Australian Government
National Health and Medical Research Council

NHMRC

CEO Statement

Release of an annotated version of the 2012 draft report *The Effectiveness of Homeopathy: an overview review of secondary evidence*

In 2015, NHMRC released the *NHMRC Statement on Homeopathy* and accompanying Information Paper.

I am aware that there has been considerable interest in an unfinished draft report on an overview of reviews of the effectiveness of homeopathy (frequently referred to as the 2012 draft report), and why it was not released.

I am also aware and concerned that a significant amount of misinformation has built up about the content of this 2012 draft report. I am releasing the report now in an annotated form to address this misinformation.

As part of the process to develop the *NHMRC Statement on Homeopathy, a*n initial contractor was engaged to review the scientific evidence on the effectiveness of homeopathy in treating a variety of clinical conditions with the aim of providing Australians with reliable information about its use. The contract was terminated in August 2012 with the mutual agreement of NHMRC and the contractor. The draft of the unfinished report, titled *The Effectiveness of Homeopathy: an overview review of secondary evidence* (i.e. the 2012 draft report), was not endorsed by the expert Homeopathy Working Committee.

A second reviewer was contracted and provided an overview of published systematic reviews and a review of submitted literature. The second contractor developed the *NHMRC Information Paper: Evidence of the effectiveness of homeopathy for treating health conditions* (published in March 2015 at the same time as the *NHMRC Statement on Homeopathy*).

The document I am releasing comprises the 2012 draft report in its entirety, with annotations that have been reviewed by the previous Chair of the Homeopathy Working Committee. These annotations have been made for context and to avoid misunderstanding of the draft report.

It must be emphasised that this is an incomplete piece of work that is not a NHMRC-endorsed report, therefore its content must be read in this context. NHMRC's usual practices of quality assurance were not applied to this document. These practices (which include methodological review, expert review, public consultation and approval from the expert committee and NHMRC's Council) can often result in significant changes to initial drafts.

NHMRC strongly encourages interested members of the community to refer to the 2015 *NHMRC Information Paper: Evidence of the effectiveness of homeopathy for treating health conditions*. Contrary to some claims, the review did not conclude that homeopathy was ineffective. Rather, it stated that "**based on the assessment of the evidence of effectiveness of homeopathy, NHMRC concludes that there are no health conditions for which there is reliable evidence that homeopathy is effective.**"

Anne Kelso.

Professor Anne Kelso AO
Chief Executive Officer

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T 1300 NHMRC (1300 064 672) or +61 2 6217 9000
16 Marcus Clarke Street, Canberra ACT 2601
GPO Box 1421, Canberra ACT 2601

info a nhmrc.gov.au
nhmrc.gov.au

The Effectiveness of Homeopathy: An overview review of secondary evidence

August 2012

Prepared for

NHMRC

Prepared by

International Centre for Allied Health Evidence (iCAHE)
University of South Australia
Adelaide, South Australia 5000

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Executive summary

Project aim

- Undertake an overview of published systematic reviews and meta-analyses published since 1997, that have evaluated the effectiveness of homeopathy, in terms of:
    - consultation between patient and homeopath (with or without the prescription of homeopathic therapeutic goods) and
    - homeopathy as a therapeutic good (self-prescription of homeopathic therapeutic goods)

Objectives of the review

- Identify and critique the peer-reviewed secondary evidence relating to the effectiveness and safety of homeopathy for human clinical conditions (symptoms, diseases, health concerns)
- Analyse findings from the included secondary evidence for specific condition, by reporting the number of relevant systematic reviews per condition, component primary studies, subjects involved in the research, collating the findings, and considering the evidence base in terms of the first three elements of the National Health and Medical Research Council (NHMRC) FORM approach for synthesising the strength of the body of evidence.

Literature review processes

Relevant literature for this overview review was secondary evidence which had been published since 1997, was available in full text and English language, and directly related to the homeopathic treatment of clinical conditions/ symptoms. Review processes were to:

- Collate a comprehensive body of secondary evidence relevant to the project aim and objectives.
    - Systematic literature reviews and meta-analyses were identified from a number of searching approaches:
        - submissions made to NHMRC by Australian Homoeopathic Association and the Australian Medical Fellowship of Homeopathy
        - independent comprehensive searching through all available databases using a broad range of MeSH and text terms/ headings
        - umbrella reviews (which were systematic reviews of secondary evidence)
        - relevant clinical guidelines (sourced from internationally-recognised guideline sources [NICE, National Guidelines Clearing House, SIGN, NHMRC, NZGG] and the internet)
        - relevant Government reports (international and national) sourced from independent internet searching undertaken by the iCAHE team
        - pearling all reference lists
- Appraise the methodological quality of the included secondary evidence using the criteria outlined in the Centre for Evidence-Based Medicine (CEBM) instrument
- Sort the included reviews into categories which report on:

1. only one clinical condition treated with homeopathy
2. one clinical condition treated with Complementary and Alternative Medicine interventions (of which homeopathy is one)
3. multiple clinical conditions treated with homeopathic interventions
4. technical or methodological reviews, which were not focused on one clinical condition, or reviews which tested the effect of homeopathy compared with that of the placebo effect, which presented technical and/ or methodological arguments for the effect of homeopathy compared with a placebo effect, or the effect from the control arms of conventional medicine studies
5. the effect of any treatment on a condition or group of conditions (of which one treatment was homeopathy)

- Collate the findings in Categories 1-3
- Summarise the findings in terms of strength of the body of evidence (NHMRC FORM)

Search Results

166 systematic reviews and meta-analyses were identified through the multiple-arm search process, of which 55 were potentially relevant to this project

- 18 classified as Category 1
- 17 classified as Category 2
- 8 classified as Category 3 [of which three were redundant, being earlier versions of the same review by the same author group]
- 9 classified as Category 4
- 3 classified as Category 5 reviews.

This provided 40 systematic reviews and meta-analyses with which to address the aims of the overview review (reviews which focused on a clinical question [18 Category 1, 17 Category 2, 5 recent Category 3]). The included literature was largely identified from the independent methodologist search (See Appendix 2). The homeopathy submissions to NHMRC provided approximately 30% systematic reviews that were found in the independent methodologists' search, and the Government technical reports identified one additional systematic review not found in the independent methodologist's search (Category 2 review). No new literature was identified from the NHMRC homeopathy submissions.

Critical appraisal

Systematic reviews: No critical appraisal, other than to determine whether a clear search question was asked, was undertaken on the Category 4 or 5 reviews. These reviews were determined as not addressing a focused clinical question, with homeopathy as the primary intervention, and were not used to inform the body of evidence in the NHMRC review overview.

Considering the 40 reviews which focused on a clinical question (18 Category 1 reviews, 17 Category 2 reviews, 5 Category 3 reviews, they were generally of moderate quality, with 26 reviews meeting three or four of the first five CEBM criteria. Only one review met all five criteria.

'Moderate quality' is not defined here.
26 out of 40 studies satisfied 3-4 out of the 5 CEBM criteria.
Does 65% of studies reaching a 'score ' of 60-80% rate a 'moderate quality' description? Not confirmed by the expert committee

University of South Australia

- Seven reviews scored Not Applicable to CEBM Criterion 4 and/or 5), where the review found no relevant studies for the review question (N=3 reviews) or only one relevant study was identified (N=4 reviews).
- Considering the 33 reviews which could provide scores for the CEBM Criteria 1-5:
    - One review positively addressed all five criteria
    - 11 reviews positively addressed four criteria
    - 12 reviews positively addressed only three criteria
    - Seven reviews positively addressed only two criteria
    - One review addressed only one criteria
    - One review addressed none of the criteria.

Non-compliance with any of the five CEBM criteria was most evident for Criterion 4 and 5 (N=23 reviews in each). These criteria dealt with the included studies not being sufficiently valid for the type of question asked, and the results not being similar from study to study.

Overview of homeopathic interventions

Homeopathic preparations: All included reviews which focused on a clinical condition reported on homeopathic interventions, which were either specific therapeutic goods (formulaic) or individualised (with, or without, the engagement of a homeopath). In each evidence summary for each clinical condition (or group of conditions), details of the homeopathic interventions which were applied in each component primary study are reported (where these details were available in the review). This information variably included the homeopathic agent and dilution, daily frequency of administration and the number of days of administration. Table A6.3 in the Appendix to this report summarises the homeopathic interventions reported in each review.

Consultation with a homeopath: This overview review found no primary studies which directly evaluated the effectiveness of the consultation between patients and homeopaths. The need for such primary studies was highlighted by many review authors, along with the caveat that such investigations would require non-experimental studies (such as observational and qualitative research designs) to explore the influence of assessment, and provider-patient relationships and expectations, patient compliance, reassessment and adjustment of homeopathic interventions throughout an episode of treatment. The closest evidence this overview review was able to provide related to the effectiveness of individualised homeopathic interventions (which were prescribed and provided by a homeopath to individual subjects in the studies). It was rare that any details were provided about the nature of the consultation or individualised homeopathic interventions.

Overview of comparators: Comparators were often not well described. Where information was available, they variably comprised inactive solutions or tablets that looked similar to the homeopathic intervention, but contained no homeopathic ingredients (such as un-medicated granules (usually lactose) or drops (alcohol diluted in water, or saline). The control intervention could also be another complementary medicine approach (acupuncture, relaxation, hydrotherapy, herbal medicines etc.), a mainstream medical approach or no treatment at all.

This summary fails to note the fact that as Table 15 in Appendix 7 suggests, of the primary studies within the included systematic reviews, only about 28% had a low risk of bias.

And conversely, as many as approximately 72% of primary studies were either medium or high risk of bias, or the authors could not attribute a score on the quality of the study .

Summary of evidence of homeopathic interventions per condition and Strength of the body of evidence

the term 'moderate' is not in the FORM matrix. It should be 'satisfactory'

The overall strength of the body of evidence for the 27 clinical conditions was poor to moderate, with the overall evidence grades being either C or D (See Table 1). The component elements of the FORM Matrix varied, as the evidence base across conditions ranged from A-D, consistency ranged from B-D, but most effects of homeopathy were D (Restricted effect). This last element attenuated the overall evidence grade assigned to each condition.

the term 'effects' is not in the FORM matrix. It should be 'clinical impact' . This is one of three key elements of FORM and as such it is important to use the term correctly

The term 'encouraging evidence' is not defined in this report. There are inconsistencies as to how it is interpreted.

There is encouraging evidence for the effectiveness of homeopathy for:

- Fibromyalgia (Grade C)
- otitis media (Grade C)
- post-operative ileus (time to first flatus) (Grade C)
- Upper Respiratory Tract Infection (URTI) in adults (Grade C)
- side effects of cancer treatment (Grade C)
    - prophylaxis of acute dermatitis during radiotherapy
    - chemotherapy-induced stomatitis

* Conclusions not confirmed by expert committee, just represent the views of the report authors.
* Grade C used here to represent 'encouraging evidence of effectiveness', but further down the page Grade C represents 'no convincing evidence'
* the FORM evidence matrix for each of these conditions has little or no mention of risk of bias - an integral criterion for quality of the evidence.

See sections on individual conditions for more specific comments on the quality of this report and the conclusions reached by the authors.

There is inconclusive or equivocal evidence for the effectiveness of homeopathy for:

- asthma (Grade D)
- chronic fatigue syndrome (CFS) (Grade C)
- hay fever, pollinitis or allergic rhinitis (Grade C)

There is no convincing evidence for the effectiveness of homeopathy for:

- acute pain (Grade D)
- arthro-rheumatic diseases
    - osteoarthritis (Grade C)
    - rheumatoid arthritis, ankylosing spondylitis or chronic polyarthritis (Grade D)
- Attention Deficit and Hyperactivity Disorder (ADHD) (Grade C)
- anxiety (Grade D)
- delayed onset muscle soreness (DOMS) (Grade D)
- dermatological conditions (Grade C)
- headache of any type (Grade C)
- induction of labour (Grade D)
- menopausal symptoms in women with a history of breast cancer (Grade C)
- obesity (Grade D)
- side effects of cancer treatment (other than acute dermatitis during radiotherapy, and chemotherapy-induced stomatitis [listed above under encouraging evidence]) (Grade C)
- sleep disorders (Grade C)
- Upper Respiratory Tract Infection (URTI) in children (Grade D)

There is no description of what 'C' or 'D' means, which makes it hard for the reader to compare the information. The NHMRC FORM Evidence matrix suggests that
* C reflects: low risk of bias (Level III evidence) or medium risk of bias (Levels I & II), some inconsistency in the included studies, and a moderate clinical impact.
* D reflects: high risk of bias (levels I-IV), inconsistent evidence and a slight or restricted clinical impact . Occasionally referred to in report as 'inconclusive evidence, but not consistently

There are inconsistencies in how these grades are applied. See sections on individual conditions for more details.

There is insufficient evidence to support a conclusion regarding the effectiveness of homeopathy for:

- depression (two primary studies dealing with different diagnoses) (Grade D)
- HIV (two old, poor quality primary studies) (Grade D)
- low back pain (only one primary study) (Grade D)
- pre-menstrual syndrome (one old, poor quality primary study) (Grade D)
- vertigo (no identifiable primary studies) (Grade D)

There is no available evidence (no relevant primary study) to support a conclusion regarding the effectiveness of homeopathy for:

- dementia (no available primary studies)
- nocturnal enuresis (no available primary studies)
- menopausal symptoms in healthy women (no available primary studies)

Table 1. Summary evidence of effect of homeopathy by condition.

Condition	Evidence Base	Summary effect of homeopathy	Evidence base	
Acute pain	1 moderate quality review of 4 poor-moderate quality RCTs • pain from dental surgery (2 studies, N=177) • orthopaedic trauma (1 study, N=20) • acute stroke (1 study, N=40)	No convincing evidence for any presentation	D	See comments on issues with this section of the report on page 19
Anxiety	2 poor-moderate quality reviews of 9 primary experimental studies (50 children, 147 students, 53 women, 384 mixed gender adults)	No convincing evidence	D	See comments on issues with this section of the report on page 22
Asthma	2 good quality, recent reviews of 16 primary studies of variable experimental design and quality (924 adults, 320 children and adolescents)	Inconclusive/ equivocal evidence	D	See comments on issues with this section of the report on page 27
Attention Deficit & Hyperactivity Disorder (ADHD)	1 high quality review of 4 poor-moderate primary studies, on 189 children	No convincing evidence	C	See comments on issues with this section of the report on page 36
Cancer-treatment symptoms	1 good quality key review, 3 'other' reviews, reporting 8 studies of variable quality of 664 individuals	Encouraging evidence for • *topical calendula* for prophylaxis of acute dermatitis during radiotherapy • *Traumeel S* mouthwash in	C	See comments on issues with this section of the report on page 40

		the treatment of chemotherapy-induced stomatitis • No convincing evidence for any other adverse effect of cancer treatment	
Chronic fatigue syndrome	2 good quality reviews reporting on 3 variable quality RCTs of 239 individuals	Inconclusive/ equivocal evidence	C
Delayed onset muscle soreness (DOMS)	2 old poor-moderate quality reviews reporting on 8 variable quality RCTs of 168 women and 143 mixed gender subjects	No convincing evidence	D
Depression	1 moderate quality review of 2 poor quality experimental studies, of 71 individuals with different types/ causes of primary depression	Insufficient evidence to reach a conclusion	D
Dementia	1 good quality review found no relevant study	No available evidence	NA
Dermatological conditions	1 good quality, recent review of 11 experimental studies of 879 individuals with seven dermatological conditions (277 children, 342 adults, 260 mixed age individuals)	No convincing evidence for any dermatological condition	C
Fibromyalgia	1 good quality key review, and six recent 'other' reviews, reported on 5 moderate quality RCTs of 265 individuals (reported in 6 papers)	Encouraging evidence of effect	C
Hay fever, pollinitis and allergic rhinitis	2 good quality reviews of 22 primary experimental, observational and case series studies of 3415 adults, and 2 experimental studies of 143 children	Inconclusive/ equivocal evidence	C
Headache	2 non-recent good quality reviews reporting on 4 RCTs of variable quality, involving 284 individuals with migraine, or mixed migraine and tension-type headache	No convincing evidence for any headache type	C
HIV/ AIDS	1 moderate quality review, reporting on two old methodologically-flawed experimental studies of 112 individuals	Insufficient evidence to reach a conclusion	D
Induction of labour	1 good quality review, of two RCTs of unclear methodology, of 133 women	No convincing evidence	D
Low back pain	1 moderate-quality review reporting on one methodologically-sound RCT of 161 individuals (equivocality study of two active arm interventions)	Insufficient evidence to reach a conclusion	D
Menopausal symptoms	*Healthy women*: 1 poor quality review of no RCTs	No evidence	

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	Women with a history of breast cancer: 1 good quality review of 2 poor-moderate quality RCTs of 124 women	No convincing evidence	C
Nocturnal enuresis	1 good quality review found no relevant study	No available evidence	NA
Obesity	1 moderate quality review of 2 moderate quality studies of 377 individuals	No convincing evidence	D
Osteoarthritis	3 good quality reviews, of six studies [total N 957] (4 moderate quality RCTs of 310 individuals, 1 CCT of 592 individuals, 1 prospective observational study of 55 individuals)	No convincing evidence	C
Otitis media	1 good quality, recent review reporting on 6 experimental studies (in seven papers) of varying design and quality, on 562 children	Encouraging evidence of effect	C
Post-operative ileus	1 good quality, non-recent systematic review with meta-analysis, of 6 primary RCTs of 1082 subjects	Encouraging evidence in reducing time to first flatus after surgery	C
Pre-menstrual syndrome	1 moderate quality review of 1 old, methodologically-biased RCT of 10 women	Insufficient evidence to reach a conclusion	D
Rheumatoid arthritis, ankylosing spondylitis, chronic polyarthritis	1 good quality meta-analysis of 6 primary experimental studies of varying age (quality assessment not available) • rheumatoid arthritis (four primary studies, total N=398) • anklyosing spondylitis (one primary study, N=104) • chronic polyarthritis (one primary study, N=111)	No convincing evidence for any condition	D
Sleep disorders	2 good quality reviews, of six poor-moderate quality experimental studies of 263 individuals	No convincing evidence	C
Upper respiratory tract infections (URTI)	1 good quality recent review of 6 poor-moderate experimental studies of 1327 children, and 15 poor-moderate quality experimental studies of 5050 adults	*Children*: No convincing evidence *Adults:* Encouraging evidence (degree of positivity diagnosis-dependent) *cough*, only study favours homeopathy; *influenza*, 3 of 4 studies favoured homeopathy, 4th	D C

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		was equivalent; *URTI*, 2 of 4 studies favoured homeopathy, 2 of 4 studies equivalent); *sinusitis*, 2 of 4 studies favoured homeopathy, 2 of 4 studies equivalent); *tonsillitis* (2 of 2 studies favouring homeopathy).	
Vertigo	1 poor quality review summarised four (unnamed) primary studies	No verifiable evidence	D

Part 1: Overview Report

Introduction

National Health and Medical Research Council (NHMRC) has a statutory responsibility to provide advice on health matters. NHMRC's current and forthcoming strategic plans identify *"examining alternative therapy claims"* as a major health issue for consideration by the organisation. This review focuses on the effectiveness of homeopathy.

