0.05)
			Sleep	No significant difference between intervention groups and placebo (p=0.078). Significant difference between intervention and placebo groups at 2 and 3 months when those with 'poorly indicated' homeopathic remedies were removed, leaving only those with 'optimal fit' (p<0.05)
Fisher 1989 *Jadad score 3*	*Rhus toxicodendron* 6c, two tablets three times daily (n=30)	Placebo – two tablets three times daily (n=30)	Number of patients with improved pain and sleep (pain and sleep VAS – combined measure)	Significantly more patients improved in the intervention group (n=53) compared to placebo (n=27); p=0.0052
			Number of tender points	Intervention group had significantly fewer tender points (10.6) compared to placebo (14.1); p<0.005[a]
Bell 2004 *Jadad score 4*	41 remedies used, given as LM potencies. Remedy and dosing regimen	Placebo (n=32)	Improvement in TPC	Significantly greater improvement in TPC in intervention group compared to placebo

	could be altered at any time after consultation with a homeopath (n=30)			(p<0.05)
			Number of patients with at least a 25% improvement in TPP on palpation	Significantly more patients experienced a 25% improvement in the intervention group (n=13/26) compared to placebo (n=4/27); Fisher's exact test, two-tailed: p=0.008
			FM scores	Significantly greater improvement in homeopathy compared to placebo group (p<0.05)
			Global health rating (adjusted for anger and depression)	Significantly greater improvement in homeopathy compared to placebo group (p<0.05). At 6 months, those who stayed in the experimental group had a greater gain in global health than the placebo-switch group
			MPQ	Greater improvement in homeopathy group compared to placebo (p<0.10)
			POMS	Greater improvement in homeopathy group compared to placebo (p<0.10)
Relton 2009 *Jadad score 2*	Individually tailored homeopathic remedies (one 1 hour baseline interview with homeopath followed by four 30 minute follow up interviews where remedy choice and potency can be assessed and changed (n=23)	Usual care with one or more of the following: physiotherapy, aerobic exercise, anti-inflammatory drugs, anti-depressants (n=24)	TPC	No significant inter-group differences
			EuroQol	No significant inter-group differences
			MYMOPS	No significant inter-group differences
			HADS	No significant inter-group differences
			FIQ pain scores	No significant inter-group differences
			FIQ total score	Significantly greater reduction in total score in the homeopathic group compared to the usual care group (p<0.01)
EXTERNAL VALIDITY				
Generalisability: Lack of demographic information on the patients limits the generalisability of the study findings. However the				

individualised remedy and dosage selection is a closer reflection on homeopathy in practice.
Comments: The authors acknowledged that the four included trials were all seriously flawed. In particular, the re-analysis of Fisher et al (1989) by Colquhoun suggested there was no evidence for the efficacy of homeopathic treatment when distribution-free randomisation tests were employed. He criticised Fisher for combining pain and sleep scores thus invalidating the results. Relton (2004) used a design that did not control for placebo effects and was also insufficiently powered due to a high drop-out rate in the usual care group

Abbreviations: EuroQol, European Quality of Life Scale; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; HADS, Hospital Anxiety and Depression Scale; ITT, intention-to-treat; LM, LM dilution factor (1 in 50,000); MPQ, McGill Pain Questionnaire; MYMOP, Measure Yourself Medical Outcome Profile; POMS, Profile of Mood States; RCT, randomised controlled trial; TPC, tender point count; TPP, tender point pain; VAS, visual analogue scale

[a] A later re-analysis of the data (Colquhoun 1991) showed that no significant treatment effects occurred after the first treatment period.

Citation: Perry R, Terry R, Ernst E (2010) A systematic review of homoeopathy for the treatment of fibromyalgia. Clin Rheumatol 29(5):457-64.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**8/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J (2006) Homeopathy for anxiety and anxiety disorders: a systematic review of the research. Homeopathy 95(3):151-62.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: NR
Conflicts of interest: NR</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 8 RCTs and 1 uncontrolled (UC) study</td><td>Level of evidence:
Level I/III</td><td colspan="2">Location/setting:
Australia (1 RCT); United States (UC study); NR (7 RCTs)</td></tr>
<tr><td colspan="2">Intervention:
Homeopathic regimen specified by authors (4 RCTs); Individualised homeopathy (2 RCTs, 1 UC study); Homeopathy – method unclear (2 RCTs)</td><td colspan="3">Comparator(s):
Placebo (5 RCTs); Active comparator (2 RCTs); Placebo or radionically prepared homeopathic remedy (1 RCT)</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 40 to 84. The uncontrolled study had 12 participants</td></tr>
<tr><td colspan="5">Population characteristics:
• Children (aged 6 months to 14 years) with post-operative agitation/anxiety (1 RCT)
• Patients with test anxiety (2 RCTs)
• Adults with generalised anxiety disorder (DSM-IV diagnosis); HAM-A >20, HAM-D <18 (1 RCT)
• Patients with reactive anxiety depression (1 RCT)
• Patients under consultation for depression, postmenopausal involution or thymo-effective dystonia (1 RCT)
• Students with above average anxiety scores (score of 18+ on part one of pre-test STAI) (1 RCT)
• Breast cancer patients with symptoms of oestrogen withdrawal (including anxiety) (1 RCT)
• Social phobia, panic disorder, residual attention-deficit hyperactivity disorder, major depression, chronic fatigue syndrome (UC study).</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: range – 4 days to 16 weeks
UC study: range – 7 to 80 weeks</td><td colspan="3">Outcome(s) measured:
Physician-assessed improvement; Benson Revised Test Anxiety Scale; TAS 36-item A. nitricum questionnaire pre- and post-treatment; HAM-A; HAM-D; BSI; PGWBI; BDI; STAI subjective distress (VAS); Sleep; Delay in sleep onset; Heart rate; ‘Emotionalism’ (measure not stated); Ratio of pre- and post-treatment scores for selected items on HAM scale; STAI; Resting pulse; Sleep loss; Test Anxiety Scale; MYMOP; HADS; Menopausal Symptom Questionnaire; EORTC QLQ-C30; CGI; Self-rated SCL-90 (in the hospital); Self-rated BSPS (in the medical practice)</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: Concealment of allocation was adequate in 4 RCTs, and unknown 4 RCTs. Recruitment into the UC study was not clear</td><td>Comparison of study groups:
Significant heterogeneity of diagnoses across included trials – 2 RCTs focused on Test Anxiety; 2 RCTs studied homeopathy in the context of moderate anxiety and generalised anxiety disorder; 2 examined anxiety associated with medical or physical conditions; 2 studied other anxiety disorders</td><td>Blinding:
Blinding was adequate in 4 RCTs and unknown in 3 RCTs; 1 RCT was not blinded</td><td>Treatment/ measurement bias:
NR</td><td>Follow-up (ITT):
Study population used in analyses not clear.
Attrition ranged from 6% to 15% in those that reported withdrawals/ dropouts (3 RCTs)</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: Jadad score</td></tr>
</table>

Quality: 2 RCTs scored 1; 1 RCT scored 2; 1 RCT scored 3; 2 RCTs scored 4; 1 RCT scored 5; 1 RCT score NR				
Overall quality assessment Rating: 8/10 according to the AMSTAR criteria Description: Comprehensive literature search (twelve databases searched); published and unpublished studies included; study provided information about patient characteristics (age, patient condition, etc); no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was described in detail; publication bias was not discussed				
RESULTS				
Overall: • The findings of many of the included studies were limited by the lack of detail about methodology and outcome measures as well as concerns that several of the studies were insufficiently powered to detect differences between treatments • The included RCTs report contradictory results • **No firm conclusions on the efficacy of homeopathy for anxiety can be drawn**				
Individual study results				
Trial (N) *Quality*	Intervention	Control	Outcome:	Results as reported in the systematic review:
Alibeu 1992 N=50 *Jadad score 2*	*Aconite*	Placebo	Physician-assessed improvement	'Effective with 95% good results'
Baker 2003 N=70 *Jadad score 4*	Traditionally prepared *Argentum nitricum* 12x, twice daily for 4 days	Radionically prepared *Argentum nitricum* 12x; or placebo (alcohol/water mixture as per treatments)	Benson Revised Test Anxiety Scale	No significant difference
			TAS 36-item *Argentum nitricum* questionnaire pre- and post-treatment (1 week later)	No significant difference
Bonne 2003 N=44 *Jadad score 3*	Individualised homeopathy (single remedy, all dilutions >10^{-30}) for 10 weeks	Placebo (non-medication impregnated globules)	HAM-A; HAM-D; BSI; PGWBI; BDI; STAI subjective distress (VAS)	Significant improvement in both groups. No significant difference between groups
Hariveau 1991 N=84 *Jadad score 1*	Lithium Microsol, 3-4 ampoules per day, twice daily for 30 days	Lorazepem 2-4mg per day, twice daily	Sleep – measure not stated	Unclear
			Delay in sleep onset – measure not stated	Unclear
			Heart rate	Unclear
			'Emotionalism' – measure not stated	Unclear
Heulluy 1985 N=60 *Jadad score 1*	Non-individualised L72 (constituents not specified), 20 drops, four times daily for 31 days. Dose increased if required	Diazepam (dose and frequency unknown)	Ratio of pre and post scores for selected items on HAM scale – details not specified	No difference – L72 as effective as diazepam on all measures
			Adverse events - drowsiness	1 patient treated with L72 and two treated with diazepam suffered from

				drowsiness
McCutcheon 1996 N=77 *Jadad score 4*	Anti-Anxiety[a], 20 drops, four times daily for 15 days	Placebo	STAI	No significant difference between groups
			Pulse rate	No significant difference between groups
			Sleep loss	Significantly less sleep loss in the homeopathy group (no p-value reported)[b]
Stanton 1981 N=40 *Quality not specified*	*Argentum nitricum* 12x	Placebo	Test Anxiety Scale	Homeopathic preparation significantly improved test anxiety compared with placebo (no p-value reported)
Thompson 2005 N=53 *Jadad score 5*	Individualised prescribing (60 minute initial consultation plus four 20 minute follow-up consultations, over 16 weeks)	Matched placebo tablet, granule or liquid	Mean HADS anxiety scores	No significant difference between the two groups; active group mean score reduced from 9.2 to 8.1, compared to 8.7 and 7.4 in the placebo group (no p-value reported)
			MYMOP	No difference between groups for either activity or profile scores (no p-value reported)
			Menopausal Symptom Questionnaire	Significant clinical improvements in both groups; between-group differences not clear
			EORTC QLQ-C30	Significant clinical improvements in both groups; between-group differences not clear
Davidson 1997 N=12	Individualised homeopathy	N/A	50% reduction on CGI scale	58% (7 patients)
			50% reduction on the SCL-90 or BSPS scale (self-rated)	50% (6 patients)
EXTERNAL VALIDITY				
Generalisability: The applicability of these results to other settings and patient groups is limited. For practical reasons when individualised homeopathy was used, prescribing was sometimes restricted to limited lists of medicines. This limits the generalisability of results as it does not reflect the flexibility of homeopathy in practice				
Comments:				

Abbreviations: BDI, Beck Depression Inventory; BSPS, Brief Social Phobia Scale; BSI, Brief Symptom Inventory; CGI, Clinical Global Impressions; DSM, Diagnostic and Statistical Manual; EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; HAM, Hamilton Rating Scale for Anxiety; ITT, intention-to-treat; MYMOP, Measure Yourself Medical Outcome Profile; NR, not reported; PGWBI, Psychological General Well-Being Index; RCT, randomised controlled trial; SCL-90, Symptom Checklist-90; STAI, State-Trait Anxiety Inventory; TAS, Test Anxiety Scale; UC, uncontrolled.