Homeopathy is an alternative medical system which was founded by the German physician Samuel Christian Hahnemann in the late 18th century. It is based on the hypothesis that a substance that causes certain symptom(s) in a healthy person (usually at high doses) can be used to treat those symptoms in a person who is ill (at small doses). This principle is known as ***'Similia similibus curantur'*** *or* 'like cures like'.

Homeopathy is described by the National Centre for Complementary and Alternative Medicine (National Institutes of Health, US) in the following manner:

> *"The alternative medical system of homeopathy was developed in Germany at the end of the 18th century. Supporters of homeopathy point to two unconventional theories: "like cures like"—the notion that a disease can be cured by a substance that produces similar symptoms in healthy people; and "law of minimum dose"—the notion that the lower the dose of the medication, the greater its effectiveness. Many homeopathic remedies are so diluted that no molecules of the original substance remain. Homeopathic remedies are derived from substances that come from plants, minerals, or animals, such as red onion, arnica (mountain herb), crushed whole bees, white arsenic, poison ivy, belladonna (deadly nightshade), and stinging nettle. Homeopathic remedies are often formulated as sugar pellets to be placed under the tongue; they may also be in other forms, such as ointments, gels, drops, creams, and tablets. Treatments are "individualised" or tailored to each person—it is not uncommon for different people with the same condition to receive different treatments"* [1]

Homeopathic interventions

Various types of homeopathy exist. The traditional form is known as ***Individualised or Classical homeopathy.*** Typically a single homeopathic medicine is prescribed which is selected on the basis of ALL patient symptoms (mental, general and constitutional), as unrelated as they may seem.

[1] http://nccam.nih.gov/health/homeopathy#hed1 Accessed 9th May 2012

Another form of homeopathy is ***Clinical homeopathy.*** In Clinical homeopathy, one or more homeopathic medicines are used for standard clinical situations or conventional diagnoses which are prescribed based on the presenting disease state rather than the totality of symptoms.

The use of several homeopathic medicines individually or in a fixed (complex) formulation is also called ***Complex or Combination homeopathy.***

Isopathy refers to the use of homeopathic dilutions of allergens or causative infectious or toxic agents (i.e. uses the patient's own product of a disease such as sputum or urine to treat the disease.

Homeopathic medicines

Homeopathic medicines are prepared by serial dilution in alcohol or distilled water, followed by forceful striking on an elastic body, called 'succussion'. Each dilution followed by succussion is assumed to increase the medicine's potency due to a transfer of energy, meaning that higher diluted preparations are considered more active.

Homeopathic medicines are used in both low dilutions, where the original substance is physically present, and in high dilutions, in which material quantities of the original substance are unlikely to be present.

In individualised homeopathy each patient may receive a different treatment for a specific ailment (i.e. headache) based on the patient's specific 'symptom picture'.

Difference between herbal and homeopathic medicines

Herbal medicines and homeopathic medicines are very different. Herbal medicines use a part or extract of a plant, contain the physical components of the plant (e.g. nutrients, phytochemicals) and are usually used at strength.
Homeopathic medicines can, but not always, originate from plant material. They undergo a process of serial dilution and succession and therefore contain little to no physical trace of the original material (i.e. plant) or its components. They are prescribed based on the principle of 'like cures like'.

Methods

An independent research team, from the University of South Australia, undertook an extensive independent literature search to identify all relevant secondary evidence related to the project aim.

Project aim

This project aimed to undertake an overview of peer-reviewed systematic reviews (SR) and meta-analyses (MA) published since 1997, which evaluated the effectiveness of homeopathy, in terms of

- consultation between patient and homeopath (with or without the prescription of homeopathic therapeutic goods) and
- homeopathy as a therapeutic good (self-prescription of homeopathic therapeutic goods)

Objectives of the review

- To identify and critique all peer-reviewed secondary evidence relating to the effectiveness and safety of homeopathy for human clinical conditions (symptoms, diseases, health concerns).
- Analyse the findings from the secondary evidence for specific conditions, by reporting the number of relevant systematic reviews per condition, component primary studies, and subjects involved in the research, collating the findings, and considering the evidence-base in terms of the first three elements of the NHMRC FORM approach for synthesising the strength of the body of evidence. The NHMRC FORM is provided in Appendix 1A. The elements of generalisability and applicability were not considered relevant to this overview review.

Search strategy

1. *Submissions:* The independent research team was given access to submissions which had been provided to NHMRC by the general public, the Australian Homeopathic Association, and the Australian Medical Fellowship of Homeopathy. The secondary evidence (systematic reviews and meta-analysis) cited in these submissions was identified, and sourced. This comprised the first evidence body.

2. *Independent searching*
   - An initial scoping search was conducted to test the text and MeSH terms required to achieve the greatest number of article returns. The initial scoping search approach was discussed with, and independently verified by, a University of South Australia Health Sciences liaison librarian. Input from the NHMRC Expert Working Party and secretariat was also sought, on different approaches to search the library databases.
   - The comprehensive literature search was then conducted, using a structured and iterative process, through the following mainstream and homeopathic databases:

     OVID (Medline, AMED, EMBASE, ICONDA), EBSCOhost (Academic Search Premier, Australian and New Zealand Reference Centre, CINAHL, HealthSource, PsychINFO, Psychology and behavioural sciences, Health business full text elite, Business Source Complete), PubMed, Cochrane library, Scopus, Web of knowledge, Sage Journals, ProQuest and UniSA Summon.

The search terms comprised MeSH headings and text terms:

Homeopathy OR homeopath OR homoeop AND Systematic review OR meta-analysis OR clinical guideline OR guideline OR practice guideline OR clinical practice guideline, Boolean operators and wild cards were used as appropriate to each database. It is noted that different search approaches, using different versions of these search terms was required, in order to effectively interrogate each database while maintaining consistency of the search terms relevant to the search objectives.

- During this search, three types of reviews were identified:
    1. Reviews which reported on primary literature (studies which had been conducted on humans for specific clinical conditions, for which homeopathy was at least one intervention)
    2. Reviews which considered non-clinical questions, where methodological arguments were proposed, for instance whether homeopathic effects were similar to the placebo effects from allopathic trials
    3. Reviews of systematic reviews and meta-analyses (which we deemed 'umbrella reviews'). Where such reviews were identified, they were not included in the overview review, however their reference lists were pearled to identify reviews which had not been identified from any other source

3. *Government reports:* Relevant Government reports (international and national) were sourced by:
    - independent internet searching undertaken by the independent research team
    - pearling the reference lists of previously included literature, and the NHMRC submissions
4. *Clinical guidelines*: relevant clinical guidelines were sought through internationally-recognised guideline sources [NICE, National Guidelines Clearing House, SIGN, NHMRC, NZGG] and the internet). If available, the clinical guidelines themselves would not be a source of information, rather their reference lists would provide another source of secondary evidence
5. *Validation:* Validation searches were then conducted using the same search terms (as for Step 2). Searching was iterated until no new systematic reviews and meta-analyses were found.
    - Additional databases which were identified from included reviews (CAM on PubMed, Web of Science, The British Library of Homeopathy (HomInform), Informit, Wiley online Library). The homeopathic databases of Refworks and CISCOM were unable to be accessed, due to licensing rights, membership access and in the case of CISCOM, the deactivation of the database.
    - Hand-searching (pearling) was conducted through the reference lists of the included reviews, to identify systematic reviews that had not been identified in the independent research teams search

- The reference lists in relevant international Government reports were searched and cited secondary evidence was cross-matched with the articles identified in other search methods.

Study selection criteria

Study selection occurred in two phases. The initial phase identified all potentially-relevant reviews, and produced a comprehensive list. The second phase considered the studies in this list in terms of their purpose and methodological quality.

Phase 1: Initial inclusion/ exclusion

Potentially-relevant reviews for this overview review comprised:

- Any English-language, full text peer-reviewed secondary evidence (systematic review or meta-analysis of the literature published since 1997), that related to the effectiveness of homeopathic management for a clinical condition, as described in the project aim and objectives. Reviews that reported on the safety of homeopathic interventions, or homeopathic interventions for disease prevention, were also included, if available.
    - Secondary evidence comprises systematic reviews and meta-analyses of primary research. Primary research relevant to this review is conducted on human subjects, for which ethics approval had been provided. Secondary evidence uses the data derived from one or more primary studies to synthesise the current body of evidence for a research question. Secondary evidence is identified by a structured search strategy, methodological quality appraisal and specified data extraction approaches.

Studies were excluded if they were:

- systematic literature reviews published prior to 1997, or not available in full text, or not written in English and not relating to research on humans (i.e. bench science or animal studies)
- 'umbrella' reviews which synthesised the findings of one of more systematic reviews
    - In this instance, as noted in the earlier section, the component systematic reviews were 'unpicked' from the reference lists of the 'umbrella' reviews, and were added to the included systematic reviews for this project, if they met the inclusion criteria, and had not previously been identified from other sources
- studies that were not systematic literature reviews. This included:
    - all primary research
    - studies that purported to be systematic literature reviews, but did not provide a search strategy.

This last exclusion suggests that a search strategy is the only criterion for a systematic review. Other reviews, such as literature reviews also have search strategies. This exclusion should stipulate a search strategy or research protocol that has: a clearly defined PICO question, rigorous methodology including relevant inclusion/ exclusion criteria, data extraction methods and how the results will be reported.

Validation of initial inclusion/exclusion decisions: All articles considered appropriate for consideration for inclusion in the overview review were validated independently by at least one other member of the iCAHE team. Where there was dispute about application of the inclusion or exclusion criteria, a third iCAHE researcher was involved and asked to make an independent ruling.

Appraisal of methodological quality

All reviews that were potentially relevant to the study aim and objectives, were critically appraised using the CEBM critical appraisal tool[2] (See Appendix 1B for the details of the CEBM instrument, Table 5 in this report for summary critical appraisal scores for the included articles, and Appendix 6 for overview details on how the potentially-relevant studies addressed the critical appraisal elements). Two researchers undertook the critical appraisal. Validation checks of the critical appraisal decisions were taken by a third independent researcher, using 12 randomly-selected articles (representing approximately 25% included systematic reviews).

Phase 2: Categorisation

Reviews which were considered potentially relevant to this overview review were categorised as:

1. Reviews which reported on only one condition which was treated with homeopathy
2. Reviews which reported on one condition treated with Complementary and Alternative Medicine interventions (of which homeopathy was one)
3. Reviews which reported on multiple conditions treated with homeopathic interventions
4. Reviews which reported on studies which were not focused on one clinical condition, which presented technical and/ or methodological arguments for the effect of homeopathy compared with a placebo effect, or the effect from the control arms of conventional medicine studies[3]
5. Reviews which reported on the effect of any treatment (mainstream medical, complementary and alternative therapies etc.) on a condition or group of conditions (of which one treatment was homeopathy)

It was the view of the NHMRC Expert Committee and the secretariat that this overview review should exclude information available from reviews in Categories 4 and 5. The reviews in Category 1 were given highest priority as they focused on only one clinical condition, with homeopathy as the only intervention. These were called 'key reviews'. Reviews in Categories 2 and 3 were used to identify additional primary component studies that were not identified in existing Category 1 (key) reviews when one existed. Reviews in Categories 2 and 3 were used as the source of best-available information when there was no available Category 1 review.

Data extraction

Data was extracted from every included review on its category, the clinical condition(s), sample characteristics, homeopathic intervention, the number and design of primary component, the

[2] http://www.cebm.net/index.aspx?o=1157 accessed 7th May 2012

[3] How to deal with systematic literature reviews that did not relate specifically to homeopathic interventions for specific and definable clinical conditions was a source of debate between the contractors, the NHMRC Expert Committee and the secretariat. Discussions included:

- reviews of the methodological quality of homeopathic research
- reviews that surveyed the published literature to test the hypothesis that homeopathic interventions were at least as effective as placebo arms in controlled allopathic trials, when considering a range of clinical conditions (not linked to specific clinical conditions or findings not able to be extrapolated to clinical conditions)
- interventions that were not specifically labelled in the literature as 'homeopathic interventions'

Footnote 3 indicates early signs of disagreement between the authors of the report and the expert committee/ NHMRC staff

number and names of databases from which studies were identified, details of the component studies in the review, outcomes and the way data had been reported and synthesized. Key findings, authors' conclusions, caveats and concerns were recorded.

Two researchers undertook data extraction. Validation of the data extraction findings was also undertaken by a third independent iCAHE reviewer, using the same 12 randomly-selected articles as for the validation of critical appraisal.

Data analysis

A. The search process was described in a study flowchart (identified and included/ excluded articles). The potentially-relevant reviews were then divided into Categories 1-5. Reviews in Categories 4 and 5 were excluded from further consideration on NHMRC advice.
B. Per condition, summaries of the findings from the key included review(s) were developed, based on the CEBM instrument criteria. 'Other' reviews (Category 2 and 3 reviews when one or more Category 1 reviews was available) were qualitatively described
C. The primary component studies identified from the key, and 'other', reviews was summarised in terms of study design, methodological quality, number and type of subjects, homeopathic interventions, control arms (if available and/or relevant), outcome measures. The study outcomes were reported briefly for each study.
D. The first three elements of the NHMRC strength of the body of evidence matrix were used to summarise the strength of the body of evidence for the clinical condition.

Results

Overview of the potentially-relevant studies

Search results

The submissions to NHMRC from the public, the AMA and the AMHA provided references to 301 peer-reviewed articles and grey literature. This included 31 SRs and MAs relevant to this review.

The iCAHE independent search identified 849 papers which purported to be literature reviews, relevant to the aim and objectives of this overview review. This body of literature came from searches of library databases (849 potentially-relevant hits), clinical guidelines (0 potentially-relevant hits), and Government reports (5 hits, all of which were papers which had been identified in the iCAHE library database search, or from the NHMRC submissions).

Of these potentially-relevant hits, 189 were deemed relevant based on reading of title and abstract, and then 33 were removed as duplicates. Upon appraisal of the full text article, a further 108 articles were removed from consideration, as they did not fit the search criteria. Figure 1 outlines the review CONSORT diagram.