[a] Constituents include: *Cicuta virosa, Ignatia, Gaultheria, Asafoetida, Corydalis, Sumbulis, Valeriana officinalis, Hyoscyamus, Avena sativa.*

[b] Authors of SR state that sleep disturbance is not a core symptom of anxiety

Citation: Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J (2006) Homeopathy for anxiety and anxiety disorders: a systematic review of the research. Homeopathy 95(3):151-62.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**8/10**	

STUDY DETAILS				
Reference: Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J (2005) Homeopathy for depression: a systematic review of the research evidence. Homeopathy 94(3):153-63.				
Affiliation/source of funds: Advice and support from the NHS Priorities Project (itself funded by the Department of Health) Conflicts of interest: not reported				
Study design: Systematic review of 2 RCTs		Level of evidence: Level I	Location/setting: France (1 RCT), UK (1 RCT)	
Intervention: Homeopathic remedies (2 RCTs)		Comparator(s): Active comparator (1 RCT); active comparator or placebo (1 RCT)		
Sample size: 2 RCTs recruited 11 and 60 patients				
Population characteristics: Depression as primary diagnosis – depression, postmenopausal involution or thymo-effective dystonia (2 RCTs)				
Length of follow-up: Only reported in one RCT (12 weeks)		Outcome(s) measured: Ratio of pre and post scores for selected items on HAMD scale, adverse events, HAMD score, CGI, SF-12, QoL questionnaire, WSDS, Pittsburgh Sleep Quality Index questionnaire, Treatment Credibility Side Effects checklist		
INTERNAL VALIDITY				
Allocation: Randomised – method of randomisation not clear (2 RCTs)	Comparison of study groups: NR	Blinding: Unknown (1 RCT); double-blind (1 RCT)	Treatment/ measurement bias: NR	Follow-up (ITT): Loss to follow-up/withdrawals not reported (1 RCT); only 55% completion of study (1 RCT)
Author-assessed quality of included studies: Method used: Standardised appraisal framework based on criteria recommended in the Centre for Reviews and Dissemination Report Number 4 (2nd Edition), Undertaking Systematic Reviews of Research on Effectiveness Quality: NR for each trial – although author's state that the studies located were of low methodological quality and had insufficient numbers of participants				
Overall quality assessment Rating: 7/10 according to the AMSTAR criteria Description: Comprehensive literature search (fifteen databases searched); published and unpublished studies included; limited information about patient characteristics (age, sex, disease severity, etc) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was considered when drawing conclusions; the likelihood of publication bias was not described; sources of support were acknowledged.				
RESULTS				
Overall: • Evidence for the effectiveness of homeopathy in depression is limited due to lack of clinical trials of high quality • One trial showed clinical improvements in a high proportion of patients, but there was no control group to provide a comparison • The evidence base is currently weak				
Individual study results				
Trial *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review:

Heulluy 1985 *Low quality*	L72 (constituents not specified) – 20 drops, 4 times daily for 31 days, dose increased if required (n=30)	Diazepam – dose and frequency unknown (n=30)	Ratio of pre and post scores for selected items on HAMD scale	No difference – L72 as effective as diazepam
Katz 2005 *Low quality*	Homeopathic remedy selected from a list of 30 remedies by a trained homeopath (using decision support software) (n=4)	Fluoxetine – 20 mg daily increased to 40mg after 4 weeks if no improvement in HAMD score, or placebo matched tablets or capsules (fluoxetine, n=4; placebo, n=3)	- HAMD score - CGI - SF-12 - QoL questionnaire - WSDS - Pittsburgh Sleep - Quality Index questionnaire - Treatment Credibility Side Effects checklist	No results reported due to low recruitment
EXTERNAL VALIDITY				
Generalisability:				
Comments: "Based on conventional measures of quality and accepted study types, ie. adequately randomised and controlled studies of sufficient power, no relevant studies were located. Those that were located were of low methodological quality, had insufficient numbers of participants or were uncontrolled". Inappropriate control intervention (Heulluy 1985)… "The use of an anxiolytic drug as a control appears inappropriate in a trial in patients with depression and further appraisal of the study revealed a lack of information on many of the measures of trial quality; the method of randomisation, whether assessors were blinded, compliance and co-interventions".				

Abbreviations: CGI, Clinical Global Improvement; HAMD, Hamilton Depression Scale; QoL, quality of life; SF-12, Short Form 12; WSDS, Work and Social Disability Scale.

Citation: Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J (2005) Homeopathy for depression: a systematic review of the research evidence. Homeopathy 94(3):153-63.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
	✓	Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**7/10**	

STUDY DETAILS		
Reference: Porter NS, Jason LA, Boulton A, Bothne N, Coleman B (2010) Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. J Altern Complement Med 16(3):235-49.		
Affiliation/source of funds and Conflicts of Interest: No competing financial interests exist		
Study design: Systematic review of 4 RCTs	Level of evidence: Level I	Location/setting: NR
Intervention: Homeopathy	Comparator(s): Placebo	
Sample size: The number of patients enrolled in the RCTs ranged from 30 to 103		
Population characteristics: 2 RCTs – patients with fibromyalgia (FM) 2 RCTs – patients with chronic fatigue syndrome (CFS)		
Length of follow-up: NR	Outcome(s) measured: Physical outcomes; quality of life; psychological outcomes	

INTERNAL VALIDITY				
Allocation: Randomised – method of allocation unclear (4 RCTs)	Comparison of study groups: Limited patient characteristics provided in any of the studies	Blinding: NR	Treatment/ measurement bias: NR	Follow-up (ITT): NR

Author-assessed quality of included studies:
Method used: Jadad score
Quality: 1 RCT scored 2; 1 RCT scored 3; 2 RCTs scored 5

Overall quality assessment
Rating: 9/10 according to the AMSTAR criteria
Description: Comprehensive literature search (five databases searched); limited information about patient characteristics (age, sex, disease severity, etc) was provided; no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; scientific quality of included trials was considered when drawing conclusions; the likelihood of publication bias was taken into account when conclusions were drawn

RESULTS

Overall:

- Both FM studies and one CFS RCT demonstrated that homeopathic treatment had a positive effect on diagnostic symptoms of fibromyalgia. The other CFS trial reported no beneficial effect or reduction in symptoms
- **Given the limited number of studies and mixed outcomes, no conclusions can be drawn on homeopathy for fibromyalgia or CFS**

Individual study results

Trial (N) *Quality*	Intervention:	Control:	Outcome:	Results as reported in the systematic review:
Fisher 1989 N=30 *Jadad score 3*	*Rhus toxicodendron*	Placebo	Physical outcomes, QoL	Positive effect shown for homeopathy – outcomes not reported separately
Bell 2004 N=62 *Jadad score 5*	Homeopathy – details not specified	Placebo	Physical and psychological outcomes	Positive effect shown for homeopathy – outcomes not reported separately
Awdry 1996 N=64 *Jadad score 2*	Homeopathy – details not specified	Placebo	Overall beneficial effect or reduction in symptoms	Null result for homeopathy

Awdry 1996 N=64 *Jadad score 2*	Homeopathy – details not specified	Placebo	QoL	Null result for homeopathy
Weatherley-Jones 2004 N=103 *Jadad score 5*	Homeopathy – details not specified	Placebo	Physical outcomes	Positive results shown for homeopathy
EXTERNAL VALIDITY				
Generalisability: Treatments used in the review do to necessarily reflect the "clinical approach used by most practitioners to treat these illnesses, which include a mix of national and unconventionally used medications and natural hormones tailored to each individual case". Conclusions are hard to generalise based on the patient-centred nature of homeopathy				
Comments: The characteristics of the included studies are described in very limited detail because the systematic review was a broader review of complementary and alternative medicines, of which homeopathy was only one				

Abbreviations: CFS, chronic fatigue syndrome; FM, fibromyalgia; ITT, intention-to-treat; NR, not reported; QoL, quality of life; RCT, randomised controlled trial.

Citation: Porter NS, Jason LA, Boulton A, Bothne N, Coleman B (2010) Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. J Altern Complement Med 16(3):235-49.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	✓	Yes
		No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**9/10**	

STUDY DETAILS

Reference: Quinn F, Hughes C, Baxter GD (2006). Complementary and alternative medicine in the treatment of low back pain: a systematic review. Phys Ther Rev 11:107-116.

Affiliation/source of funds: NR

Conflicts of interest: NR

Study design:	Level of evidence:	Location/setting:
Systematic review of 1 RCT (Level II)	Level I	NR (1 RCT)

Intervention:	Comparator(s):
Homeopathy regimen specified by authors (1 RCT)	Standard *Capsicum*-based product (1 RCT)

Sample size: The number of patients enrolled in the one RCT was 161

Population characteristics:

- Stam et al (2001): NR. Assumed to be patients with low back pain

Length of follow-up:	Outcome(s) measured:
NR (1 RCT)	VAS for pain, paracetamol use, sleep disturbance, absence from work, patient and GP satisfaction, presence of adverse effects

INTERNAL VALIDITY

Allocation: Unclear (1 RCT)	Comparison of study groups:	Blinding:	Treatment/ measurement bias:	Follow-up (ITT):
	Homeopathy vs standard *Capsicum*-based product (1 RCT)	Double-blind (1 RCT)	Unclear. (1 RCT)	Unclear (1 RCT)

Author-assessed quality of included studies:

Measure used: van Tulder methodological quality criterion

The 1 RCT scored 16/19 – "high methodological quality"

Overall quality assessment

Rating: 5/10 according to the AMSTAR criteria

Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. The conflict of interest was not stated

RESULTS

Overall:

- "The trial concluded that Spiroflor SRL and Cremor Capsici Compositus are equally effective in the treatment of lower back pack; however, Spiroflor SRL has a lower risk of adverse effects."
- "While RCTs for those therapies which were investigated produced encouraging results, including yoga, homeopathy, herbal therapies, and hypnotherapy, small sample sizes and the low number of trials investigating individual therapies prevents definite conclusions being drawn."

Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Stam et al, 2001 N=161 *High methodological quality*	Homeopathic gel (Spiroflor SRL) n=NR	Standard *Capsicum*-based product (Cremor Capsici Compositus) n=NR	VAS for pain	"Both products equally effective but homeopathic gel had less adverse effects".
			Paracetamol use	
			Sleep disturbance	
			Absence from work	
			Patient and GP satisfaction	
			Presence of adverse effects	

EXTERNAL VALIDITY

Generalisability: The age of participants and location of the RCT was not reported

Comments: None

Abbreviations: GP, general practitioner; RCT, randomised controlled trial; VAS, visual analogue scale.