Background documentation

Separate documents were prepared as background documentation on

- The NHMRC FORM *see Appendix 1A.*
- The CEBM critical appraisal tool for systematic reviews *see Appendix 1B.*
- Included studies and their source (from submissions to NHMRC, from iCAHE searches, from umbrella reviews and hand-searching) *see Appendix 2.*
- Excluded studies and reasons for exclusion *see Appendix 3.*
- 'Umbrella' reviews (meta-views of SRs and MAs) from which component SRs and MAs were extracted for analysis (NB The 'umbrella' reviews themselves were not included in the body of literature which informed this review objectives) *see Appendix 4.*
- Author and date of component studies, number of times cited and in which systematic review, sample size and quality measures, *see Appendix 5.*
- Quality appraisal information, including explanation of CEBM questions in relation to the research question and accompanying tables *see Appendix 6.*
- Details of the component primary studies, including number of times cited, review cited in, number of subjects (where available), and methodological quality measure *see Appendix 7.*

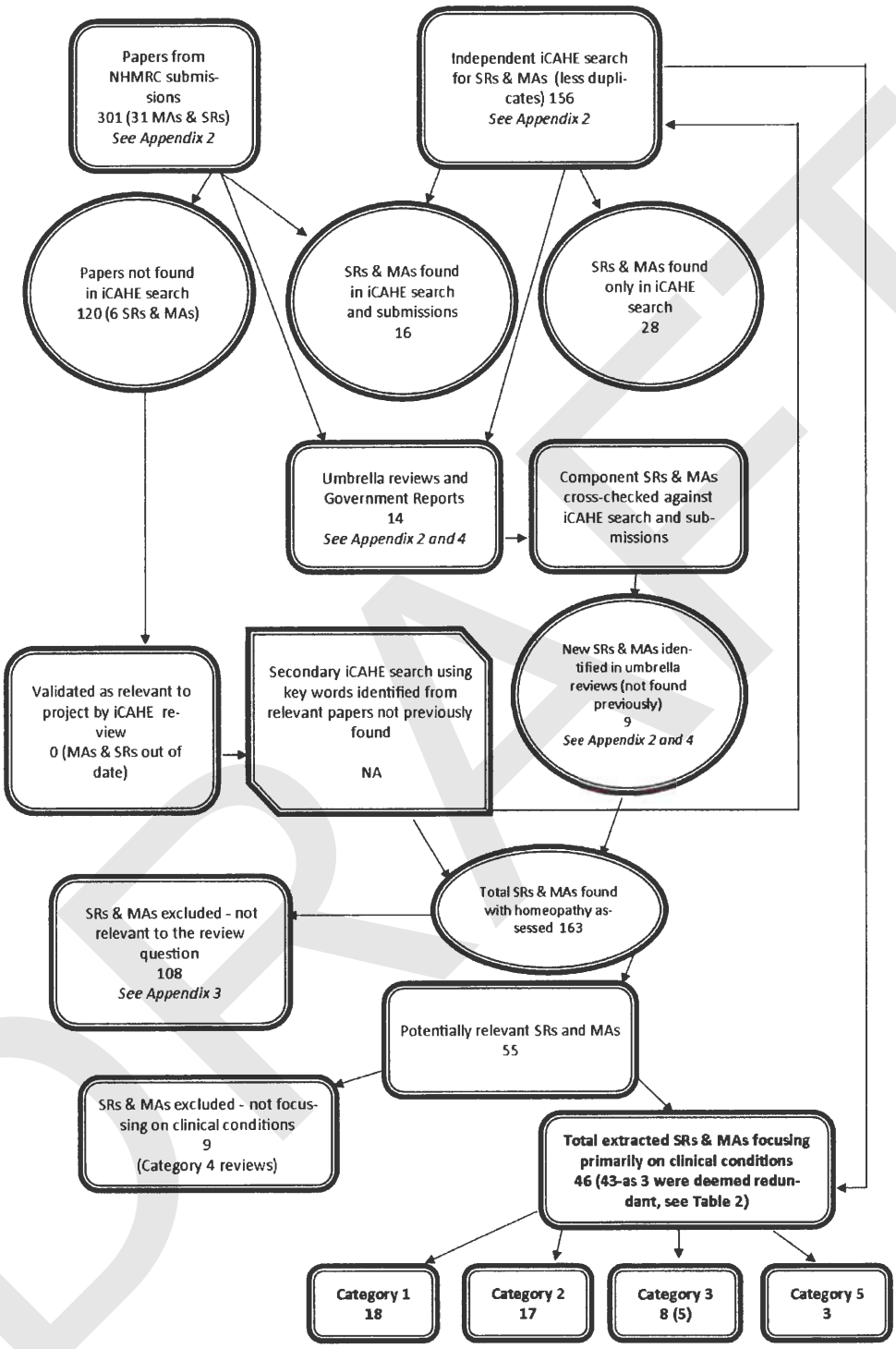

Figure 1. Review CONSORT diagram

Databases

Considering all the reviews identified as potentially-relevant to this review (N=55), the component studies (primary evidence) had been obtained from a range of library and Government databases. These included mainstream scientific, complementary medicine and homeopathic-specific databases. The databases reported in the reviews are listed in Table 2[4].

Table 2. List of databases from which the component studies in the included articles were sourced

Mainstream scientific		**Complementary Medicine (specifically searched for homeopathic publications)**
Biomed BIOSIS (BioSciences Information Service of Biological Abstracts) BNI (British Nursing Index) Br Lib Stock Alert Service CancerLit CINAHL (Cumulative Index to Nursing & Allied Health_ CIRARL ClinTrials.gov Cochrane Library of Systematic Reviews Cochrane Register of Controlled Trials Current Contents DARE/ TRIP Dissertations Abstracts EBM Reviews EBMR (Evidence-based Medicine Reviews) Econlit (American Economic Association Literature database) EMBASE ERIC (Education Resources Information Center)	GIRI (Genetic Information Research Institute) HEALTH (Health Planning and Administration) LILACS (Latin American and Caribbean Health Sciences Literature) Medline PsychINFO PSYNDEXplus PubMed SCI SIGLE (System for Information on Grey Literature in Europe) Soc Sc ToxLINE (National Library of Medicine database of toxicology (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE) UK National Research Register	AltHealthWatch AMED (Allied and Complementary Medicine Database) Asian databases (Wan Fang Database, Korean Studies Information, DBPIA, Korea Institute BHL (British Homeopathy Library) CAMbase CBM (Chinese Biomedicine) CCRH (Central Council for Research in Homeopathy) CISCOM (ceased in 1998) CNKI (Chinese Network Knowledge Infratructure) ECH (European Committee for Homeopathy) Electronic_ HomInform IDAG (Internet Database Availability Groups) LMHI (liga medicorum homeopathica internationalis) MANTIS (Manual, Alternative and Natural Therapy Index System) Non-indexed homeopathy Journals of Science and Technology Information, Research Information RefWorks Service System, KoreaMed, and National Assembly Library), Japan Science and TCMLARS (Traditional Chinese Medical Literature Analysis and Retrieval System) Technology Information Aggregator VIP (Chinese Scientific Journal Database) ZETOC http://zetoc.mimas.ac.uk/about.html#database

[4] These databases on this list, if not already searched during the initial iCAHE search, were searched (if available) as a validation step to identify a comprehensive list of relevant literature for this review

Categorised studies based on focus on homeopathy for a clinical condition

Of the 55 potentially-relevant reviews outlined in Figure 1:

Category 1: 18 reviews investigated the effectiveness of homeopathic interventions for a single clinical condition

Category 2: 17 reviews investigated the effectiveness of treating a single clinical condition with Complementary and Alternative Medicine (CAM) interventions (of which one was homeopathy)

Category 3: Eight reviews investigated the effectiveness of homeopathy for groups of conditions. Conditions were variably grouped by population (i.e. children and adolescents) or pathology (eg inflammatory conditions of the respiratory system, dermatitis). Four of these reviews were by the Bellavite group (2006a, b, 2008, 2011). The Bellavite et al. (2011) review was a comprehensive update of the literature reported in the earlier reviews, which reported on literature published in the past 30 years on the effectiveness of homeopathy for respiratory allergies, common upper respiratory infections, otorhinolaryngological complaints, and rheumatic diseases. This review was the most recent, and the most comprehensive of all the Bellavite reviews. It included literature that expanded on, and/ or superseded that reported in the previous reviews, thus it was considered to be the most comprehensive and recent evidence provided by this research group. The evidence in the earlier three reviews was therefore redundant. Thus there were 5 relevant reviews in this Category.

Category 4: Nine reviews investigated 'non-clinically-focused' questions, for instance the equivalence of a placebo effect of homeopathic interventions with allopathic medicines, clinical effects of homeopathy for any condition, homotoxicology, or adverse events from homeopathy. They did not provide evidence for a focused clinical question that could inform the clinical conditions considered in this overview review, and thus after considerable debate, these reviews were excluded

Category 5: Three reviews investigated the effectiveness of any intervention (mainstream (allopathic) medicine, CAM) for a particular clinical condition. These reviews were similar to those in Category 2, except they took an even broader approach and were not considered by the NHMRC committee to be sufficiently focused to inform the evidence base for homoeopathic management of the clinical conditions considered in this overview report.

Decision making regarding relevant homeopathic evidence

The included reviews are reported in their categories in Table 3. The key sources of information which informed the evidence reviews presented in this overview review report are those in Category 1, which investigated the effectiveness of homeopathic interventions for a single condition, and the reviews from Categories 2 and 3, from which comprehensive information could be extracted on homeopathic interventions for specific conditions.

Where evidence was *only* available for the homeopathic management of one condition from broad multi-condition reviews which did not ask a focused question, and/ or which did not report on the findings of comprehensive literature searches, it was the Committee's view that there was insufficient secondary evidence available to make a determination on the effectiveness of homeopathic interventions.

Table 3. Studies classified by purpose

Key source of evidence for this review	Validation or additional data		Excluded	
Category 1: One condition treated with homeopathy (N=18)	**Category 2: One condition treated with CAM interventions (of which homeopathy was one) (N=17)**	**Category 3: Multiple / groups of conditions treated with homeopathic interventions (N=8, N=5 used in this review)**	**Not focussing specifically on a clinical condition (N=9)**	**Any treatment of which homeopathy was one (N=3)**
Barnes (1997) Post-operative ileus ***Cooper (2009)*** Insomnia ***Ernst (1999a)*** Migraine ***Ernst & Barnes (1998b)*** Delayed Onset Muscle Soreness (DOMS) ***Ernst (2011)*** Insomnia ***Ernst (2011)*** Hay fever ***Heirs (2009)*** ADHD ***Kassab (2011)*** Adverse effects of cancer treatment ***Long & Ernst (2001)*** OA ***Milazzo (2006)*** Side effects of cancer treatment ***McCarnie (2008)*** Chronic asthma ***McCarnie (2009)*** Dementia ***Owen (2004)*** Headaches ***Perry (2010)*** Fibromyalgia ***Pilkington (2005)*** Depression & related disorders ***Pilkington (2006)*** Anxiety and anxiety disorders ***Schneider (2005)*** Vertigo ***Smith (2010)*** Induction of labour	***Alraek (2011)*** Chronic Fatigue Syndrome ***Baranowsky (2009)*** Fibromyalgia ***De Silva (2010)*** Fibromyalgia ***de Silva (2011)*** Osteoarthritis ***Holdcraft (2003)*** fibromyalgia ***Huang (2011)*** Nocturnal enuresis ***Jorm (2004)*** Anxiety ***Mills (2005)*** HIV ***Porter (2010)*** CFS & fibromyalgia ***Passalacqua (2006)*** Rhinitis and asthma ***Pittler (2005)*** Weight loss ***Quinn (2006)*** Low Back Pain ***Rada (2010)*** Menopausal symptoms ***Sarris (2011)*** Insomnia ***Seidl (1998)*** Menopausal symptoms ***Stevinson (2001)*** Pre-Menopausal Symptoms ***Vernon (1999)*** Headache	***Altunc (2007)*** Childhood ailments ***Bellavite (2006a)*** Immunology ***Bellavite (2006b)*** Immunology ***Bellavite (2008)*** Immunology and inflammatory disorders ***Bellavite (2011)*** Immunology and inflammatory disorders ***Davidson (2011)*** Psychiatric conditions ***Ernst & Pittler (1998a)*** Homeopathic Arnica ***Simonart (2011)*** Dermatology	***Cucherat (2000)*** clinical effectiveness of homeopathy for any condition ***Dantas (2000)*** Adverse events ***Ernst (1999b)*** Classical homoeopathy vs conventional treatments ***Ernst & Schmidt (2004)*** Homotoxicology ***Grabia (2003)*** Aggravations ***Linde (1997)*** Placebo effects ***Linde (1998)*** Individualised homeopathy ***Mathie (2003)*** Research base of homeopathy ***Shang (2005)*** Placebo effects	***Bagnell (2007)*** Chronic Fatigue Syndrome ***Roberts (2012)*** pain relief after orthopaedic surgery ***Van Der Wouden (2012)*** Cutaneous molluscum contagiosum

Table 4 clusters the Category 1-3 reviews by condition

- The conditions for which no relevant systematic review in Categories 1-3 was available are noted in italics. These conditions are addressed only in the systematic reviews classified as Category 4 for this overview review (see Table 3), which did not answer a focused clinical

This paragraph is poorly expressed. What it means is that these studies rated poorly on the CEBM appraisal tool, and the NHMRC committee did not make a decision about whether there was sufficient evidence on these topics

condition, or which compared homeopathy with any other type of treatment (Category 5)). The reviews in Categories 4 and 5 were therefore not considered to provide relevant evidence for this NHMRC overview review.

- The conditions are highlighted in grey in Table 4, for which the only source of evidence was a systematic review in Categories 2 or 3 which did not have a focused clinical question. The NHMRC Committee deemed that in these instances, there was insufficient review evidence to provide an evidence summary for the purpose of this project. Conditions for which an evidence summary could not be produced because of the lack of a focused evidence-review source comprised:
  - adenoid vegetation, conjunctivitis, diarrhoea (conditions for which only one unfocused Category 3 review was available)
  - influenza, tinnitus/vertigo, proctocolitis/irritable bowel syndrome/gastritis/ irritable colon, dental neuralgia, unspecified origin pain, boils and pyodema, anal fissure, cutaneous molluscum contagiosum, dystocia, mastodynia, tissue recovery following childbirth, joint sprains and contusions (specifically ankle and other joint sprains, knee joint haematoma), muscle cramps, burns, Broca's aphasia after stroke, mild acquired brain injury, seasickness, tropical diseases (cholera/ malaria), post viral fatigue, infertility, vaginal discharge, cystitis, hypertension (conditions which were only addressed by Category 4 or 5 evidence).

Poorly expressed. 'Lack of a focused evidence review source' means 'there were no quality studies'.

Poorly expressed. 'unfocused' means 'poor quality'

Table 4. Studies clustered by condition, population and sample size

Condition	Cat 1 (Key reviews)	Cat 2	Cat 3
Mental health conditions			
Anxiety and anxiety related disorders incl Benzodiazapam substitution	Pilkington 2006	Jorm 2004	Davidson 2011
Dementia	McCarney 2009		
Depression	Pilkington 2005		
Sleep disorders	Cooper 2010 Ernst 2011	Sarris 2011	Davidson 2011
ADHD	Hiers 2009		Altunc 2007, Davidson 2011
Obesity management		Pittler 2005	
Upper Respiratory Tract conditions			
Adenoid vegetation			Altunc 2007
Asthma	McCarney 2008	Passalacqua 2006	Altunc 2007 Bellavite 2011
Hay fever / pollinitis	Ernst 2011	Passalacqua 2006	Bellavite 2011
URTI and misc. otorhinolaryngologic complaints (Bronchitis, Sinusitis, tonsillitis, pharangitis, common cold)			Altunc 2007 Bellavite 2011
Influenza			

Condition	Cat 1 (Key reviews)	Cat 2	Cat 3
Ears			
Otitis media			Altunc 2007 Bellavite 2011
Tinitus, vertigo	Schneider 2005		
Eyes			
Conjunctivitis			Altunc 2007
Intestinal ailments			
Diarrhoea			Altunc 2007
Proctocolitis, Irritable bowel disease, gastritis, Irritable colon, cholecystopathia			
Postoperative Ileus	Barnes 1997		
Pain/ symptoms related to medical procedures			
Postoperative pain			Altunc 2007 Ernst & Pittler 1998
Dental neuralgia			
Pain of unspecified origins			
Dermatology			
Warts			Altunc 2007 Simonart 2011
Boils & pyoderma			
Dermatoses, seborrhoeic dermatitis, atopic eczema, minor recurrent aphthous ulceration, agne vulgaris, leg ulcers / varicous veins, uraemic pruritus, candidiasis			Simonart 2011
Anal fissure			
Cutaneous molluscum contagiosum			
Cancer treatment			
Cancer treatment and hemo-induced symptoms, radiodermatitis, stomatitis	Kassab 2011 Milazzo 2007		Bellavite 2011 Simonart 2011
Nocturnal Enuresis		Huang 2009	
Arthro-rheumatic diseases			
Rheumatic diseases			Bellavite 2011
Osteoarthritis	Long 2001	de Silva 2011	Bellavite 2011
Childbirth and associated conditions			
Dystocia			
Inducing labour	Smith 2010		
Mastodynia			

Condition	Cat 1 (Key reviews)	Cat 2	Cat 3
Tissue recovery following childbirth			
Musculoskeletal			
Ankle sprain			
Knee joint haematoma			
Delayed onset muscle soreness	Ernst & Barnes 1998		Ernst & Pittler 1998
Low Back Pain		Quinn 2005	
Cramps			
Other joint sprains and contusions			
Tissue trauma			
Burns			
Acute tissue trauma			Ernst & Pittler 1998
Headache			
Headache	Ernst 1999a Owen 2004	Vernon 1999	
Neurological			
Stroke Unnamed symptoms			Ernst & Pittler 1998
Broca's Aphasia after stroke			
Mild Acquired Brain Injury			
Seasickness			
Tropical diseases			
Cholera			
Malaria			
Viral issues			
HIV/AIDS		Mills 2005	
Post viral fatigue			
Female uro-gynaecological			
Menopausal symptoms		Rada 2010 Seidl 1998	
Pre-menstrual syndrome		Stevinson 2001	
Infertility			
Vaginal discharge			
Cystitis			
Systematic conditions			
Chronic Fatigue Syndrome		Alraek 2011 Porter 2010	
Fibromyalgia	Perry 2010	Baranowsky 2009 De Silva 2010 Holdcraft 2003 Porter 2010	Davidson 2011 Bellavite 2011
Hypertension			

Critical appraisal

No critical appraisal, other than to determine whether a clear search question was asked, was undertaken on the Category 4 or 5 reviews. Summary CEBM critical appraisal scores of Category 1-3 reviews are provided in Table 5. Considering the 40 reviews which focused on a clinical question (18 Category 1 reviews, 17 Category 2 reviews, 5 Category 3 reviews):

- Seven reviews scored not Applicable to CEBM Criterion 4 and/or 5)
    - Scoring NA to both criteria occurred when the review found no relevant studies for the review question (Huang 2011, McCarnie 2009, Seidl 1998)
    - Scoring NA to Criterion 5 occurred when there was only one relevant study identified and therefore Criterion 5 could not be addressed (Baranowski 2009, Holdcraft 2004, Quinn 2005, Stevinson 2001).

  On this basis, these studies are not included in the summary criteria below, as they could not provide scores for all five CEBM criteria. However, to put the quality of these studies in perspective:
    - Baranowski (2009) and Seidl (1998) scored positively for only one criterion (CEBM Criterion 3 and Criterion 1 respectively)
    - Holdcraft (2004), McCarnie (2009), Huang (2011), Quinn (2005) and Stevinson (2001) all scored three possible positive responses (CEBM Criteria 1-3).

Considering the 33 reviews which could provide scores for the CEBM Criteria 1-5:

- One review positively addressed all five criteria (Rada 2010)
- 11 reviews positively addressed four criteria (Alraek 2011, Barnes 1997, Bellavite 2011, Cooper 2009, De Silva 2011, Ernst 2011b, Heirs 2009, Kassab 2011, Milazzo 2006, Mills 2005, Simonart 2011)
- 12 reviews positively addressed only three criteria (Altunc 2007, de Silva 2010, Ernst 2011a, Jorm 2004, Long & Ernst 2001, Passalacqua 2006, Pilkington 2005, Pittler 2005, Perry 2010, Sarris 2011, Smith 2010, Vernon 1999)
- Seven reviews positively addressed only two criteria (Davidson 2011, Ernst & Barnes 1998, Ernst 1999a, McCarnie 2008, Owen 2004, Pilkington 2006, Porter 2010)
- One review addressed only one criteria (Ernst & Pittler 1998)
- One review addressed none of the criteria (Schneider 2005).

The frequency of non-compliance with the CEBM criteria was:

1. The review question was poorly defined in four reviews
2. Important, relevant studies were potentially missed in 11 reviews (10 Unclear, 1 Missed (N = non-compliance with criterion))
3. The criteria used to select articles for inclusion was not considered appropriate in three reviews (2 Unclear, 1 Not appropriate (N))
4. The included studies were potentially not sufficiently valid for the type of question asked, in 23 reviews (22 Unclear, 1 Not valid (N))
5. The results were not similar from study to study in 23 reviews (indicating heterogeneity of important information in the included primary studies)

The CEBM Question 6 reports on the way the study findings are reported (qual = descriptively only, pooled = attempts at a meta-analysis of data). Six reviews of clinical conditions attempted pooling and/ or meta-analysis (Barnes 1997, Heirs 2009, Kassab 2011, McCarnie 2008, Schneider 2005, Smith 2010).

Table 5. CEBM critical appraisal criteria

Key: For Question 1, Y indicates that it is unlikely that important relevant studies were missed

author	date	Category	Q1	Q2	Q3	Q4	Q5	Q6
Alraek	2011	2	Y	Y	Y	Y	N	qual
Altunc	2007	3	N	Y	Y	U	Y	qual
Bagnell	2007	5	Y	No further analysis				
Barnes	1997	1	Y	Y	Y	U	Y	qual & pooled
Baranowski	2009	2	N	U	Y	U	NA (only one study identified)	
Bellavite	2006a	redundant						
Bellavite	2006b	redundant						
Bellavite	2008	redundant						
Bellavite	2011	3	Y	Y	Y	U	Y	qual
Cooper	2009	1	Y	Y	Y	U	Y	qual
Cucherat	1999	4	N	No further analysis				
Dantas	2000	4	N	No further analysis				
Davidson	2011	3	N	Y	Y	U	N	qual
De Silva	2010	2	Y	Y	Y	U	N	qual
de Silva	2011	2	Y	Y	Y	Y	N	qual
Ernst & Pittler	1998	3	Y	U	U	U	N	qual
Ernst & Barnes	1998	1	Y	U	Y	U	N	qual
Ernst	1999a	1	Y	U	Y	U	N	qual
Ernst	1999b	4	N	No further analysis				
Ernst & Schmidt	2004	4	Y	No further analysis				
Ernst	2011a	1	Y	U	Y	Y	N	qual
Ernst	2011b	1	Y	Y	Y	U	Y	qual
Grabia	2003	4	N	No further analysis				
Heirs	2009	1	Y	Y	Y	U	Y	qual & pooled
Holdcraft	2004	2	Y	Y	Y	U	NA (only one study identified)	

Huang	2011	2	Y	Y	Y	NA	NA	
Jorm	2004	2	N	Y	Y	Y	N	qual
Kassab	2011	1	Y	Y	Y	Y	N	qual & pooled
Linde	1997	4	N	No further analysis				
Linde	1998	4	N	No further analysis				
Long&Ernst	2001	1	Y	Y	Y	U	N	qual
Mathie	2003	4	N	No further analysis				
McCarnie	2008	1	Y	U	Y	N	N	qual & pooled
McCarnie	2009	1	Y	Y	Y	NA	NA	
Milazzo	2006	1	Y	Y	Y	Y	N	qual
Mills	2005	2	Y	Y	Y	Y	U	qual
Owen	2004	1	Y	U	Y	U	N	qual
Passalacqua	2006	2	Y	Y	Y	U	N	qual
Pilkington	2005	1	Y	Y	Y	U	N	qual
Pilkington	2006	1	Y	Y	U	U	N	qual
Pittler	2005	2	Y	U	Y	Y	N	qual
Perry	2010	1	Y	Y	Y	U	N	qual
Porter	2010	2	Y	U	Y	U	N	qual
Quinn	2006	2	Y	Y	Y	Y	NA (only one study identified)	qual
Rada	2010	2	Y	Y	Y	Y	Y	qual
Roberts	2012	5	Y	No further analysis				
Sarris	2011	2	Y	Y	Y	U	N	qual
Schneider	2005	1	N	N	N	U	N	qual & pooled
Seidl	1998	2	Y	U	U	NA	NA	
Shang	2005	4	N	No further analysis				
Simonart	2011	3	Y	Y	Y	Y	N	qual
Smith	2010	1	Y	U	Y	U	Y	qual & pooled
Stevinson	2001	2	Y	Y	Y	U	NA (only one study identified)	qual
Van Der Wouden	2012	5	Y	No further analysis				
Vernon	1999	2	Y	U	Y	U	Y	qual

Part 2: Evidence Summaries.

Acute pain: Postoperative pain, pain associated with acute stroke and acute tissue trauma

Executive summary

Only one systematic review was identified in Category 3, which investigated the effectiveness of homeopathic treatments for the management of acute pain.

- This review considered the efficacy of homeopathic Arnica for a range of conditions which can produce acute pain (Ernst & Pittler 1998). The review was not classified as a key review because its focus was on the homeopathic intervention, rather than on one clinical condition, or group of related clinical conditions. Consequently the review and its findings are summarised below.

Evidence source: Ernst and Pittler (1998) conducted computerized literature searches to retrieve placebo-controlled studies on the effectiveness of homeopathic arnica for a range of conditions. The authors searched MEDLINE, EMBASE, CISCOM, and the Cochrane Library. Four relevant trials were identified (Kasiro 1984, Pinsent et al. 1984, Gibson et al. 1991, Savage et al. 1978) that addressed delayed onset muscle soreness, prevention of postsurgical complications (both from dental surgery), pain associated with acute trauma and stroke, and experimentally-induced pain. Study quality was assessed using the 5 point Jadad score. The authors considered that "Most of these studies were burdened with severe methodological flaws. On balance, they do not suggest that homeopathic arnica is more efficacious than placebo. The claim that homeopathic arnica is efficacious beyond a placebo effect is not supported by rigorous clinical trials" (p. 1187).

This evidence summary reports on postoperative pain, and pain associated with stroke and tissue trauma. This evidence summary does not report on delayed onset muscle soreness, which is addressed in a separate evidence summary.

Conclusion: There is no convincing evidence from one moderate quality systematic review, citing four component poor-moderate quality RCTs, to support the effectiveness of homeopathy for the treatment of pain from dental surgery (two studies, N=177), orthopaedic trauma (one study, N=20) or acute stroke (one study, N=40) (Grade D).

CEBM appraisal tool not reported as being used. Authors appear to have used their own judgment to reach conclusions on the quality of the studies, and consistency and clinical impact.

Evidence statement

Key question	Rating	Justification
Evidence Base	C	The review methods are sound, although the four included studies report on different conditions, and are of poor-moderate study quality.
Consistency	D	See above comment on heterogeneity
Clinical impact	D	Limited treatment effects

There is no mention of risk of bias here, which would allow the authors to reach a conclusion of study quality (yet they have still rated the evidence base as 'C')

There is no comment on heterogeneity 'above'

'Limited treatment effects' is non-standard terminology and not justified with any estimates of treatment effects being provided

Included primary literature

Dental pain

- Kaziro (1984) applied a low quality double-blinded RCT (Jadad score 2/5) for 118 patients after extraction of wisdom teeth. Arnica 200C was applied twice daily for 3 days postoperatively compared with Metronidazole 400 mg twice daily, and placebo.
    - *Outcome:* No difference between arnica and placebo in any outcome measure (Pain, trismus, edema, wound healing), Metronidazole was found to be superior to both homeopathy and placebo.
- Pinsent et al. (1984) applied a moderate quality RCT (Jadad score 4/5) to test homeopathic arnica with 59 Patients after tooth extraction (Arnica 30C 1 dose 30 min preoperatively; 3 doses each 15 min postoperatively; 1 dose every 2 h for 6 doses) compared with Placebo as per verum schedule.
    - *Outcome*: Less pain with arnica, no significant difference for bleeding.

Acute orthopaedic pain

- Gibson et al. (1991) applied a low quality RCT (Jadad score 2/5) to 20 orthopaedic patients with acute tissue trauma, to test the effectiveness of Arnica 30, compared with placebo.
    - *Outcome:* There were no intergroup differences.

Stroke

- Savage et al. (1978) applied Arnica in M potency to 40 Patients admitted to hospital up to 7 days after acute event of stroke compared the placebo, in a moderate quality RCT (Jadad score 3/5).
    - *Outcome*: At 3 months follow-up there were no differences between groups.

References

Included systematic review

Ernst E, Pittler MH. 1998. Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials. *Archives of surgery (Chicago, Ill. : 1960),* 133, 1187-1190.

Included primary studies

Kaziro GSN. 1984. Metronidazole (Flagyl) and Arnica montana in the prevention of postsurgical complications: a comparative placebo controlled clinical trial. *Br J Oral Maxillofac Surg* 22, 42-49.

Pinsent RJFM, Baker GPI, Ives G, Davey RW, Jonas S. 1984. Does arnica reduce pain and bleeding after dental extraction? *Midland Homeopathy Res Group Newslett* 11, 71-72.

Gibson J, Haslam Y, Laurneson L, Newman P, Pitt R, Robins M. 1991. Double-blind trial of arnica in acute trauma patients. *Homeopathy* 41, 54-55.

Savage RH, Roe PF. 1978. A further double blind trial to assess the benefit of Arnica montana in acute stroke illness. *Br Homoeopathic J* 67, 211-222.

Anxiety and anxiety-related disorders

Executive summary

Three relatively-recent systematic reviews were identified, that addressed the effectiveness of homeopathy for anxiety and anxiety-related disorders.

- One Category 1 review (Pilkington et al. 2006) focused only on anxiety and homeopathy and included eight randomised controlled trials. Mixed anxiety disorders were considered in this review, comprising test anxiety, moderate anxiety and anxiety-disorder, mixed anxiety and depressive disorder, and anxiety associated with medical and physical conditions. This review included eight randomised controlled trials.
- One Category 2 review (Jorm 2004), investigating CAM for anxiety, and reporting on one RCT (also reported by Pilkington et al. 2006) and one additional case series study.
- One Category 3 review (Davidson 2011) which investigated homeopathy for a range of psychiatric conditions (including anxiety expressed as Global Anxiety Disorder and test anxiety). Anxiety was one of a number of conditions for which the effectiveness of homeopathy was tested, the others being sleep problems, stress management, PMS, mild TBI, functional somatic symptoms (chronic fatigue, fibromyalgia). Davidson (2011) searched from database inception to 2010 in the follow databases: PubMed, CINAHL, PsycInfo, HomInform, Cochrane CENTRAL, Clinical Trials.gov and the Nation Centre for Complementary and Alternative Medicine Grantee Publications Database. Davidson (2011) identified three studies relevant to the review question which were included in the key evidence sources. The Committee considered that the Davidson review was too broad in focus to assist in providing evidence for this clinical question.

Key systematic reviews: Pilkington et al (2006) focused only on anxiety and homeopathy and included eight randomised controlled trials. This review was of poor-moderated ~~quality~~ and included eight randomised control trials. Jorm (2004) assessed the effectiveness of homeopathic interventions (unstated) on reducing anxiety and phobias, as part of a larger review of the effectiveness of complementary and alternative medicines. This review was of poor-moderate methodological quality and included one relevant RCT and one case series study. Thus the key evidence sources for anxiety and anxiety-related disorders were both Pilkington et al (2006) and Jorm (2004).

typographical error

There is no explanation as to how and why the authors reached a conclusion of poor-moderate quality.

Conclusion: From two reviews of poor-moderate quality, which considered nine primary studies of variable quality, reporting on samples of 50 children, 147 students, 53 women, 384 mixed gender adults, there is no convincing evidence that homeopathy is effective for the treatment of anxiety, or anxiety-related disorders (Grade D).

No mention of risk of bias (a core consideration)

Methodological assessment of the key evidence sources

Validity issue	Comment: Pilkington (2006)	Comment: Jorm (2004)
The review question (PICO)	P: anxiety (not defined) I: homeopathy (not defined other than as individualised or complex) C: any (not defined) O: rating scales and performance measures	P: anxiety and phobias I: CAM (incl homeopathy not defined) C: any O: any
Is it unlikely that that important, relevant studies were missed?	Yes. The following databases were searched up to August 2005: MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Central, Cochrane Library, MEDLINE, PubMed, TRIP, DARE; and of specialist complementary and alternative medicine (CAM) databases: AMED, CISCOM, Cochrane complementary medicine field registry, and Hom-Inform, Cochrane CCDAN review group trial register was conducted. Efforts were made to identify unpublished and ongoing research using relevant sources and experts in the field. Clinical commentaries were obtained for studies reporting clinical outcomes. Search terms were text based	Unclear but likely A small number of databases were searched: PubMed, PsycLit and the Cochrane library.
Were the criteria used to select articles for inclusion appropriate?	Unclear. The selection criteria are basic but clearly stated. However a number of studies were excluded but exclusion criteria are not reported. Types of study: "initially all clinical studies", with a main focus on controlled studies.	Unclear but unlikely A broad source of evidence informed this review, including published literature, and purposively-sampled self-help information, clinical practice guidelines
Were the included studies sufficiently valid for the type of question asked?	Unclear. RCTs evaluated using CRD tool (Jadad score reported for the included studies listed above 2, 4, 3, 1, 1, 4, ?, 5). Non-RCTs were not evaluated for quality. Studies were not excluded based on quality.	No The included literature was heterogeneous in design and source. Methodological quality was not assessed. The included literature was considered only using the NHMRC hierarchy of design evidence.
Were the results similar from study to	No. Anxiety diagnoses and included	No. By the very nature of the review,

study?	studies were heterogeneous. As reported by the review authors: "the variation in condition, methodology and intervention prevent formal statistical synthesis of the research findings and a meta-analysis would not be appropriate" (p. 159).	the diagnoses and interventions were heterogeneous, and study findings showed no significant differences within or between intervention and control groups.
How are the results presented?	A summary for each included study was provided in Table 1 "Summary of studies" (p. 156). This included study design, sample, inclusion criteria, homeopathy intervention, control intervention, outcome measures, results, methodology comments, Jaded score and clinical comments. Meta-analysis was not conducted due to heterogeneity of study samples, interventions and outcome measures.	Studies were summarised descriptively (P. S32) and no corroborating statistical information was provided to support conclusions
Main conclusion of review authors	Pilkington et al. (2006) concluded "On the basis of this review it is not possible to draw firm conclusions on the efficacy or effectiveness of homeopathy for anxiety" (p. 151).	'No convincing evidence' Table 3, p. S40.
Other issues	A number of anxiety manifestations were tested in non-homogeneous samples. There was variable evidence of significant within group change, but consistent evidence of no between group difference when comparing homeopathic intervention with control. On this basis, the clinical impact would appear to be moderate at best, but more likely slight.	This review considered a range of CAM methods of treating anxiety, of which homeopathy was one. The intention of the review was to provide an overview of CAM effectiveness rather than consider one treatment approach in detail.