Citation: Quinn F, Hughes C, Baxter GD (2006). Complementary and alternative medicine in the treatment of low back pain: a systematic review. Phys Ther Rev 11:107-116.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer

		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**5/10**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Raak C, Bussing A, Gassmann G, Boehm K, Ostermann T (2012) A systematic review and meta-analysis on the use of Hypericum perforatum (St. John's Wort) for pain conditions in dental practice. Homeopathy 101(4):204-10.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: NR
Conflicts of interest: NR</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 5 RCTs</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
Various</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy</td><td colspan="3">Comparator(s):
Placebo</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 24 to 200 (150 verum and 50 placebo)</td></tr>
<tr><td colspan="5">Population characteristics:
Patients with: post extraction pain and swelling (1 RCT); dental neuropathic pain (1 RCT); postoperative pain and other inflammatory events after bilateral oral surgery (1 RCT); trismus and postoperative pain after third molar surgery (1 RCT); burning mouth syndrome (1 RCT)</td></tr>
<tr><td colspan="2">Length of follow-up:
Range – 2 days to 12 weeks</td><td colspan="3">Outcome(s) measured:
Pain relief; swelling; postoperative bleeding; reduction of trismus; intensity of burning pain</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
Appropriate and adequately described randomisation method (2 RCTs); unclear or NR (3 RCTs)</td><td>Comparison of study groups:
NR</td><td>Blinding:
Double-blind (1 RCT); patient-blind, outcome assessor-blind not clear (1 RCT); non-blinded (1 RCT); unclear (2 RCTs)</td><td>Treatment/ measurement bias:
Standardised measures for pain intensity (2 RCTs); poor quality outcome measures (2 RCTs); unclear (1 RCT)</td><td>Follow-up (ITT):
Withdrawals/ dropouts NR</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: Quality Assessment Tool for Quantitative Studies
Quality: 3 RCTs were ‘weak’; 1 RCT was ‘strong’; quality for 1 RCT was not reported</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 7/11 according to the AMSTAR criteria
Description: Comprehensive literature search (five databases searched); study provided no information about patient characteristics (age, patient condition, etc); a meta-analysis conducted to examine the pooled effect – Chi-sqaured test results were provided; scientific quality of included trials was described in detail; publication bias was not discussed, and nor was conflict of interest</td></tr>
<tr><td colspan="5">RESULTS</td></tr>
<tr><td colspan="5">Overall:
Evidence from RCTs does not support the use of Hypericum perforatum alone, for pain conditions in dental care
It is highly likely that the trials are confounded, mostly by the use of Arnica
The meta-analysis showed that the effects of Hypericum on dental pain were highly heterogeneous.
The effect favoured Hypericum but was not statistically significant
The exclusion of each of the three methodologically weak trials, respectively, did not yield statistically significant results
The use of Hypericum perforatum is currently not adequately supported by properly conducted clinical</td></tr>
</table>

trials with *Hypericum perforatum* alone				
Individual study results				
Trial (N) *Quality*	Intervention:	Control:	Outcome:	Results as reported in the systematic review:
Bendre 1980 N=200 *Weak*	4 globuli of *Arnica/Hypericum* directly after tooth extraction and 15 minutes later	Placebo	Pain relief and swelling (not reported separately)	"93% of patients showed significant improvements in pain relief and swelling after 48 hours"
Albertini 1984 N=60 *Weak*	4+4 granula of *Arnica/Hypericum* directly after the visit and for 2 days	Placebo	Pain reduction	"Significant improvements after Day 2"
Lökken 1995 N=24 *Weak*	3 globuli of *Arnica/Hypericum* D30, 3 hours after tooth extraction and 2 doses before bedtime and the morning after	Placebo	Pain relief	No significant results
			Swelling	No significant results, but treatment tended to improve ability to open mouth
			Postoperative bleeding	No significant results
Rafai 2004 N=41 *Strong*	3+3 globuli of *Arnica/Hypericum* D30 before surgery and continued for 5 postoperative days	Placebo	Reduction of trismus	No significant results
			Pain relief	No significant results
Sardella 2008 N=39 *Quality not specified*	300mg capsules containing *H. perforatum* extract (hypericin 0.31% and hyperforin 3.0%) three times a day for 12 weeks	Placebo	Pain relief	No significant results
			Number of sites with reported burning sensation	"Reduced significantly" (unclear whether vs placebo or baseline)
Meta-analysis[a]				
Overall effect:	Favours:	95% CI	Significance	Heterogeneity:
0.24	*Hypericum*	0.06, 1.03	Not significant	Chi-square = 26.46; I^2 = 0.89
EXTERNAL VALIDITY				
Generalisability:				
Comments:				

Abbreviations: ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial

[a] The study by Sardella et al (2008) was not eligible to be included in the meta-analysis

Citation: Raak C, Bussing A, Gassmann G, Boehm K, Ostermann T (2012) A systematic review and meta-analysis on the use of Hypericum perforatum (St. John's Wort) for pain conditions in dental practice. Homeopathy 101(4):204-10.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	✓	Yes
		No
		Can't answer
		Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**7/11**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Rada G, Capurro D, Pantoja T, Corbalan J, Moreno G, Letelier LM, Vera C (2010) Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev 9:CD004923.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: Financial support (author's salaries) from the Pontifica Universidad Católica de Chile, Chile
Conflicts of interest: Authors stated that there was no conflict of interest</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 2 RCTs</td><td>Level of evidence:
Level I</td><td colspan="2">Location/setting:
UK and US</td></tr>
<tr><td colspan="2">Intervention:
Homeopathy</td><td colspan="3">Comparator(s):
Placebo</td></tr>
<tr><td colspan="5">Sample size: The numbers of patients enrolled in the RCTs were 53 and 83; the number of patients who completed the study were 45 and 79, respectively</td></tr>
<tr><td colspan="5">Population characteristics:
Women with non-metastatic breast cancer with more than 3 hot flushes per day (1 RCT); women with a history of breast cancer (carcinoma in situ and stages I to III) and at least 3 episodes of hot flushes per day for at least one month (1 RCT)</td></tr>
<tr><td colspan="2">Length of follow-up:
Follow up ranged from 16 weeks to 1 year</td><td colspan="3">Outcome(s) measured:
Profile score (MYMOP) that includes symptom scores; daily living disruption and general well-being; frequency and severity of hot flushes; quality of life (EORTC QLQ-C30); Hospital Anxiety and Depression Scale (HADS); overall satisfaction with homeopathy; side-effects; total number of hot flushes; hot flush score; Kupperman Menopausal Index; SF-36 quality of life score</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation:
[Random numbers table kept by pharmacy (1 RCT); computer-generated randomisation (1 RCT)</td><td>Comparison of study groups:
1 RCT: women with a mean age of 52 years; 80% on tamoxifen; baseline hot flush frequency 7.5 per day
1 RCT: women with a mean age of 55.5 years; 58% on tamoxifen; 65% taking unspecified hormones</td><td>Blinding:
Double-blind (1 RCT); participant-blinded (1 RCT)</td><td>Treatment/ measurement bias:
NR</td><td>Follow-up (ITT):
8 patients (15%) lost to follow-up. All randomised women were analysed, but not clear if withdrawals considered for calculations (1 RCT); 28 withdrawals – not clear if considered for calculations. 4 (5%) lost to follow-up – ITT analyses (1 RCT)</td></tr>
<tr><td colspan="5">Author-assessed quality of included studies:
Method used: GRADE scoring system
Quality: Rating of the two homeopathy trials is unclear</td></tr>
<tr><td colspan="5">Overall quality assessment
Rating: 8/10 according to the AMSTAR criteria
Description: Comprehensive literature search of published and unpublished studies; study provided sufficient information</td></tr>
</table>

about patient characteristics (age, patient condition, etc); no meta-analysis completed – the results of individual included studies were discussed and a descriptive overall conclusion was drawn by the authors; authors stated that the scientific quality of trials was assessed using the GRADE scoring system, but results for the two homeopathy trials were not reported; limited discussion about the quality of the trials when drawing conclusions; publication bias was not discussed

RESULTS

Overall:

- **The available evidence suggests that homeopathy provides no significant benefit compared to placebo**
- **Even though the studies had limited power to show an effect, none of them showed significant benefit or supported the use of homeopathy**

Individual study results

Trial (N) *Quality*	Intervention:	Comparator:	Outcome:	Results as reported in the systematic review:
Thompson 2005 N=53 *Quality not specified*	Individualised homeopathy	Placebo	MYMOP	No significant difference between treatment and placebo groups. Mean difference -0.10; 95% CI -4.86 to 4.66
			Daily living disruption and general well-being	No significant difference between treatment and placebo groups.
			Frequency and severity of hot flushes	No significant difference between treatment and placebo groups.
			QoL (EORTC QLQ-C30)	No significant difference between treatment and placebo groups.
			HADS	No significant difference between treatment and placebo groups.
			Overall satisfaction with homeopathy (measure not specified)	No significant difference between treatment and placebo groups.
			Impact on daily living	No significant difference between treatment and placebo groups.
			Side-effects	No significant difference between treatment and placebo groups.
Jacobs 2005 N=83 *Quality not specified*	Single *or* combination homeopathic remedies. (Combination therapy: Hyland's menopause)	Placebo	SF-36	Significant improvement in quality of life scores in women using single or combination

				homeopathy (p-value NR)
			Total number of hot flushes	No significant difference between treatment and placebo groups.
			Hot flush score	No significant difference between treatment and placebo groups.
			Kupperman Menopausal Index	No significant difference between treatment and placebo groups.
EXTERNAL VALIDITY				
Generalisability:				
Comments: Loss to follow up was a major limitation of the included studies				

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; GRADE, Grades of Recommendation Assessment, Development and Evaluation; HADS, Hospital Anxiety and Depression Scale; ITT, intention-to-treat ; MYMOP, Measure Your Medical Outcome Profile; NR, not reported; RCT, randomised controlled trial; SF-36, Short Form-36

Citation: Rada G, Capurro D, Pantoja T, Corbalan J, Moreno G, Letelier LM, Vera C (2010) Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev 9:CD004923.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
	✓	Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**8/10**	