Evidence statement EVIDENCE STATEMENTS AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review methods were variable (one moderate quality, one poor quality review) and the included studies were relatively small, and of variable (or unstated) quality.
Consistency	D	See above comment on heterogeneity
Clinical impact	C-D	see 'Other issues' above

no comment as to why the authors reached a conclusion of poor or moderate quality. No mention of risk of bias

Whilst the CEBM appraisal refers to heterogeneity, the authors do not address it or comment on it in their synthesis of the quality of the evidence

Included primary studies: There were nine studies in total which are summarised in the two reviews.

The Pilkington et al. (2006) review included eight randomised control trials.

- Alibeu and Jobert (1992) assessed 50 hospitalised children, aged six months – 14 years with post-operative anxiety, using *Aconite*. Quality assessed on Jadad score 2/5
    - *Outcomes:* Effective with 95% good results (Table 1, p155)
- Baker et al. (2003) included 70 university students with test anxiety, treated with traditionally prepared *Argentum nitricum 12C compared with* radionically prepared *Argentum nitricum 12x*. Jadad score = 4/5
    - *Outcomes:* No significant differences were found between treatments
- Bonne et al. (2003) treated 44 adults with generalised anxiety disorder (DSM-IV diagnosis) using Individualised homeopathy (single remedy, all dilutions $>10^{-30}$) for 10 weeks, compared with placebo non-medicated impregnated globules. Jadad score =3/5.
    - *Outcomes:* Significant improvement in most measures in both groups. No significant difference between groups
- Hariveau et al. (1991) tested 84 subjects (age not stated) with reactive anxiety and depression using *Lithium Microsol compared with* Lorazepem 2–4 mg per day twice daily. Jadad score =1
    - Outcomes: not reported clearly
- Heulluy (1985) tested 60 subjects under consultation for depression, postmenopausal involution or thymo-effective dystonia using non-individualised L72 compared with diazepam (dose and frequency not known). Jadad score = 1/5
    - *Outcomes:* 'L72 as effective as diazepam on all measures'
- McCutcheon (1996) recruited 77 student with above average anxiety scores (non-individualsed '*Anti-Anxiety'* for 15 days compared with placebo. Jadad score = 4/5
    - *Outcomes*: No significant differences in stress measures or pulse rate between groups Significantly less sleep loss in homeopathy group
- Stanton (1981) tested 40 individuals with test anxiety using *Argentum nitricum 12x* vs placebo. Jadad score not reported.
    - *Outcomes*: Homeopathic preparation significantly improved test anxiety compared with placebo
- Thompson et al. (2005) assessed 53 women with symptoms of oestrogen withdrawal (including anxiety), using individualised prescribing (details not available) with placebo (matched tablet, granules or liquid). Jadad score =5/5.
    - *Outcomes:* No significant differences between groups

The review by Jorm (2004) also reported on the McCutcheon (1996) study, and included one additional low hierarchy study

- Cialdella P et al (2001) which considered the substitution of homeopathic remedies for benzodiazapines for 96 adults (case series).
    - Outcomes: Intervention and outcome measures, and study outcomes not clearly reported.

References

Included systematic reviews

Jorm, A. F., Christensen, H., Griffiths, K. M., Parslow, R. A., Rodgers, B. & Blewitt, K. A. 2004. Effectiveness of complementary and self-help treatments for anxiety disorders. *Medical Journal of Australia,* 181**,** S29-46.

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**,** 151-162.

Primary included studies

Alibeu JP, Jobert J. [Aconite in homeopathic relief of postoperative pain and agitation in children.] Aconit en dilution homeopathique et agitation post-operatoire de l'enfant. Pediatrie 1990; 45: 465–466 (Also reported as Alibeu J, Jobert J. Etude sur Aconit en dilution homeopathique sur l'agitation post-operatoire de l'enfant. Homeopathie Francaise 1992; 80:10–12.).

Baker DG, Myers SP, Howden I, Brooks L. The effects of homeopathic Argentum nitricum on test anxiety. *Complement Ther Med* 2003; 11: 65–71.

Bonne O, Shemer Y, Gorali Y, Katz M, Shalev A. A randomized, double-blind, placebo-controlled study of classical homeopathy in generalized anxiety disorder. *J Clin Psychiatry* 2003; 64: 282–287.

Cialdella P, Boissel JP, Belon P (2001): Homeopathic specialities as substitutes for benzodiazapenes: double blind vs placebo study. Therapie 56: 397-402

Hariveau E, Albertini C, Rufo M. Comparaison de Lithium Microsol a lorazepam dans les manifestations anxiodepressives reactionnelles de l'adulte [Comparison of Lithium Microsol with lorazepam in reactive anxiodepressive manifestation in adults.]. *Homeopathie Francaise* 1991; 79: 59–62.

Heulluy B. Essai randomise´ ouvert de L 72 (spe´ cialite´ home´opathique) contre diaze´pam 2 dans les e´ tats anxiode´ - pressifs [Randomised trial of L.72 (homeopathic speciality) with Diazepam 2 in cases of nervous depression.] Laboratoires Lehning, Metz; Unpublished study, 1985.

McCutcheon, LE. Treatment of anxiety with a homeopathic remedy. J APP NUTR 1996; 48:2-6.
Stanton HE. Test anxiety—a five drop solution. *Educ News* 1981; 17: 12–15.

Thompson EA, Montgomery A, Douglas D, Reilly D. A pilot, randomized, double-blinded, placebo-controlled trial of individualized homeopathy for symptoms of estrogen withdrawal in breast-cancer survivors. *J Altern Complement Med* 2005; 11: 13–20.

Asthma

Executive summary

Four systematic reviews were identified in Categories 1-3, which investigated the effectiveness of homeopathic treatments for asthma.

- One Category 1 review (McCarney et al. 2008, an updated Cochrane review) focused specifically on the effectiveness of homeopathic treatment on chronic stable asthma.
- One Category 2 review (Passalacqua 2006) considered the effectiveness of CAM for allergic rhinitis and asthma.
- Two Category 3 reviews (Altunc 2007 and Bellavite et al. 2011) both considered the effectiveness of homeopathic treatment for groups of conditions which included asthma.

Key systematic reviews

a) McCarney et al. (2008) focused specifically on the effectiveness of homeopathic treatment on chronic stable asthma (Category 1). This review was of high methodological quality, and included six primary studies (Reilly 1994, Freitas 1999, Lewith 2002, Matusiewicz 1995, Matusiewicz and Wasniewski 1999, White 2003).

typographical error - date Freitas 1995

b) Bellavite et al. (2011) considered the effectiveness of homeopathic treatment for groups of conditions which included asthma (reviewing the past 30 years of research in respiratory allergies, common Upper Respiratory Tract Infections, otorhinolaryngologic complains and rheumatic diseases) and reported on the effectiveness of individualised homeopathy, and homeopathic immunology for allergic asthma. This review was of high methodological quality, had conducted a comprehensive search and included 16 relevant primary studies (Reilly 1994, Castellsagu 1992, Colin 2006, Eizayaga and Eizayaga 1996, Frenkel and Hermoni 2002, Lara-Marquez et al. 1997, Lewith 2002, Li et al. 2003, Matusiewicz 1995, 1996 & 1997, Matusiewicz and Wasniewski 1999, Mosquera 1990, Riveron-Garrote et al. 1998, White 2003, Witt et al. 2005).

Bellavite et al (2011) and McCarney et al (2008) were thus considered as the key evidence sources. This evidence base reflects information on 924 adults (age stated or presumed) and 320 children and adolescents (age stated).

Other systematic reviews

a) Passalacqua et al (2006) was a Category 2 review and considered the effectiveness of CAM for allergic rhinitis and asthma. This review included three relevant primary studies (Lewith et al. 2002, Reilly 1994, White 2002) which were also included in the McCarney et al. (2009) review.

b) Altunc et al (2007) considered the effectiveness of homeopathic treatment for groups of conditions which included asthma (childhood ailments including adenoid vegetation, ADHD, asthma, otitis media, conjunctivitis, diarrhea, post-operative pain, URTI and warts). Altunc (2007) included two relevant primary studies, which were also included in the review by Bellavite et al. (2011) (Freitas 1999, White 2003).

Summary of reviews in which primary study has been reported

	McCarney et al (2008)	*Bellavite et al (2011)*	*Passalcqua et al (2006)*	*Altuncet al (2007)*
Reilly (1994)	√	√	√	
Castellsagu (1992)		√		
Colin (2006)		√		
Eizayaga and Eizayaga (1996)		√		
Freitas (1999)	√			√
Frenkel and Hermoni (2002)		√		
Lara-Marquez et al. (1997)		√		
Lewith (2002)	√	√	√	
Li et al. (2003)		√		
Matusiewicz (1995)	√	√		
Matusiewicz (1996)		√		
Matusiewicz (1997)		√		
Matusiewicz and Wasniewski (1999)	√	√		
Mosquera (1990)		√		
Riveron-Garrote et al. (1998)		√		
White (2003)	√	√	√	√
Witt et al. (2005)		√		

Conclusion: There is inconclusive evidence from two good quality, recent, comprehensive key systematic reviews reporting on 16 primary studies of variable study design and quality (924 adults, 320 children and adolescents), regarding the effectiveness of homeopathy for the treatment of chronic stable asthma, and allergic asthma (Grade D).

Methodological assessment of the key evidence sources

Validity issue	Comment: McCarney et al (2008)	Comment: Bellavite et al (2011)
The review question (PICO)	P: patients with stable chronic asthma or asthma-like symptoms I: homeopathically prepared remedies C: any (not defined) O: symptoms (primary outcomes), secondary outcomes, lung function, change in medication use, quality of life, wellbeing and global assessment.	P: adults and children with allergic asthma I: homeopathically prepared remedies C: any (not defined) O: symptoms (primary outcomes), secondary outcomes, lung function, change in medication use, quality of life, wellbeing and global assessment.
Is it unlikely that that important, relevant studies were missed?	Unclear. The following database was searched up to August 2007: Cochrane Airways Group Specialised Register of trials. Search terms were text or MeSH based	No. it is not unlikely The review sought experimental research on humans, published between 1978 and 2010. Data came from "current reading of major complementary and alternative medicine journals, screening of the Hominform Information Service databases (British Homeopathic Library, http://hominform.soutron.com/), literature searches using Medline, the Cochrane Database of Systematic Reviews, and cross-referencing between published papers' (p. 1364). The authors also 'consulted previously published systematic reviews and meta-analyses that have covered trials of immunoallergology" (p. 1364). "All forms of homeopathic therapy were included in the review, namely: a) classical individualised homeopathy, b) ailment-specific remedies and complexes, c) isotherapy where indicated" (p. 1364).
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. Randomised control trials were sought.	Yes. The selection criteria are clearly stated. "Analysis included controlled clinical trials (with and without randomisation), observational studies and case series, but excluded single case reports" (p. 1364).
Were the included studies sufficiently valid for the type of question asked?	No. The included studies were of variable quality, as assessed by the three item Jaded score (random allocation, blinding, description of dropouts and withdrawals (5 points	Unclear. The included studies were not assessed for methodological quality, only described by experimental design, evidence source and study population. All studies assessed classical

	total). Blinding and description of dropouts and withdrawals were common problems. Studies not excluded based on quality.	individualised homeopathy using experimental designs which variably including randomisation and controlling.
Were the results similar from study to study?	No. Studies are heterogeneous in terms of population and interventions. The authors attempted meta-analysis (p. 16-22) where data could be combined.	No. Studies are heterogeneous in terms of populations and interventions.
How are the results presented?	Different homeopathic treatments precluded pooling of results for the primary outcome. Meta-analysis presents findings of secondary outcomes where available (p. 16-22). Characteristics of included studies are included in tables (p. 10-13), reporting methods, participants, interventions, outcomes and risk of bias.	Characteristics of included studies are included in Table 1 (p. 1366), reporting authors, study design, participant type and N, treatment, outcomes and key results. Study findings are summarised in Table 4 (p. 1381) as strength of the body of evidence per condition, with the study name and type, and peer-reviewed journal source identified
Main conclusion of review authors	The authors concluded "No significant difference in validated symptom scales for chronic stable asthma...conflicting results in terms of lung function...limited attempts to measure a 'package of care' effect" (p. 1).	For *individualized homeopathy* in allergic asthma, there was consistently positive evidence from nine studies (Mosquera Pardo 1990, Castellsagu 1992, Eizayaga and Eizayaga 1996, Lara-Marquez, Pocino *et al.* 1997, Riveron-Garrote *et al.* 1998, Witt, Keil *et al.* 2005, Colin 2006, Goossens, Laekeman *et al.* 2009), and there was no evidence of effectiveness in one (White, Slade *et al.* 2003). For *homeopathic immunotherapy* for allergic asthma, there was less consistent and convincing evidence. There was positive evidence from six studies (Hardy 1984, Reilly, Taylor et al. 1986, Nolleveaux 1992, Reilly, Taylor et al. 1994, Taylor, Reilly et al. 2000, Kim, Riedlinger et al. 2000). There was no evidence of effectiveness in four studies (Aabel 2000, Aabel 2001, Hyland and Lewith 2002, Li, Bush et al. 2003).
Other issues	McCarney et al. (2008) note that "Standardized treatments in these trials are unlikely to represent common homeopathy practice, where treatment tends to be individualized" (p. 1).	The authors indicate that "The evidence for individualised homeopathic therapy in the field of upper respiratory tract infections and for homeopathic immunotherapy in respiratory allergies is (more) conflicting. Pragmatic equivalence trials suggest that, in primary care,

The term 'positive evidence' is not backed up with any justification or explanation. It would be more useful and appropriate to comment on the study designs, quality of the evidence, risk of bias and consistency (all important concepts when assessing the quality of the evidence). This would help determine the confidence you can have in whatever conclusion can be reached.

		homeopathic treatment is not inferior to conventional treatment. A larger number of observational studies and of clinical trials -- conducted in a methodologically correct manner without altering the treatment setting-- are needed before sure conclusions concerning the application of homeopathy for specific diseases can be drawn" (p. 1363).

Evidence statement NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	Both key review methods are sound, however the included primary studies are of variable study design and quality
Consistency	D	See above comment on heterogeneity, and main conclusions of authors
Clinical impact	D	Inconclusive and restricted for individualised homeopathy for chronic stable asthma, individualised homeopathy for allergic asthma and for homeopathic immunotherapy, as indicated by the lack of homogeneity of primary study designs, primary outcome measures, and the lack of effect on pooled secondary outcome measures (McCarney 2008).

Included primary literature

- Campbell et al. (1990) (reported in Reilly (1994)), conducted a parallel group randomised control trial of 28 people (>16 years). Homeopathic intervention consisted of 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). Reilly (1994) Jadad score 4/5 (minimum drop outs).
    - *Outcomes:* No change in PEF, pulmonary function, and histamine challenge; significant improvement in the visual analog scale
- Castellsagu (1992), in a retrospective case series, tested 26 children (age not reported) with allergic asthma with individualised homeopathy. High Risk of Bias
    - *Outcomes:* 'general improvement', with improvement (uncontrolled) in most patients.
- Colin (2006) in a retrospective case series of 147 individuals (age not reported) with respiratory allergies, tested classic homeopathy on symptoms. High Risk of Bias
    - *Outcomes:* better outcomes in the homeopathy group
- Eizayaga and Eizayaga (1996) in a retrospective case series, investigated 62 individuals (age not reported) with allergic asthma, treated with individualised homeopathy. Unknown Risk of Bias
    - *Outcomes*: significant decrease of symptoms after therapy (uncontrolled)
- Freitas (1999) conducted a parallel group randomised control trial of 69 children (1-12 years). Homeopathic intervention consisted of *Blatta officinalis* C6 or indistinguishable placebo, 2 globules 3 times per day for 6 months. The Jadad score 4/5 (problems with drop outs and blinding).