STUDY DETAILS				
Reference: Reid S, Chalder T, Cleare A, Hotopf M, Wessely S (2011) Chronic fatigue syndrome. Clin Evid (Online) 2011 pii:1101.				
Affiliation/source of funds: NR Conflicts of interest: TC has received occasional payments from universities and conference organisers for conducting workshops on the treatment of CFS. AC has received reimbursement for speaking and consulting from Eli Lilly. SW has received funds and is the author of some studies referenced in this review. SR and MH declare that they have no competing interests				
Study design: Systematic review of 1 RCT		Level of evidence: Level I	Location/setting: NR	
Intervention: Homeopathy		Comparator(s): Placebo		
Sample size: N=103				
Population characteristics: Adults with chronic fatigue syndrome (Oxford criteria)				
Length of follow-up: 6 months		Outcome(s) measured: MFI; Activity; Overall improvement; QoL (motivation)		
INTERNAL VALIDITY				
Allocation: NR	Comparison of study groups: NR	Blinding: NR	Treatment/ measurement bias: NR	Follow-up (ITT): Analysis was reported by ITT, however people who failed to provide outcome measures were excluded
Author-assessed quality of included studies: Method used: GRADE scoring system Quality: Moderate GRADE score for functional status, overall improvement and quality of life. Overall GRADE = moderate quality				
Overall quality assessment Rating: 5/10 according to the AMSTAR criteria Description: A priori design provided. Duplicate study selection, but data extraction not clear. Comprehensive literature search performed. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were stated				
RESULTS				
Mean change in MFI general fatigue subscale favours homeopathy at 6 months (p=0.04); all other outcomes not significant Overall: • **It remains unclear whether homeopathy is more effective at improving measures of fatigue than placebo (low-quality evidence)** • **Homeopathy seems no more effective at improving overall symptoms of chronic fatigue at 6 months (moderate-quality evidence)** • **There is insufficient evidence to recommend homeopathy as a treatment in CFS**				
Individual study results				
Trial (N) *Quality*	Intervention	Control	Outcome	Results as reported in the systematic review:
Weatherley-Jones	Individualised	Placebo	Mean change in MFI	Significant

2004 N=103 *Moderate quality*	homeopathy		general fatigue subscale (self-reported), 6 months	improvement for homeopathy over placebo. Mean change: 2.70 and 1.35 in the homeopathy and placebo groups, respectively (p=0.04)
			Mean change in MFI physical fatigue subscale, 6 months	No significant difference between groups. Mean change: 2.13 and 1.28 in the homeopathy and placebo groups, respectively (p=0.21)
			Mean change in MFI mental fatigue subscale, 6 months	No significant difference between groups. Mean change: 2.70 and 2.05 in the homeopathy and placebo groups, respectively (p=0.30)
			Mean change in MFI reduced activity subscale, 6 months	No significant difference between groups. Mean change: 2.72 and 1.81 in the homeopathy and placebo groups, respectively (p=0.16)
			Percentage of patients with clinically significant improvement at 6 months[a]	No significant difference between groups; 26% (n=11/43) and 9% (4/43) in the homeopathy and placebo groups, respectively (p=0.09)
			Mean change in MFI reduced motivation subscale, 6 months	No significant difference between groups. Mean change: 1.35 and 1.65 in the homeopathy and placebo groups, respectively

				(p=0.82)
EXTERNAL VALIDITY				
Generalisability:				
Comments:				

Abbreviations: CFS, chronic fatigue syndrome; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; ITT, intention-to-treat; MFI, Multidimensional Fatigue Inventory; NR, not reported; QoL, quality of life; RCT, randomised controlled trial.

[a] defined as at least 3 points improvement on the 5 MFI subscales

Citation: Reid S, Chalder T, Cleare A, Hotopf M, Wessely S (2011) Chronic fatigue syndrome. Clin Evid (Online) 2011 pii:1101.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**5/10**	

7/STUDY DETAILS				
Reference: Roberts M, Brodribb W, Mitchell G (2012) Reducing the Pain: A Systematic Review of Postdischarge Analgesia Following Elective Orthopedic Surgery. Pain Med 13(5):711-27.				
Affiliation/source of funds and conflicts of interest: The project was supported by the Primary Health Care Research, Evaluation and Development Scholarship given by the Discipline of General Practice at the University of Queensland, School of Medicine to the first author				
Study design: Systematic review of 3 RCTs		Level of evidence: Level I	Location/setting: Various	
Intervention: Homeopathy (Arnica)		Comparator(s): Placebo		
Sample size: The number of patients enrolled in the RCTs ranged from 37 to 82				
Population characteristics: Patients undergoing carpal tunnel release procedures (2 RCTs); patients undergoing knee procedures (cruciate ligament, or knee arthroscopy) (1 RCT)				
Length of follow-up: Range – 8 days (cruciate ligament) to 14 days (carpal tunnel)		Outcome(s) measured: Reduction in pain intensity		
INTERNAL VALIDITY				
Allocation: All studies randomised, but method of allocation/concealment is not clear	Comparison of study groups: NR	Blinding: Double-blind (3 RCTs)	Treatment/ measurement bias: NR	Follow-up (ITT): NR
Author-assessed quality of included studies: Method used: Oxford Quality Score Quality: All studies scored 5 (out of 5)				
Overall quality assessment Rating: 7/10 according to the AMSTAR criteria Description: Comprehensive literature search conducted; study provided limited about patient characteristics (beyond indication); a meta-analysis was not conducted; scientific quality of included trials was described in sufficient detail; publication bias was not discussed; the conflict of interest was stated				
RESULTS • Stevinson et al (2003): No major differences between intervention and placebo groups, although placebo group had less pain on Day 9 • Jeffrey and Belcher (2002): Reduced hand discomfort during Week 2 despite the use of higher potency arnica and preoperative medication • Brinkaus et al (2006) No significant differences in any outcome measures between the intervention and placebo groups Overall: • **No studies demonstrated significant reductions in pain intensity** • **Homeopathy is not an effective analgesic modality**				
Individual study results				
Trial: *Quality*	Intervention (n):	Control (n):	Outcome:	Results as reported in the systematic review:
Stevinson et al 2003 N=62 *5/5*	Arnica 30C or Arnica 6C following elective carpal tunnel surgery, three times per day (30C: n=20; 6C: n=20)	Placebo, three times per day (n=22)	Pain reduction	No significant differences between intervention and placebo groups, although placebo

				group had less pain on Day 9
Jeffrey and Belcher 2002 N=37 *5/5*	Arnica D6 tablets and ointment following endoscopic carpal tunnel release (bilateral), three times per day (n=20)	Placebo, three time per day (n=17)	Level of pain	"Reduced hand discomfort during Week 2 despite the use of higher potency arnica and preoperative medication"
Brinkhaus et al 2006 N=82 *5/5*	Homeopathic arnica following knee surgery (cruciate ligament repair or knee arthroplasty) (n=46)	Placebo (n=36)	Pain reduction	No difference between the intervention and placebo groups
EXTERNAL VALIDITY				
Generalisability:				
Comments:				

Abbreviations: ITT, intention-to-treat; NR, not reported; RCT, randomised controlled trial

Citation: Roberts M, Brodribb W, Mitchell G (2012) Reducing the Pain: A Systematic Review of Postdischarge Analgesia Following Elective Orthopedic Surgery. Pain Med 13(5):711-27.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
	✓	No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**7/10**	

STUDY DETAILS					
Reference: Sarris J, Byrne GJ (2011) A systematic review of insomnia and complementary medicine. Sleep Med Rev 15(2):99-106.					
Affiliation/source of funds: Not reported Conflicts of interest: Not reported					
Study design: Systematic review of RCTs		Level of evidence: NA	Location/setting: NA		
Intervention: NA		Comparator(s): NA			
Sample size: NA					
Population characteristics: NA					
Length of follow-up: NA		Outcome(s) measured: NA			
INTERNAL VALIDITY					
Allocation: NA	Comparison of study groups: NA	Blinding: NA	Treatment/ measurement bias: NA	Follow-up (ITT): NA	
Author-assessed quality of included studies: NA					
Overall quality assessment Rating: 3/5 according to the AMSTAR criteria Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search was performed. The status of publication was used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were not stated.					
RESULTS					
Overall: • "It was surprising that studies involving several mainstream complementary and alternative medicine therapies including homeopathy were not located or did not meet basic inclusion criteria".					
Outcome:	Intervention group:	Control group:	Measure of effect/effect size:	Benefits (NNT):	95% CI:
NA					
EXTERNAL VALIDITY					
Generalisability: NA					
Comments: None					

Abbreviations: NA, not applicable; RCT, randomised controlled trial.

Citation: Sarris J, Byrne GJ (2011) A systematic review of insomnia and complementary medicine. Sleep Med Rev 15(2):99-106.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer
	✓	Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.		Yes
		No
		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**3/5**	

<table>
<tr><th colspan="5">STUDY DETAILS</th></tr>
<tr><td colspan="5">Reference: Simonart T, Kabagabo C, De Maertelaer V (2011) Homoeopathic remedies in dermatology: A systematic review of controlled clinical trials . Br J Dermatol 165(4):897-905.</td></tr>
<tr><td colspan="5">Affiliation/source of funds: None
Conflicts of interest: “none declared”</td></tr>
<tr><td colspan="2">Study design:
Systematic review of 8 RCTs (Level II) and 4 non-randomised controlled studies (Level III-2)</td><td>Level of evidence:
Level I/III</td><td colspan="2">Location/setting:
NR for all of the included studies</td></tr>
<tr><td colspan="2">Intervention:
• Homeopathy regimen specified by authors (3 RCT, 2 non-randomised controlled studies)
• Individualised homeopathy (5 RCTs, 2 non-randomised controlled study)</td><td colspan="3">Comparator(s):
• Placebo (7 RCTs, 2 non-randomised controlled study)
• Convention therapy (1 RCT, 2 non-randomised controlled studies)</td></tr>
<tr><td colspan="5">Sample size: The number of patients enrolled in the RCTs ranged from 24 to 174. The number of patients enrolled in the non-randomised controlled studies ranged from 23 to 135</td></tr>
<tr><td colspan="5">Population characteristics:
Atopic dermatitis
• Seibenwirth et al, 2009 (RCT): Young adults aged 18-35 years with atopic dermatitis
• Keil et al, 2009 (non-randomised controlled trial): Children less than 17 years of age with atopic dermatitis
• Witt et al, 2009 (non-randomised controlled trial): Children aged 1-14 years with atopic dermatitis
Leg ulcers
• Garrett et al, 2007 (non-randomised controlled trial): Patients aged 53-87 years with leg ulcers
Minor recurrent aphthous ulceration
• Mousavi et al, 2009 (RCT): Patients aged 18-65 years with 1-5 aphthous ulcers of less than 24 hours duration
Radiodermatitis
• Balzarini et al, 2000 (RCT): Breast cancer patients undergoing radiotherapy aged 28-70 years
Recurrent vulvovaginal candidiasis
• Witt et al, 2009 (RCT): Women with recurrent vulvovaginal candidiasis
Seborrhoeic dermatitis
• Smith et al, 2002 (RCT): Patients aged 20-77 years with typical seborrhoeic dermatitis or dandruff
Uraemic pruritis
• Cavalcanti et al, 2003 (RCT): Patients with uraemic pruritus
Warts
• Labrecque et al, 1992 (RCT): Children and adults with ordinary warts on the feet only
• Kainz et al, 1996 (RCT): Children aged 6-12 years with ordinary warts at the back of the hands
• Villeda et al, 2001 (non-randomised controlled study): Children and adults with ordinary warts anywhere</td></tr>
<tr><td colspan="2">Length of follow-up:
RCTs: ranged from 6 weeks to 12 months
Non-randomised controlled trials: ranged from 1 month to 12 months</td><td colspan="3">Outcome(s) measured:
MP score; Quality of life; Coping and global assessments of treatment success; Extent of improvement of signs/symptoms of eczema as assessed by the patients or their parents and by the physician; quality of life; SCORAD; Improvement in ulcer size; Mean pain score; Breast skin colour score; Warmth score; Swelling score; Pigmentation score; Culture free status; Level of discomfort; SASI improvement; Pruritus score; Complete clearance rates</td></tr>
<tr><td colspan="5">INTERNAL VALIDITY</td></tr>
<tr><td>Allocation: Concealment of allocation was unclear in 8 RCTs. Of the non-</td><td>Comparison of study groups:
All included studies either focused on homeopathy vs placebo or</td><td>Blinding:
Double-blind (6 RCTs, 1 non-</td><td>Treatment/ measurement bias:</td><td>Follow-up (ITT):
With the exception of one</td></tr>
</table>

randomised controlled studies, two were non-randomised and two were uncertain	homeopathy vs conventional therapy	randomised controlled study); Open study (3 non-randomised controlled studies); Single-blind (1 RCT); Uncertain blinding (1 RCT)	See comments section. Unclear in all studies	non-randomised controlled study, loss to follow up was reported in all included studies

Author-assessed quality of included studies:
"The reviewers assessed the quality of the methods from concealment of allocation, blinding of outcome assessment and handling of withdrawals and dropouts. They also considered the adequacy of sample size, comparability of treatment groups at baseline, overall quality of reporting and handling of data."

Overall quality assessment
Rating: 8/10 according to the AMSTAR criteria
Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. List of included and excluded studies were provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were stated

RESULTS

Overall:

- "We identified no comparative (controlled) trials investigating the efficacy of homeopathy in other common skin diseases such as acne, mollusca contagiosa, psoriasis, urticarial, melanoma or nonmelanoma skin cancers."
- "The hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence. The evidence in our overall analysis would be more compelling if there were independently replicated, large-scale rigorous homeopathic trials. Until more compelling results are available, homeopathy cannot be viewed as an evidence-based form of therapy in dermatology."

Individual study results

Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Atopic dermatitis				
Siebenwirth et al, 2009 N=24 *Quality not specified*	Individually selected homeopathic remedies for 32 weeks n=NR	Placebo n=NR	MP score	No significant difference (decrease of the MP score from 54.5±11.0 to 40.7±12.5 in the homeopathy group and 45.9±7.6 to 32.7±21.8 in the placebo group)
			Quality of life	No significant difference
			Coping and global assessments of treatment success	No significant difference
Keil et al, 2008 N=118 *Quality not specified*	Individually selected homeopathic remedies for 12 months n=NR	Conventional therapy n=NR	Extent of improvement of signs/symptoms of eczema as assessed by the patients or their parents on a 0-10 numerical scale	No significant difference (Homeopathy group 3.5 to 2.5; Conventional therapy group 3.6 to 2.6)

			Extent of improvement of signs/symptoms of eczema as assessed by the physician on a 0-10 numerical scale	Significant difference (P<0.001) (Homeopathy group 4.5 to 1.8; Conventional therapy group 3.6 to 2.6)
			Quality of life	No significant difference
Witt et al, 2009 N=135 *Quality not specified*	Individually selected homeopathic remedies for 12 months n=NR	Conventional therapy n=NR	SCORAD	No significant difference (SCORAD at 12 months: 17.41±3.01 in the homeopathy group; 17.29±2.31 in the conventional therapy group)
Leg ulcers				
Garrett et al, 1997 N=23 *Quality not specified*	Sulphur, silica and carbo-vegetabilis 6 cH for a mean duration of 4.2 weeks n=NR	Placebo n=NR	Improvement in ulcer size	No significant difference (Improvement in ulcer size: 55±44% in homeopathy group; 10±42% in placebo group)
Minor recurrent aphthous ulceration				
Mousavi et al, 2009 N=100 *Quality not specified*	Individually selected homeopathic remedies (two doses) n=NR	Placebo n=NR	Improvement in ulcer size	Significant difference (P<0.05) (Proportion of responders: improvement in ulcer size; 96% homeopathy group and 72% placebo group)
			Mean pain score	Significant difference in favour of homeopathy (lower pain intensity) (P<0.05)
Radiodermatitis				
Balzarini et al, 2000 N=66 *Quality not specified*	Belladona 7 cH and X-ray 15 cH for 10 weeks n=NR	Placebo n=NR	Breast skin colour score	No significant difference
			Warmth score	No significant difference
			Swelling score	No significant difference
			Pigmentation score	No significant difference
Recurrent vulvovaginal candidiasis				
Witt et al, 2009 N=150 *Quality not specified*	Individually selected homeopathic remedies for 12 months n=NR	Conventional therapy n=NR	Culture free status	Conventional therapy group reached a culture-free status significantly earlier than homeopathy group (P<0.0001) (9/23 in homeopathy group and 18/23 in conventional therapy group)
			Level of discomfort	Significantly lower level of discomfort in conventional therapy group (P<0.001) (VAS score 36.8 in homeopathy group and 25.1 in conventional therapy group)

			Level of satisfaction	Conventional therapy group were significantly more satisfied than homeopathy group (P<0.0001)
Seborrhoeic dermatitis				
Smith et al, 2002 N=41 *Quality not specified*	Homeopathic mineral therapy (potassium bromide 1X, sodium bromide 2X, nickel sulphate 3X, sodium chloride 6X) for 10 weeks n=NR	Placebo n=NR	SASI improvement	Significant difference (P=0.03) (SASI improvement 38±42% in homeopathy group and -10±66% in placebo group)
Uraemic pruritis				
Cavalcanti et al, 2003 N=28 *Quality not specified*	Individually selected homeopathic remedies for 2 months n=NR	Placebo n=NR	Percentage of maximum pruritis score before and during treatment	No significant difference
			Percentage of responders (reduction >50% in pruritis score)	Significant difference in favour of homeopathy at 30 days (P=0.0.38) (0% responders in placebo group, 45% responders in homeopathy group)
			Percentage of pruritis reduction evaluated by the homeopathic physician, dermatologist and patients	No significant difference
Warts				
Labrecque et al, 1992 N=174 *Quality not specified*	Homeopathic therapy (Thuya 30 cH plus antimony [8] Placebo crudm 7 cH plus nitricium acidum 8 ch) for 6 weeks n=NR	Placebo n=NR	Complete clearance rates	No significant difference
Kainz et al, 1996 N=67 *Quality not specified*	Individually selected homeopathic therapies for 6 weeks n=NR	Placebo n=NR	Complete clearance rates	No significant difference
Villeda et al, 2001 N=26 *Quality not specified*	Homeopathic therapy (Thuya 6 cH) for 1 month n=NR	Placebo n=NR	Complete clearance rates	No significant difference
EXTERNAL VALIDITY				
Generalisability: Participants within the included studies were of varying ages. Location of the included studies was not reported				
Comments: Comments about the included studies from Simonart 2011				

- Siebenwirth et al, 2009: High percentage of ineligible patients and high proportion of dropouts
- Keil et al, 2008 : Patients recruited at the homeopathic or conventional doctor's practices and thus having already made their own choice of preferred therapeutic approach
- Witt et al, 2009: Patients recruited at the homeopathic or conventional doctor's practices and thus having already made their own choice of preferred therapeutic approach. Use of conventional therapies allowed in homeopathic group
- Garrett et al, 1997: No blinding. Poor randomisation. Small number of patients. Variable treatment duration. Each patient had conventional local or systemic therapy continued during the trial period
- Witt et al, 2009: High dropout rate. Blinding not certain
- Smith et al, 2002: High proportion of dropouts
- Cavalcanti et al, 2003: Older mean age and higher dialysis dose in the placebo group so that the significance of the results of the trial remain uncertain
- Villeda et al, 2001: Randomisation not certain

Abbreviations: ITT, intention-to-treat; MP score, Costa and Saurat's multiparameter atopic dermatitis score; NR, not reported; SASI, Seborrhoea Area and Severity Index; SCORAD, Scoring Atopic Dermatitis; VAS, visual analogue scale.

Citation: Simonart T, Kabagabo C, De Maertelaer V (2011) Homoeopathic remedies in dermatology: A systematic review of controlled clinical trials . Br J Dermatol 165(4):897-905.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**8/10**	

STUDY DETAILS		
Reference: Simonart T, De Maertelaer V (2012) Systemic treatments for cutaneous warts: A systematic review. J Dermatol Treat 23(1):72-7.		
Affiliation/source of funds: NR Conflicts of interest: "The authors report no conflicts of interest"		
Study design: Systematic review of 2 RCTs (Level II) and one placebo-controlled trial (Level III-2)	Level of evidence: Level I/III	Location/setting: NR for all included studies
Intervention: Homeopathy regimen specified by authors (all included studies)	Comparator(s): Placebo (all included studies)	
Sample size: The number of patients enrolled in the 2 RCTs was 174 and 67. 25 patients were enrolled in the placebo-controlled trial		
Population characteristics: • Labrecque et al, 1992 (RCT): Children and adults, ordinary warts on the feet only • Kainz et al, 1996 (RCT): Children aged 6-12 years, ordinary warts on the back of the hands only • Villeda et al, 2001 (placebo-controlled trial): Children and adults, ordinary warts anywhere		
Length of follow-up: RCTs: 6 weeks Placebo-controlled trial: 1 month	Outcome(s) measured: Complete clearance of warts	

INTERNAL VALIDITY				
Allocation: Concealment of allocation was unclear in the 2 RCTs. Randomisation was uncertain in the placebo-controlled trial	Comparison of study groups: All of the included studies focused on homeopathy vs placebo in patients with warts	Blinding: Unclear for all included studies	Treatment/ measurement bias: Unclear for all included studies	Follow-up (ITT): Loss to follow up was reported in the 2 RCTs. Loss to follow up was not specified in the placebo-controlled trial

Author-assessed quality of included studies:
Quality of the individual, included studies was not assessed but comment was made in the discussion about the limited quality of many trials and the issue of heterogeneity. "Many of the trials reviewed concerning systemic treatment for cutaneous warts were of limited quality."

Overall quality assessment
Rating: 6/10 according to the AMSTAR criteria
Description: A priori design provided. Unclear if there was duplicate study selection and data extraction. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies in general was assessed and appropriately considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were stated

RESULTS

Overall:
- "Both studies (randomised clinical trials) failed to demonstrate the effectiveness of individualised homeopathic treatment for reducing cutaneous warts. Another smaller study for which randomisation is not certain also failed to demonstrate any significant difference in complete clearance rates."
- "One randomised clinical trial found no significant difference between homeopathy and placebo in the proportion of patients with adverse events. The other two trials gave no information on adverse events."
- "Evidence for the efficacy of homeopathy is lacking."