- *Outcome:* No intergroup differences in intensity, frequency or duration of asthma attacks

- Frenkel and Hermoni (2002) conducted a retrospective case series of 48 individuals (age unstated) with allergic asthma and other allergies, comparing homeopathic care (various) with conventional medicine consumption. Low Risk of Bias
  - *Outcomes:* The homeopathic intervention led to reduction in the use of medications (uncontrolled)
- Lara-Marquez et al. (1997) used a randomised controlled blinded experimental study comparing individualised homeopathy to placebo for 19 individuals (age unstated). Quality score not stated
  - *Outcomes:* Symptoms, spirometry parameters and immunological markers with verum better than placebo, significant changes of laboratory markers.
- Lewith (2002) conducted a parallel group randomised control trial of 242 adults (mean age 38 years). Homeopathic intervention consisted of Isopathy (30C house dust mite) or indistinguishable placebo (same without house dust mite), 3 doses orally in 24 hours. Jadad score 5/5, equal numbers of drop outs in treatment and control.
  - *Outcome:* No difference between active and placebo in FEV1, PEF, symptoms, use of b2-agonists, and asthma score
- Li et al. (2003), in a prospective observational study of 12 children (age not reported) with allergic asthma, and tested H.I.T. prepared from individual allergen vs. placebo. Low Risk of Bias
  - *Outcomes:* spirometric tests, with no improvement after treatment.
- Matusiewicz (1995, 1996, 1997) conducted a parallel group randomised control trial of 40 individuals (age not stated). The study findings were reported in three papers. Homeopathic intervention consisted of ampoule *Engystol N* (a complex remedy consisting of the homeopathic remedies *Vincetoxin D6/D10/ D30, Sulfur D4/D10*) or placebo injected subcutaneously at intervals of 5 to 7 days. In addition patients received methylxanthines for mucolysis and tetracycline in case of exacerbations. Jadad score 1/5 (allocation concealment and drop outs not stated).
  - *Outcomes:* respiratory tests, with clinical improvement only in the verum group
- Matusiewicz and Wasniewski (1999) conducted a parallel group randomised control trial of 84 individuals (age not stated). Homeopathic intervention consisted of ampoule of *Asthma H* (a complex remedy consisting of 14 homeopathic potencies of D3, D4, D5 and D6) or placebo injected subcutaneously at intervals of 5 to 7 days. Jadad score 2/5
  - *Outcomes:* Slight decrease of conventional medication and infections; no change in spirometric tests
- Mosquera (1990) in a retrospective case series, assessed the outcome of management of 120 children with allergic asthma, using individualised homeopathy. Quality score not stated
  - *Outcomes*: general improvement, and there was improvement (uncontrolled) in most patients.
- Riveron-Garrote et al. (1998) used a randomised controlled blinded experimental study comparing individualised homeopathy to placebo for 80 individuals (age unstated). Quality score not stated
  - *Outcomes:* General symptoms, and attack frequency. There was a higher reduction of attack frequency in the verum group.
- White (2003) conducted a parallel group randomised control trial of 93 children and adolescents (5-15 years). Homeopathic intervention consisted of any number of individualised homeopathy

or placebo prescriptions. Up to six consultations (plus telephone consultations if required) were provided throughout the year. Use of adjunctive therapies as allowed by practitioners. Jadad score 5/5.

  - *Outcomes:* No difference between active and placebo in asthma-related QOL, PEF, use of b2-agonists, missing days

- Witt et al. (2005) considered 178 individuals (age not reported) with allergic diseases including rhinitis and asthma, in a non-randomised controlled clinical trial. They tested classic homeopathy vs. conventional care and measured symptoms, quality-of-life questionnaires, costs. High Risk of Bias
  - *Outcomes:* Better outcomes in homeopathic group

References

Included systematic reviews

McCarney RW, Linde K, Lasserson TJ. 2008. Homeopathy for chronic asthma. *Cochrane Database of Systematic ReviewsPrimary included studies*

Bellavite P, Marzotto M, Chirumbolo S, Conforti A. 2011. Advances in homeopathy and immunology: a review of clinical research. *Frontiers in Bioscience* S3, 1363-1389.

Altunç U, Pittler MH, Ernst E. 2007. Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic proceedings. Mayo Clinic* 82, 69-75.

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, 1054-62.

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Castellsagu API. 1992. Evolution of 26 cases of bronchial asthma with homeopathic treatment. *Br Homeopath J* 81, 173–5.

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Eizayaga FX, Eizayaga J. 1996. Homeopathic treatment of bronchial asthma. *Br Hom J* 85, 28–33.

Freitas LA, Goldenstein E, Sanna OM. 1995. The indirect doctor patient relationship and the homeopathic treatment of asthma in children. *Revista de Homeopatia* 60(2), 26–31.

Frenkel M, Hermoni D. 2002. Effects of homeopathic intervention on medication consumption in atopic and allergic disorders. *Altern Ther Health Med* 8, 76–9.

Lara-Marquez ML, Pocino M, Rodriguez F, Carvallo GE, Ortega CF, Rodriguez C. 1997. Homeopathic treatment for atopic asthma lung function and immunological outcomes in a randomized clinical trial in Venezuela. Proceedings of the 52nd LMHI Congress. Seattle, USA, 73.

Lewith GT, Watkins AD, Hyland ME, Shaw S, Broomfield JA, Dolan G, et al. 2002. Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite: double blind randomised controlled clinical trial. *BMJ* 324, 1–5.

Li AM, Bush A, Wilson NM. 2003. Homeopathy in childhood asthma. *Thorax* 58, 826.

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Matusiewicz R. 1997. The homeopathic treatment of corticosteroid dependent asthma: a doubleblind, placebo-controlled study. *Biomed Ther* 4, 117–22.

Matusiewicz R, Wasniewski J, Sterna- Bazanska A, Hulsberg M. 1999. Treatment of asthma with a complex homeopathic remedy [Behandlung des chronischen asthma bronchiale mit einem homoopathischen komplexmittel]. *EHK* 6, 367–74.

Mosquera Pardo MF. 1990. Bronchial asthma in childhood: management by means of homeopathia. Proceedings of the 2nd OMHI Congress, 156–66.

Reilly DT, Taylor MA, Beattie NG, Campbell JH, McSharry C, Aitchison TC, et al. 1994. Is evidence for homoeopathy reproducible? *Lancet* 344, 1601-1606

Riveron-Garrote M, Fernandez-Argulles R, Moron-Rodriguez F, Campistrou-Labaut JL. 1998. Ensayo cli`nico controlado aleatorizado del tratamiento homeopa`tico del asma bronquial. *Bol Mex Hom* 31, 54–61.

White A, Slade P, Hunt C, Hart A, Ernst E. 2003. Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomised placebo controlled trial. *Thorax* 58,317–21.

Witt C, Keil T, Selim D, Roll S, Vance W, Wegscheider K, et al. 2005. Outcome and costs of homeopathic and conventional treatment strategies: a comparative cohort study in patients with chronic disorders. *Complement Ther Med* 13, 79–86.

Attention Deficit Hyperactivity Disorder (ADHD)

Executive summary

Three systematic reviews were identified in Categories 1 and 3, which investigated the effectiveness of homeopathic treatments for ADHD.

- One Category 1 review (Heirs and Dean 2009, an updated Cochrane review), focused specifically on the effectiveness of homeopathic treatment for ADHD
- Two Category 3 reviews (Altunc 2007, Davidson 2011) considered the effectiveness of homeopathic treatment for groups of conditions which included ADHD.

Typographical error
Should be 2007, not 2009

The NHMRC Committee considered that the Davidson (2011) and Altunc (2007) reviews were too broad in focus to assist in providing evidence for this clinical question. Therefore Heirs and Dean (2009) was considered as the key evidence source.

Key systematic review: Heirs and Dean (2009) focused specifically on the effectiveness of homeopathic treatment for ADHD (Category 1). This review was of high methodological quality, and included four primary studies (Frei et al. 2005, Jacobs et al. 2005, Lamont 1997, Strauss 2000). This evidence base reflects information on 189 children.

Other systematic reviews

a) Altunc (2007) considered the effectiveness of homeopathy for childhood ailments including adenoid vegetation, ADHD, asthma, otitis media, conjunctivitis, diarrhea, post-operative pain, URTI and warts. Altunc searched a range of databases to identify relevant literature, including MEDLINE, EMBASE, AMED, CINAHL, Cohrane Central, British Homeopathic Library, ClinicalTrials.gov, and the UK National Research Register up to January 2006. Considering the effectiveness of homeopathy for ADHD, Altunc included three relevant primary studies (randomised trials) (Frei et al 2005, Jacobs et al 2005, Strauss 2000). These trials had all been included in the Heirs and Dean review (key evidence source). The Committee considered that the Altunc review was too broad in focus to assist in providing evidence for this clinical question.

b) Davidson (2011) considered the effectiveness of homeopathy (individualised) for a number of conditions including ADHD, the others being sleep problems, stress management, PMS, mild TBI and functional somatic symptoms (chronic fatigue, fibromyalgia). Davidson (2011) searched from database inception to 2010 in the follow databases: PubMed, CINAHL, PsycInfo, HomInform, Cochrane CENTRAL, Clinical Trials.gov and the National Centre for Complementary and Alternative Medicine Grantee Publications Database. Davidson (2011) identified three primary studies relevant to the review question, all of which were included in the key evidence source.

Conclusion: There is no convincing evidence from one high quality systematic review of four poor-moderate primary studies, on 189 children, regarding the effectiveness of homeopathy for the management of any manifestation or symptom of ADHD (Grade C).

How can this be given a grade C when the authors' conclusion is that there is no convincing evidence?

Methodological assessment of the key evidence source

Validity issue	Comment: Heirs & Dean (2009)
The review question (PICO)	P: diagnosed with ADHD or hyper kinetic disorder, diagnosed according to DSM-IV or ICD 10 I: homeopathic medicine C: placebo O: incidence or severity of problem behaviours measured using rating scales, incidence/ severity of core symptoms, school performance, depression or anxiety using rating scales, adverse events, and quality of life, using rating scales.
Is it unlikely that that important, relevant studies were missed?	Yes. The following databases were searched up to 2010: CENTRAL, MEDLINE, AMED, BIOSIS, CISCOM, CINAHL, Dissertation Abstracts, ECH (European Committee for Homeopathy thesis database), EMBASE, ERIC, HomInform (Glasgow Homeopathic Hospital Library), LILACS, PsycINFO, Science Citation Index, SIGLE, GIRI - International congress on ultra-low doses, Liga Medicorum Homeopathica Internationalis. Search terms were text and MeSH based
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. The study focus was on controlled randomised trials.
Were the included studies sufficiently valid for the type of question asked?	Unclear. Included studies were evaluated using Cochrane assessment of risk of bias, considering sequence generation, concealment of allocation, blinding, and incomplete outcome data (scored out of four (4, 3, 0, 2)). Studies were of variable quality. Studies not excluded based on quality.
Were the results similar from study to study?	Yes. Meta-analysis was conducted for behaviour scores, hyperactivity, inattention and anxiety, demonstrating similarity of effect.
How are the results presented?	Narrative summaries and forest plots are provided, p. 23-31. Summaries of each included study are provided in "characteristics of studies" (p. 17-20). This included methods, participants, interventions, outcomes and risk of bias assessment.
Main conclusion of review authors	Heirs and Dean (2009) concluded "The forms of homeopathy evaluated to date do not suggest significant treatment effects for the global symptoms, core symptoms of inattention, hyperactivity or impulsivity, or related symptoms such as anxiety in ADHD" (p. 2).
Other issues	Heterogeneity in interventions prompted the authors to suggest that "Development of optimal treatment protocols is recommended prior to further randomised controlled trials being undertaken" (p. 2).

This question should refer to risk of bias. It was assessed, using a Cochrane ROB tool.

NOT CONFIRMED BY EXPERT COMMITTEE

The authors' conclusion that the methods are sound is flawed, if studies of variable quality were included

Evidence statement

Key question	Rating	Justification
Evidence Base	C	The review methods are sound but the included studies are of variable quality. Small sample size - 189 children
Consistency	B	The studies are generally consistent in that three out of four demonstrated no effect of homeopathy on manifestations of ADHD.
Clinical impact	D	Slight or restricted as indicated in the meta-analyses.

Included primary studies

- Frei et al. (2005) in a randomised crossover trial tested 83 children (age not stated) with confirmed ADHD by neuropsychological assessment. Homeopathic intervention was individualised LM potency daily liquid doses, prescribed according to Hahnemann and Bönninghausen, with minimised non-specific effects. Quality score- High Risk of Bias.
    - *Outcomes:* a significant benefit from homeopathy in overall symptoms (global rating as assessed by parents)
- Jacobs et al. (2005) in a parallel arm, randomised control trial tested 43 children with confirmed ADHD (mean age 9 years). Classical individualised homeopathy using the Bombay or Sankaran method that mirrored usual practice. Placebo was identical placebo homeopathy (a matching sugar pill or solution. Jadad score 5/5
    - Outcomes: no significant difference between verum and placebo in core symptoms of ADHD
- Lamont (1997) in a quasi-randomised controlled trial with partial cross-over treated 43 children with ADHD confirmed by psychological testing (mean age of 10 years). Individualised homeopathic medicines were prescribed following a consultation using classical homeopathic prescribing and the RADAR repertory software. Medicines were given as 6 x 200c pills daily for up to 5 days. Placebo was identical placebo homeopathy (a matching sugar pill or solution. The study was of poor quality with no sequence generation, no allocation concealment, incomplete outcome data and unclear blinding. Jadad score 2/5
    - *Outcomes:* no evidence of the effectiveness of homeopathy in improving hyperactivity in children with ADHD
- Strauss (2000) conducted a randomised control trial of 20 children aged between 7-10 years with an earlier diagnosis of ADHD. Formulaic homeopathy containing *selenium in 10X, 15X, 30X, 200X* with *potassium phosphate in 2X, 10X, 30X, 200X*, compared with identical placebo homeopathy (a matching sugar pill or solution). Jadad score 5/5
    - *Outcomes:* no difference between placebo and verum for core symptoms of ADHD

References

Included systematic reviews

Altunç U., Pittler MH, Ernst E. 2007. Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic proceedings. Mayo Clinic* 82, 69-75.

Davidson JR, Crawford C, Ives JA, Jonas WB. 2011. Homeopathic treatments in psychiatry: a systematic review of randomized placebo-controlled studies (Provisional abstract). *Journal of Clinical Psychiatry* [Online]. Available: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12011004329/frame.html.

Heirs M, Dean ME. 2007. Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. *Cochrane Database of Systematic Reviews*.

Primary included studies

Frei H, Everts R, von Ammon K, Kaufmann F, Walther D, Hsu-Schmitz S, Collenberg M, Fuhrer K, Hassink R, Steinlin M, Thurneysen A. 2005. Homeopathic treatment of children with attention deficit hyperactivity disorder: a randomised double-blind, placebo-controlled crossover trial.. *European Journal of Pediatrics* 164(12), 758–767.

Jacobs J, Williams A, Girard C, Njike VY, Katz D. 2005. Homeopathy for attention-deficit/hyperactivity disorder: a pilot randomized controlled trial. *Journal of Alternative and Complementary Medicine* 11(5), 799–806.

Lamont J. 1997. Homoeopathic treatment of attention deficit hyperactivity disorder. *Br Hom* 86, 196-200.

Strauss LC. 2000. The efficacy of a homeopathic preparation in the management of attention deficit hyperactivity disorder. *Biomedical Therapy* 18(2), 197–201.

Symptoms associated with treatment for cancer

Executive summary

Four systematic reviews were identified in Category 1 and 3. They investigated the effectiveness of homeopathy for the treatment of symptoms associated with cancer.

- Two Category 1 reviews (Kassab et al 2011, Milazzo et al 2007) focused entirely on studies of homeopathy as a treatment for chemotherapy-induced symptoms.
- Two Category 3 reviews (Bellavite et al 2011, Simonart 2011) considered the effectiveness of homeopathic treatment for groups of cancer-treatment-related conditions.

The most recent, comprehensive review (Kessab et al 2011) was considered to be the key evidence source for this evidence review.

Typographical error . Kassab et al was published in 2009 not 2011

Key systematic review: Kassab et al. (2011) was a Cochrane review which included eight randomised control trials (Balzarini 2000, Bourgeois 1984, Daub 2005, Jacobs 2005, Kulkarni 1998, Oberbaum 2001, Pommier 2004, Thompson 2005[5]). The number of studies and conditions addressed by these reviews were:

Typographical error. Kulkarni published 1988 not 1998

- Three studies on homeopathy and adverse effects of radiotherapy (Balzarini 2000, Kulkarni 1988, Pommier 2004).
- Two studies on homeopathy on adverse effects of chemotherapy (Daub 2005, Oberbaum 2001)
- One study on homeopathy for adverse effects of venous cannulation in patients receiving chemotherapy (Bourgois 1984).
- Two studies on homeopathic medicines for menopausal symptoms due to therapies as part of the management of breast cancer (Jacobs 2005, Thompson 2005).

Other systematic reviews

a) Milazzo et al. (2007) included five relevant randomised control trials (Kulkami 1988, Balzarini 2000, Oberbaum 2001, Jacobs 2005, Thompson 2005), all of which were included in Kassab et al (2011).

b) Bellavite et al. (2011) considered the effectiveness of homeopathic treatment for groups of conditions (reviewing the past 30 years of research in respiratory allergies, common upper respiratory tract infections, otorhinolaryngologic complains and rheumatic diseases) and reported on the effectiveness of individualised homeopathy and immunological disorders. This review was of high methodological quality, had conducted a comprehensive search and included one experimental study relevant to chemotherapy-induced symptoms (Oberbaum et al. 2001). This study was identified in both key reviews. This review concluded on the

[5] The Jacobs and Thompson studies were also included in the separate evidence review on management of menopausal symptoms.

basis of this one study that homeopathic therapy homeopathic complex *Traumeel-S* versus placebo is useful to prevent stomatitis development.

c) Simonart (2011) reviewed the effectiveness of homeopathic remedies in dermatology, using a systematic review of relevant controlled clinical trials (January 1962–April 2011) from MEDLINE, PubMed, Current Contents, HomInform (Glasgow), reference lists, specialist textbooks and contacts with homoeopathic manufacturers. There was no restriction on language. The review identified one relevant controlled trial for breast cancer (Balzarini et al. 2000) which used *Belladona 7 cH* and *X-ray 15 cH*. This study had been identified in both key reviews. The authors concluded that there was no evidence that homoeopathy is efficacious for cancer-treatment-induced dermatological conditions.