Individual study results

Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review

Labrecque et al, 1992 N=174 *Quality not specified*	Homeopathic therapy (Thuya 30CH plus antimonium crudum 7CH plus nitricium acidum 7CH) for 6 weeks n=74	Placebo n=71	Complete clearance of warts	No significant difference (complete clearance of warts in 4/74 (5%) patients in intervention group and 4/71 (5%) patients in control group)
			Adverse events	No significant difference
Kainz et al, 1996 N=67 *Quality not specified*	Homeopathic therapy (individually selected regimen) for 6 weeks n=30	Placebo n=30	Complete clearance of warts	No significant difference (complete clearance of warts in 9/30 (30%) patients in intervention group and 7/30 (23%) patients in control group)
Villeda et al, 2001 N=26 *Quality not specified*	Homeopathic therapy (Thuya 6CH) for 1 month n=12	Placebo n=14	Complete clearance of warts	No significant difference (complete clearance of warts in 1/12 (8%) patients in intervention group and 0/14 (0%) patients in control group)
EXTERNAL VALIDITY				
Generalisability: The included studies featured both adults and children. Age not specified. Location of the included studies was not reported				
Comments: None				

Abbreviations: ITT, intention-to-treat; NR, not reported

Citation: Simonart T, De Maertelaer V (2012) Systemic treatments for cutaneous warts: A systematic review. J Dermatol Treat 23(1):72-7.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
		No
	✓	Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**6/10**	

STUDY DETAILS		
Reference: Smith CA. Homoeopathy for induction of labour. Cochrane Database Syst Rev 2010, Issue 4. Art. No.:CD003399. DOI: 10.1002/14651858.CD003399.		
Affiliation/source of funds: • University of Adelaide, Adelaide, Australia • University of South Australia, Adelaide, Australia Conflicts of interest: "none known"		
Study design: Systematic review of two randomised placebo-controlled trials (Level II)	Level of evidence: Level I	Location/setting: One study took place in Germany, the other took place in France.
Intervention: Homeopathic regimen specified by authors (all included studies)	Comparator(s): Placebo (all included studies)	
Sample size: The number of patients enrolled in the 2 RCTs was 40 and 93		
Population characteristics: • Beer 1999 (placebo-controlled trial): Women at 38-42 weeks' gestation with prelabour rupture of membranes • Dorfman 1987 (placebo-controlled trial): Women at 36 weeks' gestation. Women were excluded from the study if they had a history of a poor obstetric history, a current history of hypertension, diabetes, previous caesarean section or cephalo-pelvic disproportion		
Length of follow-up: NR for all included studies	Outcome(s) measured: Time to the onset of regular uterine contractions; Labour and delivery outcomes; Maternal and neonatal infection; Average length of labour; Difficult labour	

INTERNAL VALIDITY				
Allocation: Concealment of allocation was unclear in all included studies	Comparison of study groups: All of the included studies focused on homeopathy vs placebo in women at or after 36 weeks gestation	Blinding: All of the included studies were double-blind	Treatment/ measurement bias: Unclear in all included studies	Follow-up (ITT): No losses to follow up in all included studies. Unclear if ITT analysis was performed
Author-assessed quality of included studies: • "The quality of the trials was difficult to assess because of insufficient detail in the research papers, and the small sample sizes provide inadequate power." • "The trials were placebo-controlled and double-blind, but the quality was not high."				
Overall quality assessment Rating: 8/10 according to the AMSTAR criteria Description: A priori design provided. Duplicate study selection and data extraction was not performed due to the large volume and complexity of trial data relating to labour induction. Comprehensive literature search performed. The status of publication was used as an inclusion criterion and a list of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and considered in formulating conclusions. No meta-analysis was conducted. The likelihood of publication bias was not assessed. Conflicts of interest were stated				

RESULTS				
Overall: • "There is insufficient evidence to recommend the use of any homeopathic therapies as a method of induction of labour."				
Individual study results				
Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results
Beer 1999 N=40	Caulophyllum D4, doses were repeated	Placebo n=NR	Caesarean section	No significant difference (p=0.29)

Quality not specified	hourly for 7 hours or until labour started n=NR			RR 5.00 (95% CI 0.26, 98.00)
			Vaginal delivery not achieved within 24 hours	No significant difference (p=0.49) RR 0.33 (95% CI 0.01, 7.72)
			Augmentation with oxytocin	No significant difference (p=1.0) RR 1.00 (95% CI 0.50, 1.98)
			Instrumental delivery	No significant difference (p=1.0) RR 1.00 (95% CI 0.54, 1.86)
Dorfman 1987 N=93 *Quality not specified*	Five homeopathic therapies: caulophyllum, arnica, actea racemosa, pulsatilla and geranium, with 3 granules administered morning and evening from 36 weeks' gestation. When labour commenced, the same dosage was given every 15 minutes and stopped after 2 hours or sooner if the woman was comfortable. No details provided on the precise dosage n=53	Placebo n=40	Length of labour	No significant difference (p=0.91) MD -0.40 (95% CI -7.21, 6.41)
			Difficult labour	Significant difference in favour of placebo RR 0.28 (95% CI 0.12, 0.66)
EXTERNAL VALIDITY				
Generalisability: Age of participants in the included studies were not reported in the article. Included studies took place in Germany and France				
Comments: None				

Abbreviations: CI, confidence interval; ITT, intention-to-treat; NA, not applicable; NR, not reported; RR, relative risk; SD, standard deviation.

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Citation: Smith CA. Homoeopathy for induction of labour. Cochrane Database Syst Rev 2010, Issue 4. Art. No.:CD003399. DOI: 10.1002/14651858.CD003399.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
	✓	No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.	✓	Yes
		No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided	✓	Yes
		No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**8/10**	

STUDY DETAILS				
Reference: Stevinson C, Ernst E (2001) Complementary/alternative therapies for premenstrual syndrome: A systematic review of randomized controlled trials. Am J Obstet Gynecol 185(1):227-35				
Affiliation/source of funds: NR Conflicts of interest: NR				
Study design: Systematic review of 1 RCT (Level II)		Level of evidence: Level I	Location/setting: NR (1 RCT)	
Intervention: Homeopathy – method unclear (1 RCT)		Comparator(s): Placebo (1 RCT)		
Sample size: 10 patients were enrolled in the one included RCT				
Population characteristics: • Chapman et al, 1994 (RCT): NR				
Length of follow-up: NR (1 RCT)		Outcome(s) measured: Diary		
INTERNAL VALIDITY				
Allocation: Unclear. Method for random sequence allocation not specified	Comparison of study groups: Homeopathy vs placebo in an unknown population	Blinding: Placebo	Treatment/ measurement bias: Unclear. Not specified by authors	Follow-up (ITT): Unclear. Not specified by authors
Author-assessed quality of included studies: Quantitative assessment of methodologic quality was not reported, but comments on the rigour of individual studies were included on the basis of aspects of patient recruitment, trial design, and statistical analysis				
Overall quality assessment Rating: 6/10 according to the AMSTAR criteria Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search was performed but key words not reported. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided but no population characteristics were given. Scientific quality of the included studies was not quantitatively assessed but comments on the rigour of individual studies were included. No pooled results of findings. The likelihood of publication bias was not assessed. Conflicts of interest were not stated				
RESULTS				
Overall: "The current evidence for homeopathy is not particularly promising, with trial results indicating little more than a placebo response."				
Individual study results				
Trial (N) *Quality*	Intervention (n)	Control (n)	Outcome	Results as reported in the systematic review
Chapman et al, 1994 N=10 *Quality not specified*	Homeopathy, 3 doses monthly for 4 cycles n=NR	Placebo n=NR	Diary	"A placebo response of 47% in the pretreatment washout phase illustrates the powerful effect of placebo on premenstrual symptoms and suggests that the depth and empathy of the homeopathic interview may have a therapeutic effect."
EXTERNAL VALIDITY				
Generalisability: The age of participants within the included RCT was not reported by the systematic reviewers. The location of the included RCT was not reported				
Comments: There was only one published RCT investigating the efficacy of homeopathy treatments for PMS, and although it was rigorously designed the selection criteria were so strict that only 10 of the 205 women screened actually participated.				

The lack of statistical power renders the results inconclusive

Abbreviations: ITT, intention-to-treat; NR, not reported; PMS, premenstrual syndrome; RCT, randomised controlled trial

Citation: Stevinson C, Ernst E (2001) Complementary/alternative therapies for premenstrual syndrome: A systematic review of randomized controlled trials. Am J Obstet Gynecol 185(1):227-35.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer
		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**6/10**	

STUDY DETAILS					
Reference: Tabbers MM, Boluyt N, Berger MY, Benninga MA (2011) Nonpharmacologic treatments for childhood constipation: Systematic review. Pediatrics 128(4):753-61.					
Affiliation/source of funds: NR Conflicts of interest: "The authors have indicated they have no financial relationships relevant to this article to disclose"					
Study design: NA			Level of evidence: NA	Location/setting: NA	
Intervention: NA			Comparator(s): NA		
Sample size: NA					
Population characteristics: NA					
Length of follow-up: NA			Outcome(s) measured: NA		
INTERNAL VALIDITY					
Allocation: NA	Comparison of study groups: NA	Blinding: NA	Treatment/ measurement bias: NA	Follow-up (ITT): NA	
Author-assessed quality of included studies: NA					
Overall quality assessment Rating: 4/5 according to the AMSTAR criteria Description: A priori design provided. Duplicate study selection and data extraction. Comprehensive literature search was performed. Unclear if the status of publication was used as an inclusion criterion. The literature search found no relevant studies. Therefore, a list of included and excluded studies, characteristics of the included studies, scientific quality of the included studies, pooled analysis of findings and the assessment of the likelihood of publication bias was not applicable. Conflicts of interest were stated					
RESULTS					
Overall: No RCTs on the effects of homeopathy for children with constipation were found.					
Outcome:	Intervention group:	Control group:	Measure of effect/effect size:	Benefits (NNT):	95% CI:
NA					
EXTERNAL VALIDITY					
Generalisability: NA					
Comments: None					

Abbreviations: NA, not applicable; NR, not reported; RCT, randomised controlled trial.