Conclusion: One good quality, recent review of 664 individuals in eight variable-quality primary experimental studies indicated encouraging evidence for topical calendula for prophylaxis of acute dermatitis during radiotherapy, and for *Traumeel S* mouthwash in the treatment of chemotherapy-induced stomatitis. There is no convincing evidence for the efficacy of homeopathic medicines for any other adverse effects of cancer treatment (Grade C).

incorrect - see below

Given the issues described below and the comments provided on the Evidence Statement on p 43, this 'C' rating should be a 'D'.

The conclusions for topical calendula and Traumeel S cannot be justified by the evidence AND WERE NOT CONFIRMED BY THE EXPERT COMMITEE:

* The author of the systematic review (Kassab et al 2011) reported that 'topical calendula may be considered as an option....although this intervention requires further evaluation.....' this is based on ONE clinical trial of 254 participants.

The other outcome of Traumeel S homeopathic mouthwash is based on ONE clinical trial of 32 participants

* The report authors have concluded results for 664 individuals across eight primary studies, but this is incorrect:
  - the result for topical calendula was found in only one of the eight trials (Pommier 2004), and N= 254.

* The other seven trials assessed other homeopathic remedies.
  - the result for Traumeel S mouthwash was found for only one of the eight trials (Oberbaum 2001), with the mouthwash 'appearing to show promise' in the treatment of chemotherapy induced stomatitis. N = 32

Methodological assessment of the key evidence source

Validity issue	Comment: Kassab et al. (2011)
The review question (PICO)	P: Participants with a clinical or histological diagnosis of any cancer who wanted to prevent or treat adverse effects associated with their cancer treatments. All ages, at any stage of disease, were included I: Homeopathy, defined as homeopathic medicines prepared in accordance with officially recognised homeopathic pharmacopoeia C: any (not defined) O: subjective or objective outcome measures related to adverse events of cancer treatment. Also adverse reactions to homeopathy
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely. The following databases were searched up to November 2008: Cochrane PaPaS Trials Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; CINAHL; BNI; CancerLIT; AMED; CISCOM; Hom-Inform; SIGLE; National Research Register; Zetoc; www.controlled-trials.com; http://clinicaltrials.gov; Liga Medicorum Homeopathica Internationalis (LMHI, Liga) conference proceedings; reference lists of relevant studies were checked; and homeopathic manufacturers. MeSH and text search terms were used
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. The focus was on randomised controlled clinical studies.
Were the included studies sufficiently valid for the type of question asked?	Yes. RCTs evaluated using the following criteria: Was a method of randomisation performed?, Was the treatment allocation concealed?, Were the groups similar at baseline regarding the most important prognostic indicators?, Were the eligibility criteria specified?, Was the outcome assessor blinded?, Was the care provider blinded?, Was the patient blinded?, Were point estimates and measures of variability presented for the primary outcome measures?, Did the analysis include an intention to treat analysis? Studies were not excluded based on quality. Studies were generally of moderate to good quality, with only two scoring poorly (Bourgouis, Kulkarni).
Were the results similar from study to study?	No. Studies are heterogeneous in terms of conditions, age groups and interventions. There was no outcome measure for which two or more studies could be compared
How are the results presented?	Qualitatively and pooled A summary for each included study was provided in "Characteristics of included studies" (p. 14-26). This included methods, participants, interventions, outcomes and risk of bias. Meta-analysis was attempted, however due to heterogeneity of study samples, interventions and outcome measures, there was no opportunity to compare two or more studies (pp31-37).
Main conclusion of review authors	Kassab et al. (2011) concluded "Prophylactic use of calendula ointment may be considered as an option for patients undergoing radiotherapy for breast cancer, although this intervention requires further evaluation. Compared with trolamine, it reduced the incidence of acute dermatitis of

Typographical error. Kassab published 2009 not 2011

	grade two or above in women undergoing radiotherapy for breast cancer in one clinical trial involving 254 participants. The calendula ointment used in this study was prepared according to the German Homeopathic Pharmacopoeia and so the results may not apply to topical preparations of calendula extracts prepared by different methods. There is no convincing evidence for the efficacy of other homeopathic medicines for adverse symptoms and skin reactions related to radiotherapy. Two small studies were positive but both had an unclear risk of bias. Based on a single trial involving 32 participants, one particular homeopathic combination (Traumeel S - a proprietary complex homeopathic medicine) appears to show promise in the treatment of chemotherapy-induced stomatitis. High quality trials to date provide no evidence for the efficacy of homeopathic medicines over placebo in women with breast cancer suffering from menopausal symptoms. No serious adverse effects that could be attributed to homeopathic medicines or interactions with conventional treatment were reported in the included studies. No cancer treatments were modified or stopped because of the homeopathic interventions." (p. 11).
Other issues	From meta-analysis which included the Balzarini, Pommier, Thompson, Bougeouis and Oberbaum studies, promising weighted mean differences of effect between intervention and placebo were reported, which favoured homeopathy (pp31-37).

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Evidence statement

This should only refer to one, not eight trials (see comments p41). Also the sample size was very small - only 254 people participated, which is not large enough to base any firm conclusions on.

There is not a clear justification for this Grade B. The results of the risk of bias assessment are not reported, just the questions asked (see table above). The CEBM even states that studies were not excluded based on quality.

Key question	Rating	Justification
Evidence Base	B	The review methods are sound and six (of 8) included studies are of good quality.
Consistency	C	There is some inconsistency reflecting genuine uncertainty around clinical question, which can be explained by heterogeneity
Clinical impact	C-D	The meta-analyses and descriptive summaries suggest that there is a moderate effect for homeopathic interventions for some symptoms associated with cancer treatment, eg *topical calendula* for prophylaxis of acute dermatitis during radiotherapy, and for *Traumeel S* mouthwash in the treatment of chemotherapy-induced stomatitis. There is no evidence of impact for any other side effects of cancer treatment. See Meta-analyses p31-37

Consistency should be rated 'D' given the CEBM comment: *Studies are heterogeneous in terms of conditions, age groups and interventions. there was no outcome measure for which two or more studies could be compared.* 'Some inconsistency' is incorrect

The Clinical impact score of C-D should be downsized to a D. It is unclear as to how the authors reached a conclusion that there was a 'moderate effect' of topical calendula or Traumeel S mouthwash as indicated in this evidence statement (see comments p 41)

Included primary literature

- Balzarini (2000), who assessed 66 women following conservative surgery for breast cancer and who were being treated with radiotherapy. Mean age of sample 52.7 years. The study design was prospective randomised double blind (subject and observer blind) placebo controlled trial with two parallel arms, with moderate risk of bias. Subjects were treated with homeopathic medicines - *Belladonna 7c* three granules twice daily and *X-ray 15c* three granules once daily, or placebo.
    - *Outcome:* no significant difference in the total severity of skin reactions during radiotherapy, but a statistically important reduction in severity during recovery for homeopathy group ($p = 0.05$)
- Bourgeois (1984) who conducted a randomised, double-blind controlled trial of 29 women with breast cancer undergoing intravenous chemotherapy, mean age: 54.4 years. The study had a high risk of bias. Intervention was homeopathic *Arnica 5c* or placebo, both administered as three granules four times a day for three days before and three days after treatment for two chemotherapy cycles
    - *Outcome*: no statistically significant differences between groups
- Daub (2005) conducted a prospective randomised placebo controlled trial with two parallel arms, for 65 women undergoing chemotherapy for breast cancer (aged 28-67 years). The study had a low to moderate risk of bias. The prescribing strategy was homotoxicology, specifically "On day 2, if symptomatic (conventional antiemetics were used for the first day) a) *Vomitusheel S* - a proprietary complex homeopathic medicine containing *Ipecacuanha D2* (1.1 mg), *Aesthusea D2* (1.1 mg), *Nux vomica* D2 (1.1 mg), *Apomorphium hydrochloricum* D4 (1.65 mg), *Colchicum D4* (2.75 mg), *Ignatia D4* (3.3 mg) given as a suppository and *Gastricumeel* (a proprietary complex homeopathic medicine containing *Argentum nitricum* D6 (30 mg), *Acidum arsenicosum* D6 (30 mg), *Pulsatilla D4* (60 mg), *Nux vomica D4* (60 mg), *Carbo vegetablis D6* (60 mg), *Antimonium crudum D6* (60 mg)) given as oral tablets b) *Sambucus nigra D3* oral tablets used as the placebo. If symptoms did not resolve within two hours, conventional antiemetics were given" (p17). The placebo was another homeopathic medicine that the authors chose because it has been demonstrated to have no antiemetic properties.
    - *Outcome*: No significant difference between groups
- Jacobs (2005) applied a prospective randomised triple blind placebo controlled trial with three parallel arms of 83 women (mean age 55.5 years) with a history of carcinoma in situ or Stage I to III breast cancer who had completed all surgery, chemotherapy and radiotherapy, with hot flushes. The study had a low risk of bias. Interventions were individualised homeopathy (single medicine given once monthly or bimonthly), and complex homeopathy, *Hyland's Menopause*, a proprietary combination homeopathic medicine (*Amyl Nitrate 3x*, *Sanguinaria canadensis 3x* and *Lachesis 12x)* given three times a day, or placebo
    - *Outcome:* There were no statistical differences among comparisons for the frequency or severity of hot flushes
- Kulkarni (1998) used a prospective randomised placebo controlled trial design with three parallel arms to test 82 participants with head and neck, pelvic or thoracic cancers undergoing a course of radiotherapy treatment. The study had a high risk of bias.

Interventions included clinical homeopathy homeopathic *Cobaltum 30*, homeopathic *Causticum 30* or placebo. Each treatment taken as 3 pills each morning throughout the entire course of radiotherapy. The dilution method of the homeopathic medicines was not stated

  - *Outcome*: approximately 30% reduction in the degree of reactions in both groups taking homeopathic medicines compared with placebo

- Oberbaum (2001) applied a prospective randomised placebo controlled trial with two parallel arms to 32 children and young adults (aged 3-25 years) suffering from malignant diseases who had undergone allogeneic or autologous stem cell transplantation. The study had a low risk of bias. Intervention took a homotoxicology approach using Traumeel S (a proprietary complex homeopathic medicine) or saline placebo. Each 2.2 ml active intervention ampoule contained: *Arnica montana D2* (2.2 mg), *calendula officianalis D2* (2.2 mg), *Achillea millefolium D3* (2.2 mg), *Matricharia chamomilla D2* (2.2 mg), *Symphytum officinale D6* (2.2 mg), *Atropa belladonna D2* (2.2 mg), *Aconitum napelus D2* (1.32 mg) , *Bellis perenis D2* (1.1 mg), *Hypericum perfoliatum D2* (0.66 mg), *Echinacea angustifoliaD2* (2.2 mg), *Echinacea purpurea D2* (2.2 mg), *Hammamelis virginica D1* (0.22 mg), *Mercurius solubilis D1* (1.1 mg) and *Hepar sulphuris D6* (2.2 mg).
  - *Outcome*: Less stomatitis in verum group, decrease of symptoms
- Pommier (2004) conducted a prospective randomised single blind randomised controlled trial of 254 women aged between 18 to 75 years, with non-metastatic breast cancer treated with either lumpectomy or mastectomy, with or without adjuvant postoperative chemotherapy or hormonal treatment. The study had a low risk of bias. The intervention took a clinical homeopathy approach of Calendula extract ointment prepared according to the German homeopathic pharmacopoeia (consisting of a soft paraffin extract of fresh *Calendula officinalis* flowering tops (20% w/w) or *Trolamine* topical agent. (Biafine; Genmedix Ltd, France) consisting of purified water, liquid paraffin, ethylene glycol monostearate, stearic acid, propylene glycol, paraffin wax, squalane, avocado oil, trolamine/sodium alginate, triethanolamine, cetyl palmitate, methylparaben (sodium salt), sorbic acid (potassium salt), propylparaben (sodium salt), and fragrance. Topical agents were used at the onset of radiotherapy, twice daily or more depending on occurrence of dermatitis or pain until completion of radiotherapy. No other creams, lotions or gels were used.
  - *Outcome*: occurrence of acute dermatitis grade two or higher was significantly lower (41% versus 63% $P < 0.001$) with the use of calendula than with trolamine.
- Thompson (2005) using a parallel group design experiment of moderate risk of bias, investigated 53 women (45 assessable) who had breast cancer with more than 3 hot flushes per day (mean age 52 years). The study had a low risk of bias. They received a tailored homeopathic prescriptions delivered in two arms, or placebo. Two active arms consisted of single homeopathic remedy or combination homeopathic remedy (Hyland's menopause). The placebo looked the same as the active interventions.
  - *Outcome:* There were no significant effects observed in self-rated symptoms of severity or frequency of hot flushes, activities of daily living and general well-being

References

Included systematic reviews

Bellavite P, Ortolani R, Pontarollo F, Piasere V, Benato G, Conforti A. 2006a. Immunology and Homeopathy. 4. Clinical Studies—Part 1. *eCAM,* 3, 293-301.

Kassab S, Cummings M, Berkovitz S, Van Haselen R, Fisher P. 2009. Homeopathic medicines for adverse effects of cancer treatments. *Cochrane database of systematic reviews (Online)*, CD004845.

Simonart T, Kabagabo C, De Maertelaer V. 2011. Homoeopathic remedies in dermatology: a systematic review of controlled clinical trials. *British Journal of Dermatology,* 165, 897-905.

Primary included studies

Balzarini A, Felisi E, Martini A, De Conno F. 2000. Efficacy of homeopathic treatment of skin reactions during radiotherapy for breast cancer: a randomised, double-blind clinical trial. *British Homeopathic Journal* 89(1), 8–12.

Bourgois JC. 1984. Protection of the venous capital at the perfusees with a long course in breast cancer. Double blind Clinical trial: Arnica with a placebo control [Protection du capital veineux chez les perfusees au long cours dans cancer du sein. Essai clinique en double aveugle: Arnica contreplacebo]. Thesis 89.

Daub EA, Gerhard I, Bastert G. Homeopathic antiemesis for chemotherapy, a prospective randomised trial [Homoopathische Antiemetika bei Chemotherapie, eine prospektiv, randomisierte Studie]. *Geburtshilfe und Frauenheilkunde* 2005;**60**:S157.

Jacobs J, Herman P, Heron K, Olsen S, Vaughters L. 2005. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled trial. *Journal of Alternative and Complementary Medicine* 11(1), 21–7.

Kulkarni A, Nagarkar BM, Burde GS. 1988. Radiation protection by use of homoeopathic medicines. *Hahnemann Homoeopath Sand* 12, 20–3.

Oberbaum M, Yaniv I, Ben Gal Y, Stein J, Ben Zvi N, Freedman LS, et al. 2001. A randomized, controlled clinical trial of the homeopathic medication TRAUMEEL S in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. *Cancer* 92(3), 684–90.

Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X. 2004. Phase III randomized trial of Calendula officinalis compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. *Journal of Clinical Oncology* 22(8), 1447–53.

Thompson EA, Montgomery A, Douglas D, Reilly D. 2005. A pilot, randomized, double-blinded, placebo-controlled trial of individualized homeopathy for symptoms of estrogen withdrawal in breast-cancer survivors. *Journal of Alternative and Complementary Medicine* 11(1), 13–20.

Chronic Fatigue Syndrome

Executive Summary

Two systematic reviews were identified in Category 2, which considered the effectiveness of CAM interventions for Chronic Fatigue Syndrome (Alraek et al. 2011, Porter et al. 2010).

a) Alraec et al. (2011) comprehensively reviewed the literature to 2010 for the effectiveness of CAM for Chronic Fatigue Syndrome. This review identified two relevant RCTs for homeopathy (Awdry 1996, Weatherley-Jones 2004).
b) Porter et al. (2010) reviewed the literature to 2009 related to alternative and complementary treatments for Myalgic Encephalomyelitis (ME)/ Chronic Fatigue Syndrome and Fibromyalgia. This review identified three relevant RCTs for chronic fatigue syndrome (the same two as identified by Alraec et al. (2011), and a third RCT of mixed diagnoses (CFS, ME, Fibromyalgia) (Teitelbaum et al. 2001)).

Key systematic reviews: Both the Alraec et al. (2011) and Porter et al. (2010) reviews were recent, and they reported on the effectiveness of homeopathy as part of CAM interventions. They were both used as key evidence sources for this condition.

Conclusion: Two good quality recent key reviews which reported on the effectiveness of CAM (including homeopathy) and Chronic Fatigue Syndrome, identified three variable-quality RCTs (including up to 239 individuals). The study numbers are unclear because of the mixed sample in Teitelbaum et al. (2001).