Citation: Tabbers MM, Boluyt N, Berger MY, Benninga MA (2011) Nonpharmacologic treatments for childhood constipation: Systematic review. Pediatrics 128(4):753-61.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	✓	Yes
		No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
		No
	✓	Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
		No
		Can't answer
	✓	Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.		Yes
		No
		Can't answer
	✓	Not applicable

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.		Yes
		No
		Can't answer
	✓	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.		Yes
		No
		Can't answer
	✓	Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
		No
		Can't answer
	✓	Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	✓	Yes
		No
		Can't answer
		Not applicable
Total score	**4/5**	

STUDY DETAILS				
Reference: Turnbull N, Shaw EJ, Baker R, Dunsdon S, Costin N, Britton G, Kuntze S, Norman R (2007). Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children. London: Royal College of General Practitioners.				
Affiliation/source of funds: • The National Collaborating Centre for Primary Care • Royal College of General Practitioners Conflicts of interest: not reported				
Study design: Systematic review of 2 RCTs (Level II)		Level of evidence: Level I	Location/setting: NR (all included studies)	
Intervention: Individualised homeopathy (all included studies)		Comparator(s): Placebo (all included studies)		
Sample size: The number of patients enrolled in the RCTs were 64 and 103 patients				
Population characteristics: • Awdry 1996 (RCT): Patients aged less than 65 years; Diagnosed with CFS using the Oxford criteria; Had the illness for less than 10 years duration • Weatherley-Jones 2004 (RCT): Patients aged over 18 years old; Diagnosed with CFS using the Oxford criteria				
Length of follow-up: 1 year (1 RCT); NR (1 RCT)		Outcome(s) measured: Daily graphs completed by each patient; End of trial self-assessment charts completed by each patient; Multidimensional Fatigue Inventory; Fatigue Impact Scale; Functional Limitations Profile		
INTERNAL VALIDITY				
Allocation: Unclear (all included studies)	Comparison of study groups: Homeopathy vs placebo in patients with CFS (all included studies)	Blinding: Double-blind (1 RCT); NR (1 RCT)	Treatment/ measurement bias: Unclear (all included studies)	Follow-up (ITT): Loss to follow up was reported in all included studies
Author-assessed quality of included studies: • Awdry 1996 (RCT): Level of evidence 1 • Weatherley: Level of evidence 1++				
Overall quality assessment Rating: 5/10 according to the AMSTAR criteria Description: A priori design provided. Study selection and data extraction was by one reviewer and checked by another. Comprehensive literature search performed. Unclear if the status of publication was used as an inclusion criterion. No list of included and excluded studies provided. Characteristics of the included studies were provided. Scientific quality of the included studies was assessed and appropriately reported and considered in formulating conclusions. No pooled results of findings. The likelihood of publication bias was not assessed. The conflict of interest was not stated.				
RESULTS				
Overall: • "One high-quality study of homeopathic treatments showed a significant improvement in fatigue and on some physical dimensions of the functional limitations profile." • "The evidence found on the effects of complementary therapies to CFS/ME is inadequate in terms of quantity and/or quality."				
Individual study results				
Trial (N)	Intervention (n)	Control (n)	Outcome	Results as reported in

Quality				the systematic review
Awdry 1996 N=64 *SIGN EL 1*	Variety of homeopathic remedies "as indicated", assessed by homeopath n=32	Placebo n=32	Daily graphs completed by each patient	"Cumulative results presented graphically for a small part of the scale - not clear on how to extract data or how meaningful this is"
			End of trial self-assessment charts completed by each patient	Homeopathy group: 6 recovered, 4 greatly improved, 3 improved, 6 were slightly better and 11 largely unchanged. Placebo group: 0 recovered, 1 greatly improved, 0 improved, 4 were slightly better and 26 largely unchanged.
Weatherley-Jones 2004 N=103 *SIGN EL 1++*	Homeopathic consultations over a 6 month period with consultations at monthly periods when individualised prescriptions were made n=53	Placebo n=50	Multidimensional Fatigue Inventory	• Significant difference for the general fatigue scale of the MFI (P=0.04) • 26% of patients in treatment group showed clinical improvements on all subscales of the MFI compared to 9% of the placebo group
			Fatigue Impact Scale	No significant difference
			Functional Limitations Profile	Significant difference in score changes for physical dimension scale (P=0.04)
EXTERNAL VALIDITY				
Generalisability: One RCT enrolled both children and adults; One RCT enrolled adults only. The location of the RCTs was not specified				
Comments: None				

Abbreviations: CFS, chronic fatigue syndrome; EL, evidence level; ME, Myalgic encephalomyelitis; MFI, Multidimensional Fatigue Inventory; NR, not reported; RCT, randomised controlled trial; SIGN, Scottish Intercollegiate Guidelines Network.

Citation: Turnbull N, Shaw EJ, Baker R, Dunsdon S, Costin N, Britton G, Kuntze S, Norman R (2007). Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children. London: Royal College of General Practitioners.		
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of a review.	✓	Yes
		No
		Can't answer
		Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.		Yes
	✓	No
		Can't answer
		Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	✓	Yes
		No
		Can't answer
		Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reported (from the systematic review), based on their publication status, language, etc.		Yes
	✓	No
		Can't answer
		Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided		Yes
	✓	No
		Can't answer
		Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	✓	Yes
		No
		Can't answer
		Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	✓	Yes
		No
		Can't answer

		Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	✓	Yes
		No
		Can't answer
		Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).		Yes
		No
		Can't answer
	✓	Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).		Yes
	✓	No
		Can't answer
		Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.		Yes
	✓	No
		Can't answer
		Not applicable
Total score	**5/10**	

Appendix B – AMSTAR Measurement Toolkit

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

Appendix C – Criteria for development of evidence statements

Purpose and role of the criteria

The purpose of the evidence statements is to advise members of the community about the effectiveness of homeopathy for a particular clinical condition, to enable them to make informed decisions about their health care.

There is no relevant guidance or standard endorsed by NHMRC or a relevant international organisation relating to the development and content of evidence statements. Given the large number of clinical conditions (68) that are covered by the overview, the HWC agreed that it was necessary to develop a set of criteria to guide the content and formulation of the evidence statements. Such guidance was considered important to ensure that the approach for developing the evidence statements was consistent and transparent across each of the 68 clinical conditions in the overview.

The criteria in this document were not developed a priori, but rather were developed by the HWC with the assistance of the evidence reviewer over a number of months following the completion of the overview. The criteria reflect the discussions and agreement of the HWC members about the key features of the evidence base that should be captured in each evidence statement.

These criteria should not be treated as universal rules or principles that are applicable to all clinical contexts. The criteria were developed in response to a specific activity – NHMRC's overview of the effectiveness of homeopathy for treating clinical conditions in humans. The nature of these criteria, and indeed the need for them at all, reflects many of the features of this evidence review, particularly:

- it was very broad in nature and it captured a large number of clinical conditions;
- being an overview, the data on individual trials available to the evidence review was limited by the information reported in the included systematic reviews and the quality, reliability and currency of those systematic reviews; and
- the overall shortcomings of the primary evidence base, which was largely comprised of small trials that were not of high quality.

Introduction to the criteria

A standard format for evidence statements was developed, comprising three elements:

Element 1: Body of evidence

A description of the body of evidence including the number of systematic reviews and included studies, the quality of these, the total number of participants, and a statement of findings.

Element 2: Level of confidence

A level of confidence (LOC) rating for the body of evidence as a whole.

Element 3: Conclusion

A concluding statement that described the effectiveness of homeopathy as a treatment for a particular condition, compared with either placebo or other treatment(s).

The three elements of the evidence statement are designed to be read together, to give an overall impression of the body of evidence.

When there was a body of evidence addressing the intervention versus placebo, and another body of evidence addressing the intervention versus another comparator, two separate evidence statements were generally prepared (with all 'other comparators' included in the one evidence statement).

Separate evidence statements were not developed where there was more than one specific type of homeopathic intervention. For example, where one study examined 'X' homeopathic treatment and another examined 'Y' homeopathic treatment, the evidence statement refers broadly to 'homeopathy' rather than the specific treatment.

Guidance for Element 1 – Describing the body of evidence

The description of the body of evidence included:

1. A statement of the number of systematic reviews and the quality of those reviews.

- The quality of systematic reviews was assessed using the AMSTAR instrument. For the homeopathy overview, a score of 5 or less was considered poor, 6-8 medium, and 9+ good (out of a total score of either 10 or 11).

2. The number of studies in those reviews, stratified by the type of those studies if relevant (RCTs or prospectively designed, non-randomised controlled studies).

- Where relevant, the different levels of evidence were separately described, for example Level II evidence was described first, followed by Level III-1 and then Level III-2 evidence.

3. The quality of studies included within systematic reviews.

- The quality of studies was an interpretation of the quality ratings assigned to individual studies in the systematic review/s by the authors of each review. The systematic reviews used a range of systems to assess the methodological quality of the included studies. For the homeopathy overview, trials were categorised as poor, medium or good quality based on the following:
    - Jadad scores: 1 or 2 = poor; 3 or 4 = medium; 5 = good.
    - SIGN scores: a negative (-) sign = poor; a positive (+) sign = good.
    - Internal validity scores: 0-2.5 = poor; 3-4.5 = medium; 5-6 = good.
    - Scores out of 100 and scores expressed as percentages: 0-40 = poor; 40-70 = medium; >70 = good.
    - Risk of bias assessments: 'low' risk of bias = good; 'high' risk of bias = poor; 'unclear' risk of bias = quality unclear.
    - Scores 'expressed as Jadad / internal validity score' (used in Linde et al (1997)), where two separate quality scores are shown as percentages of the total maximum score (ie out of 100), separated by a ' / ' : The first score (Jadad score expressed out of 100) was used to assess the quality of the primary studies as it was the most commonly used scoring system throughout the overview. This means that where the first score was 20 or 40 = poor; 60 or 80 = medium; 100 = good.
- If several systematic reviews reported different quality levels for the same trial there were two ways that the decision was made (i) if more than two reviews reported a quality score, the quality reported by the majority was used for the purpose of formulating evidence statements; (ii) if only two reviews reported quality scores and they were conflicting, the quality score from the review with the highest AMSTAR score was used for the purpose of

formulating evidence statements. If the reviews still could not be split, the lower quality score was used in the evidence statement to avoid any overestimation of the trial's quality.

- If the quality of studies was variable, the quality range was stated, for example 'poor – medium'; 'poor – good'.
- If the authors did not assess quality then it was stated as 'unreported'.

4. The number of participants (total number of participants across all trials and the range).

- Number of participants was listed as the total number of participants ever randomised for each question, and a range for the smallest to largest trial.
- Where there were only two included studies, the number of participants for each study was stated, rather than the total number of participants or the range.
- Where there was only one trial, the description of the body of evidence included the size of the trial described in words, as follows:[1]
    - < 50 : very small
    - 50 to 149: small
    - 150 to 499: medium
    - 500 to 999: large
    - ≥1000: very large

5. A description of the intervention.

- Where all studies examined one specific homeopathic treatment (eg homeopathic *Arnica*), this was explicitly stated. Otherwise, the intervention was simply described as 'homeopathy'.

6. A description of the comparator.

- As noted above, placebo and 'other' comparators were addressed separately, in two distinct evidence statements.
- Where multiple 'other comparators' were examined, these were referred to as 'other therapies', with details provided in brackets.
- Where only one or two other comparators were examined, the comparator was explicitly described, rather than using the term 'other therapy'.

[1]Thresholds for descriptions of trial sizes were determined by the HWC as a general guide for intervention studies of this nature, based on the (generally) continuous outcomes measured in the trials. HWC considered the following study in the development of these thresholds: Influence of trial sample size on treatment effect estimates: meta-epidemiological study. *BMJ2013;346:f2304*

7. A statement about the findings of the included studies / reviews.

- A description of the findings of the included studies / reviews was **only** included in the evidence statement where there were good-quality studies of sufficient size, for example:

  'The one medium sized, good-quality trial ([number] participants) did not detect a difference between homeopathy and placebo in the treatment of people with [condition].'

  - For the purposes of the homeopathy overview, studies were considered to be of sufficient size where N>150 (i.e. those studies categorised as 'medium' sized or larger), as the outcomes were generally continuous outcomes.
  - If different systematic reviews reported different numbers of participants for the same trial, it was generally assumed that the trial was of the smallest size reported to avoid any overestimation of the sample size.
  - If the study quality was unreported, it was generally assumed to be poor quality to avoid any overestimation of the trial's quality.
  - If different systematic reviews reported different quality scores for the same trial, it was generally assumed that the trial was of the lowest quality reported to avoid any overestimation of the trial's quality.
- In theory, the results of meta-analyses may have also been discussed in this part of the evidence statement. However, the evidence reviewer and the HWC considered that all of the meta-analyses for specific conditions (i.e. those that had the potential to be included in evidence statements) had included studies that were of poor methodological quality/had a high risk of bias. A decision was made by the HWC to state the findings of studies that were of good methodological quality and sufficient size in favour of meta-analyses that included poor quality studies.
- If there was more than one study that suggested that homeopathy is more effective than placebo or as effective as other therapies but due to the number, size and/or quality of those studies the findings are not reliable, a general statement to that effect was made, for example:

  'These studies are of insufficient [quality] / [size] / [quality and size] / [quality and/or size] / [quality or size] to warrant further consideration of their findings.'
- In all other circumstances, no 'statement of findings' was included in the evidence statement.

Where a systematic review did not identify any studies, this was stated and the date of the systematic review was included, for example:

'One systematic review ([year]) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy in people with [condition].'

Guidance for Element 2 – Assigning a level of confidence

A level of confidence (LOC) rating was assigned to the body of evidence as a whole, for each condition.

Assigning a LOC was based on judgment and expertise using a framework informed by the GRADE framework. Usually GRADE is applied outcome by outcome rather than to the body of evidence as a whole. This is because the availability and quality of evidence may differ for each outcome. However, the HWC used an adapted version of GRADE in order to make broad statements about the LOC in the body of evidence as a whole.

As per the GRADE methodology, each condition's evidence base was assigned a starting LOC of 'high' (Table 1). The LOC was then upgraded or downgraded depending on the limitations or strengths of the studies contained in the systematic reviews (see Table 2).

Table 1: Level of confidence (adapted from GRADE)

Approximate GRADE rating *(reflecting level of confidence in the evidence)*	**GRADE description**
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Table 2: Upgrading and downgrading

Decrease grade if:	Increase grade if:
• Serious (− 1) or very serious (− 2) limitation to study quality • Important inconsistency (− 1) • Some (− 1) or major (− 2) uncertainty about directness • Imprecise or sparse data (− 1) • High probability of reporting bias (− 1)	• Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) • Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) • Evidence of a dose response gradient (+1) • All plausible confounders would have reduced the effect (+1)

For the homeopathy overview, the information available for downgrading evidence was predominantly as follows:

- Quality: -1 or -2 depending on seriousness of limitation to study quality.
    - If quality of the included studies was not reported in the systematic review then those studies were assumed to be poor quality (-2).
    - NB: if quality is assessed using Jadad then any score <5 could indicate serious or very serious bias. Therefore it was often appropriate to give a range for the LOC (i.e. subtracting both -1 and -2) e.g. moderate-low
- Precision: related to the number of participants in individual studies and as a whole. Small is relative but in general any trial with less than 150 participants is small.
    - Very sparse data = ≤50 (-2)
    - Sparse data = 51 – 149 (-1)
    - A level of judgement was required. For example, three small / very small studies with a total sample size of 110 might be considered 'sparse' to 'very sparse', so would be downgraded by 1-2 and a range presented.

The remaining GRADE factors were difficult to apply to an overview; however, downgrading based on the quality of the systematic review/s was also appropriate in some situations (as a poorer quality systematic review is more likely to result in bias)

For further information on the GRADE methodology see: *Grading Quality of Evidence and Strength of Recommendations*. Grade Working Group. BMJ V328, 19 June 2004.

Guidance for Element 3 – Final conclusion

The final statement provides a conclusion (defined by the Oxford Dictionary as 'a judgement or decision reached by reasoning') about the effectiveness of the homeopathy as a treatment for a particular condition, compared with either placebo or other treatment(s).

The conclusions were generally based on whether or not any statistically significant findings were reported for any outcome (unless the HWC determined that the outcome had no clinical relevance). The evidence reviewer and HWC acknowledge that the assessment of 'effectiveness' based on statistical significance and not clinical significance is not ideal. This was, however, necessary due to the poor reporting (e.g. no reporting of primary outcomes, effect estimates or confidence intervals) and lack of analyses by the included systematic reviews and primary studies. Further, it was not possible to create a hierarchy of clinically relevant outcomes prior to conducting the overview (due to the number of conditions and systematic reviews included in the overview), and making post hoc decisions about the importance of outcomes is likely to be subject to bias.

In general, separate conclusions were not developed where there was more than one specific type of homeopathic intervention. That is, where one study examined 'X' homeopathic treatment and another examined 'Y' homeopathic treatment, the conclusion refers broadly to 'homeopathy' rather than the specific treatment. The only exception to this principle was for the condition 'Children with diarrhoea', where there was a difference in the evidence base for 'combined homeopathy' and 'individualised homeopathy'. In this instance, the conclusion sentence separately reflected the evidence base for each type of homeopathy.

For each clinical condition, the null hypothesis was that homeopathy has no effect as a treatment for that condition. The HWC decided that the null hypothesis would be assumed, unless there is sufficient reliable evidence to demonstrate otherwise.

The only exceptions to this principle were:

- where there were no studies (or only one small and/or poor/unknown quality study) identified for a particular clinical condition; or
- where the evidence was so poorly reported so as to be uninterpretable.

In these cases, the HWC determined that no conclusion could be drawn about effectiveness, rather than assuming the null hypothesis.

In the final concluding statement, the intervention is described as 'homeopathy' even if a more detailed description is provided in Element 1 of the evidence statement.

Placebo

For studies that compare homeopathy with placebo, the null hypothesis assumed by the HWC was that homeopathy is no more effective than placebo.

The possible conclusions developed for the evidence base of the homeopathy overview were:

Description of evidence base	Conclusion
A significant difference in favour of homeopathy is consistently reported by multiple studies of good quality and sufficient size OR A large body of good-quality evidence has been appropriately meta-analysed and found a significant difference in favour of homeopathy	1. Based on the body of evidence evaluated in this review there is **reliable evidence** that homeopathy is **more effective** than placebo for the treatment of Y*
A significant difference in favour of homeopathy is consistently reported by some studies of good quality and sufficient size; however, these need to be replicated OR A small body of good-quality evidence has been appropriately meta-analysed and found a significant difference in favour of homeopathy	2. Based on the body of evidence evaluated in this review there is **some evidence** that homeopathy is **more effective** than placebo for the treatment of Y*
A significant difference in favour of homeopathy is reported by all (or a substantial proportion of) studies, but these studies are undersized and/or of poor methodological quality	3. Based on the body of evidence evaluated in this review there is **no reliable evidence** that homeopathy is more effective than placebo for the treatment of Y
No significant difference is reported by any study (or by a substantial majority of good-quality, decently sized studies)	4. Based on the body of evidence evaluated in this review homeopathy is **not more effective** than placebo for the treatment of Y
One small and/or poor/unknown quality study	5. Based on only one [small] study [of poor/unknown quality] there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of Y
The evidence is too poorly reported to enable interpretation	6. The evidence is too poorly reported to enable interpretation and no conclusion can be drawn about the effectiveness of homeopathy compared to placebo for the treatment of Y*
Where no studies were identified	7. N/A (no concluding statement)

*These conclusions were developed for completeness but were not used because the applicable evidence base did not arise for any of the clinical conditions in the overview. For that reason, the proposed wording has not had the same degree of consideration by the HWC as the other concluding statements.

Other comparators

For studies that compare homeopathy with another therapy, the null hypothesis assumed by the HWC was that homeopathy is not as effective as the other therapy.

Due to the scope of the homeopathy overview, the appropriateness of the comparator was generally not assessed by the evidence reviewer or the HWC. For the purpose of framing the null hypothesis, an implicit assumption has been made that the comparator is more effective than placebo (i.e. the concluding statement is based around whether homeopathy is 'as effective as' another treatment, without a consideration of the appropriateness of that treatment). The HWC acknowledged that this could mean that homeopathy is found to be 'as effective as' an ineffective treatment. This evidence base arose for only one of the clinical conditions (Lower back pain). In this case, an explicit statement was included in the concluding part of the evidence statement that the effectiveness of the comparator used in the study (Cremor Capsici Compositus) is unclear.

Where only one or two other comparators were examined, the comparator was explicitly described, rather than using the term 'other therapy'. Where multiple other comparators were examined, these were referred to as 'the other therapies', without repeating the details of those therapies that were provided in brackets in Element 1 of the evidence statement.

The possible conclusions developed for the evidence base of the homeopathy overview were:

Description of evidence base	**Conclusion**
A significant difference in favour of homeopathy is consistently reported by multiple studies of good quality and sufficient size OR A large body of good-quality evidence has been appropriately meta-analysed and found a significant difference in favour of homeopathy	1A. Based on the body of evidence evaluated in this review there is **reliable evidence** that homeopathy is **more effective** than [the other therapies] for the treatment of Y*
No significant difference is consistently reported by multiple studies of good quality and sufficient size OR A large body of good-quality evidence has been appropriately meta-analysed and found no significant difference ('good evidence of equivalence')	1B. Based on the body of evidence evaluated in this review there is **reliable evidence** that homeopathy is **as effective** as [the other therapies]for the treatment of Y*
A significant difference in favour of homeopathy is consistently reported by some studies of good quality and sufficient size; however, these need to be replicated OR A small body of good-quality evidence has been appropriately meta-analysed and found a significant difference in favour of homeopathy	2A. Based on the body of evidence evaluated in this review there is **some evidence** that homeopathy is **more effective** than [the other therapies]for the treatment of Y*

Description of evidence base	Conclusion
No significant difference is consistently reported by some studies of good quality and sufficient size; however, these need to be replicated OR A small body of good-quality evidence has been appropriately meta-analysed and found no significant difference ('some evidence of equivalence')	2B. Based on the body of evidence evaluated in this review there is **some evidence** that homeopathy is **as effective** as [the other therapies]for the treatment of Y
No significant difference (or a significant difference in favour of homeopathy) reported by all studies (or a substantial proportion of studies), but these studies are undersized and/or of poor methodological quality ('unreliable evidence of equivalence or of homeopathy being more effective')	3. Based on the body of evidence evaluated in this review there is **no reliable evidence** that homeopathy is as effective as [the other therapies]for the treatment of Y
A significant difference in favour of other therapies is reported by all studies (or by a substantial majority of good-quality, decently sized studies)	4. Based on the body of evidence evaluated in this review homeopathy is **not as effective** as [the other therapies]for the treatment of Y
One small and/or poor/unknown quality study	5. Based on only one [small] study [of poor/unknown quality] there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to [the other therapies] for the treatment of Y
The evidence is too poorly reported to enable interpretation	6. The evidence is too poorly reported to enable interpretation and no conclusion can be drawn about the effectiveness of homeopathy compared to [the other therapies] for the treatment of Y*
Where no studies were identified	7. N/A (no concluding statement)

*These conclusions were developed for completeness but were not used because the applicable evidence base did not arise for any of the clinical conditions in the overview. For that reason, the proposed wording has not had the same degree of consideration by the HWC as the other concluding statements.