There is inconclusive evidence that homeopathy has benefits in the treatment of Chronic Fatigue Syndrome (Grade C).

Methodological assessment of the key evidence sources

Validity issue	Comment: Alraek (2011)	Comment: Porter (2010)
The review question (PICO)	P: Chronic Fatigue Syndrome I: CAM C: any O: symptoms, scales	P: Myalgic Encephalomyelitis / Chronic Fatigue Syndrome and Fibromyalgia I: Alternative medical interventions C: any (not defined) O: symptoms, rating scales and performance measures
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely Sources were searched to 13th August 2011 including Medline, PsycInfo, Alternative Medicine (AMED), Cumulative Index to Nursing & Allied Health Literature (CINAHL), EMBASE, and the Cochrane Library 2011 (Issue 5). Searching also occurred in the Chinese databases (China Network Knowledge Infrastructure (CNKI; 1979-2010), the Chinese Scientific Journal Database VIP (1989-2010), the Wan Fang Database (1985-2010), and the Chinese Biomedicine (CBM) database (1978-2010); the Korean medical databases (including Korean Studies Information, DBPIA, Korea Institute of Science and Technology Information, Research Information Service System, KoreaMed, and National Assembly Library); and Japanese databases (Japan Science and Technology Information Aggregator, Electronic). Authors manually searched Focus on Alternative and Complementary Therapies and Forschende Komplementärmedizin. The references in all located articles were also searched. Search terms were MeSH and text based	Unclear The authors searched MEDLINE, Psych INFO, PubMed, Social Science Citation index, and the Cochran database of systematic reviews for randomised and non-randomised controlled trials regarding adults and children.
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. Included studies were RCTs.	Yes The selection criteria are clearly stated. Included studies were RCTs.
Were the included studies sufficiently valid for the type of question asked?	Yes Study quality was evaluated using Cochrane classifications of random sequence generation, allocation concealment, patient blinding,	Unclear Quality assessment was reported via the Jadad scale, although little information was provided on the compromised elements of

	assessor blinding, reporting of dropout or withdrawal, intention-to-treat analysis, selective outcome reporting and other potential biases	methodological quality
Were the results similar from study to study?	No. Awdry reported no significant benefits (poor quality study), while Weatherley-Jones (higher quality study) reported positive benefits.	No. The studies were heterogeneous for population, diagnosis, intervention and outcome measures
How are the results presented?	A summary for each included study was provided in Table 1 "Results Table" (p. 4). This included sample size, participant groups, main outcomes, intergroup differences, adverse effects.	A summary for each included study was provided in Table 1 "Summary of Study Results" (p. 237). This included sample size, treatment/ intervention, condition type and diagnostic criterion, outcomes investigated, control condition, any effect, diagnostic symptoms, Jadad score.
Main conclusion of review authors	Alraek et al. (2011) concluded "Compared with placebo, homeopathy had insufficient evidence of symptom improvement in CFS." (p. 9).	Porter et al. (2010) concluded that "treatment types are often heterogeneous between studies and between individuals within studies. Given the limited number of studies and mixed outcomes, no conclusions can be offered on this treatment type, although the [....] positive results suggest potential for future research" (p.241) NB this conclusion was also provided for fibromyalgia
Other issues	The quality of the included studies varied, as did the outcome measures and quality of reporting.	The mixed samples for ME/ CFS in one study preclude confidence in its diagnostic inclusion criteria

It is difficult to see how the authors reached a conclusion of 'sound review methods'. The risk of bias assessment referred to above just documents the questions asked, but does not report the responses. The other systematic review reports an 'unclear or inconclusive' quality assessment .

Evidence statement

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review methods are sound but there are only three included studies of variable quality, and mixed diagnoses.
Consistency	C	Heterogeneity of studies suggests some inconsistency reflecting genuine uncertainty around clinical question
Clinical impact	D	see 'Main conclusion of review authors' and 'Other issues' above

Consistency rating should be downgraded to a D: The above table (pp48 & 49) states that results in the two systematic reviews were not similar. Alraek reported an effect in different directions, whilst the Porter studies were heterogeneous in population, diagnosis, intervention and outcome measures.

Primary included studies

- Awdry (1996) was a poor quality (Jadad score 2/5) RCT which tested 64 individuals with CFS or ME, using homeopathy (unstated) interventions with placebo
    - *Outcomes:* no significant difference within or between groups, although there were beneficial effects reported on symptoms
- Weatherley-Jones (2004) conducted a good quality RCT (Jadad score 5/5), on 103 individuals with ME/ CFS, with (unstated) homeopathic interventions
    - *Outcome:* positive effect of homeopathy on fatigue and function
- Teitelbaum et al. (2001) considered the effectiveness of multiple homeopathic agents for mixed chronic fatigue syndrome and fibromyalgia in 72 individuals. The study was of good quality (Jadad score 5/5)
    - *Outcomes:* Positive effect of on symptoms

References

Included systematic reviews

Alraek T, Myeong, SL, Tae-Young, C, Cao H, Jianping L. 2011. Complementary and alternative medicine for patients with chronic fatigue syndrome: A systematic review. *BMC Complementary and Alternative Medicine*, 11, 87 http://www.biomedcentral.com/1472-6882/11/87.

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. *Journal of Alternative & Complementary Medicine,* 16, 235-249.

Primary included studies

Awdry R. 1996. Homeopathy may help ME. *Int J Altern Complement Med;* 14:12–16.

Weatherley-Jones E, Nicholl JP, Thomas KJ, et al. 2004. A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. *J Psychosom Res* 56, 189–197.

Teitelbaum JE, Bird B, Greenfield RM, et al. 2001. Effective treatment of chronic fatigue syndrome and fibromyalgia: A randomized double-blind, placebo-controlled, intent-to-treat study. *J Chron Fatigue Syndr* 8, 3–28.

Delayed-onset muscle soreness (DOMS)

Executive summary

Two systematic reviews were identified in Categories 1 and 3, which investigated the effectiveness of homeopathic treatments for DOMS. Both reviews were more than 10 years old (Ernst & Barnes 1998, Ernst & Pittler 1998).

- The Category 1 review (Ernst & Barnes 1998) focused specifically on the effectiveness of homeopathic treatment on DOMS.
- The Category 3 review (Ernst & Pittler 1998) considered the effectiveness of homeopathic treatment for groups of conditions which included DOMS.

Key evidence source: The Ernst and Barnes review (1998) (Category 1) was the only one to focus specifically on studies of homeopathy as a treatment for DOMS. It included eight primary studies, three reporting one study each (Tveiten 1991, Jawara 1991, Vickers 1997), and five primary studies reporting one randomised controlled trial with four arms and multiple time points of measurement (Hildebrandt 1983a,b,c,d, Hildebrandt 1984). This review was determined as the key evidence source.

Other evidence source: The other systematic review by Ernst and Pittler (1998) addressed the treatment of DOMS using homeopathy. These authors assessed the effectiveness of homeopathic *Arnica* on a number of acutely painful presentations (including DOMS). These authors searched MEDLINE, EMBASE, CISCOM, and the Cochrane Library. They identified two studies relevant to the review question (Hildebrandt et al. 1984, Tveiten 1991), both of which were included in Ernst and Barnes (1998). On the basis of these two studies, Ernst and Pittler (1997) concluded that homeopathic *Arnica* is no more effective than placebo for DOMS.

Conclusion: There is no convincing evidence from two non-recent systematic reviews reporting on eight variable quality RCTs (N=168 women, 143 mixed gender) to support a conclusion about the effectiveness of homeopathy for the treatment of delayed onset muscle soreness (DOMS) (Grade D).

Methodological assessment of the key evidence source

Validity issue	Comment: Ernst & Barnes (1998)
The review question (PICO)	P: Human volunteers with DOMS I: homeopathy (not defined other than as individualised or complex) C: placebo (not defined) O: quantitative data on muscle soreness
Is it unlikely that that important, relevant studies were missed?	Unclear. The following databases were searched up to July 1997: MEDLINE, EMBASE, CISCOM, Cochrane Library. Published reviews of homeopathy and DOMS were considered, and hand-searching was undertaken. Search terms not specified
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated.
Were the included studies sufficiently valid for the type of question asked?	Yes. Included studies had to be placebo-controlled and were evaluated using criteria by Kleijnen (1991), where scores ≥55 indicated studies of higher quality. Studies were excluded on design (not placebo-controlled) but not on quality. Only three studies met the higher quality criteria (Tveiten 1991, Jawara 1997, Vickers 1997)
Were the results similar from study to study?	No. While the studies all indicated no significant findings for any homeopathic intervention, within intervention arm, or comparing intervention and placebo arms, there was a high level of heterogeneity between the included studies in regards to homeopathic remedies and induction of DOMS.
How are the results presented?	A summary for each included study was provided in Table 1 (pp 6-7). This included trial design, sample, homeopathy intervention, control intervention, outcome measures, main results, comments and quality score. Meta-analysis was not mentioned.
Main conclusion of review authors	Ernst and Barnes (1997) concluded "The published evidence to date does not support the hypothesis that homeopathic remedies are more efficacious than placebo for alleviating the symptoms of DOMS" (p. 4).
Other issues	Subjects were volunteers, which constrains external generalizability.

Evidence statement NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	D	The reviews have moderate quality methods but they are both over 10 years old, and include a small number of primary studies of variable quality (one study reported in five different papers).
Consistency	C	There was consistent evidence that homeopathy had no effect on alleviating the symptoms of DOMS, but the included studies are heterogeneous.
Clinical impact	D	Restricted, as results were generally non-significant within intervention groups, and between intervention and placebo groups. There was constrained external generalizability because of constrained sample types.

Included primary literature

Hildebrandt (1983a,b,c,d) was a four arm study which was separately reported. It was a poor quality double-blind placebo-controlled trial, with a High Risk of Bias

- Hildebrandt (1983a) tested 28 women using *Rhus toxicodendron D4* (5 drops daily for 7 days post-exercise) compared with placebo.
    - *Outcome*: less decrease in muscle strength in experimental group, no significant intergroup differences
- Hildebrandt (1983b) tested 32 women using *Rhus toxicodendron D4 using four different doses* (1 x 50 drops daily, 3 x 16 drops daily, 5 x 10 drops daily, 6 x 8 drops daily) for seven days post exercise compared with placebo.
    - *Outcome*: less decrease in muscle strength in experimental groups 1 x 50 drops daily, and 6 x 8 drops daily) compared with placebo, otherwise no significant intergroup differences
- Hildebrandt (1983c) tested 24 women using *Rhus toxicodendron D4 using four different doses* (1 x 5 drops daily, 3 x 5 drops daily, 5 x 10 drops daily) for seven days post exercise compared with placebo.
    - *Outcome*: less decrease in muscle strength in experimental groups 3 x 5 drops daily, and 5 x 10 drops daily) compared with placebo, otherwise no significant intergroup differences
- Hildebrandt (1983d) tested 42 women using *Rhus toxicodendron D4* using six different doses for seven days post exercise *(D2, D3, D4, D5, D6, D8)* (3 x 16 drops daily) compared with placebo.
    - *Outcome*: less decrease in muscle strength in D2 and D4 experimental groups compared with placebo, otherwise no significant intergroup differences, lower serum CK concentrations in D2 group versus placebo.

- Hildebrandt (1984), using the same study data as reported by Hildebrandt in 1983, tested 42 women using *Rhus toxicodendron D4* using six different doses for 3 x 16 drops daily, for six days post exercise *(D2, D3, D4, D5, D6, D8)* compared with placebo. Jadad score 1/5
    - *Outcome*: less decrease in muscle strength in D3 experimental group compared with placebo, otherwise no significant intergroup differences, shorter duration soreness in D3 and D4 groups versus placebo.
- Tveiten (1991) tested 36 participants in the Oslo marathon in a moderate quality randomised double-blind placebo-controlled trial (Jadad score 4/5) using *Arnica Montana D30* (5 pills daily for five days starting 1 day prior to the race) versus placebo.
    - *Outcomes:* No significant inter-group differences, although there was a trend for CK concentrations to be lower with the verum group
- Jawara (1997) (designed as a pilot study) used a high quality randomised double-blind placebo-controlled trial (quality score 85/100) to test 50 volunteers, applying a combination of *Rhus toxicodendron C30 and Arnica C30* versus placebo
    - *Outcomes:* No intergroup differences but trends favoured verum

- Vickers (1997) used a high quality randomised double-blind placebo-controlled trial (quality score 85/100) to test 57 healthy volunteers a combination of *Rhus toxicodendron C30, Arnica C30* and *sarcolactic acid 30C* (one tablet prior to exercise and ceased when muscles stopped being sore) versus placebo.
    - *Outcomes:* no significant intergroup differences, but a trend for muscles to be less sore in the placebo group

References

Included systematic reviews

Ernst, E. & Barnes, J. 1998. Are homoeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo-controlled trials. *PERFUSION,* 11, 4-4.

Ernst, E. & Pittler, M. H. 1998. Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials. *Archives of surgery (Chicago, Ill. : 1960),* 133, 1187-1190.

Primary included studies

Hildebrandt G, Eltze Ch 1983a. Ùber die Wirksamkeit einer Behandlung des Muskelkaters mit *Rhus toxicodendron D4. Wiss Arch Hufelandges Gesamtmed* 1, 1-18.

Hildebrandt G, Eltze Ch 1983a. Ùber die Wirksamkeit verscheidener Dosen und Potenzen von *Rhus toxicodendron D4* beim experimentell ausgelösten Muskelkaters. *Wiss Arch Hufelandges Gesamtmed* 1, 19-35.

Hildebrandt G, Eltze Ch 1984. Ùber die Wirksamkeit verscheidener Potenzen von *Arnica* beim experimentell erzeugten Muskelkaters. *Erfahrungsheilkunde* 7, 430-435.

Jawara N et al. 1997. Homeopathic *Arnica* and *Rhus toxicodendron* for delayed onset muscle soreness. A pilot for a randomised, double-blind, placebo-controlled trial. *Br Hom J* 10-15.

Tveiten D et al. 1991. Effect of Arnica D30 on hard physical exercise. A double blind controlled trial during the Oslo Marathon. *Tidsskr. Nor. Lægeforen* 111, 3630-3631.

Vickers AJ et al. 1997. Homeopathy for delayed-onset muscle soreness, a randomised, double-blind, placebo-controlled trial. *Br J Sports Med* 3, 304-307.

Dementia

Executive summary

Only one systematic review (Category 1) was identified, relating to the treatment of dementia with homeopathy (McCarney et al 2009). This is a Cochrane review, which considered the effectiveness and safety profile, and acceptability, of homeopathically-prepared medications in treating dementia.

This review found no relevant primary research, following a comprehensive search.

Conclusion: There is no current information regarding the effectiveness of homeopathic interventions for dementia.

Methodological assessment of key evidence source

Validity issue	Comment: McCarney (2009)
The review question (PICO)	P: dementia (any type, any severity) based on accepted diagnostic criteria, such as ICD 10, DSM IV, NINCDS-ADRDA. I: homeopathically prepared medications C: placebo or other treatment O: rating scales and performance measures designed to assess cognitive and behavioural functioning, quality of lifer, functional performance, caregiver quality of life, global impression of clinical change and rates of institutionalisation.
Is it unlikely that that important, relevant studies were missed?	No. The following databases were searched up to March 2009: Specialized Register of the Cochrane Dementia and Cognitive Improvement Group, *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS, clinical trials registries, CISCOM, AMED, HomInform. Search terms were text based.
Were the criteria used to select articles for inclusion appropriate?	Yes. Randomised control trials with a sample size of more than 20 were eligible for consideration.
Were the included studies sufficiently valid for the type of question asked?	NA
Were the results similar from study to study?	NA
How are the results presented?	NA
Main conclusion of review authors	The McCarney et al. (2009) review concluded that "there were no studies that fulfilled the criteria for inclusion and no data to present. In view of the absence of evidence it is not possible to comment on the use of homeopathy in treating dementia. The extent of homeopathic prescribing for people with dementia is not clear and so it is difficult to comment on the importance of conducting trials in this area." (p.1-2).
Other issues	

Evidence statement NOT CONFIRMED BY EXPERT COMMITTEE

The McCarney et al. (2009) Cochrane review was the only secondary evidence found regarding the treatment of dementia with homeopathy. As no primary research evidence was included in this review, following a comprehensive search, there is no current primary evidence regarding the effectiveness of homeopathic interventions for dementia. It was therefore not possible to construct a table of the strength of the body of evidence.

References

Secondary evidence

McCarney RW, Warner J, Fisher P, Van Haselen R. 2009. Homeopathy for dementia. *Cochrane Database of Systematic Reviews*.

Depression

Executive summary

One systematic review was identified for the treatment of depression with homeopathy. The Pilkington et al. (2005) review (Category 1) focused on the efficacy of homeopathy for the treatment of depression and depression-related disorders. This was determined as the key review for this clinical question.

Key systematic review: Pilkington et al. (2005) considered two forms of depression in this review: depression as a primary diagnosis and depression as a diagnosis secondary to another condition. The evidence summary presented here focuses on the evidence for depression as a primary diagnosis. The Pilkington et al. (2005) review included two relevant randomised control trials for this condition (Huelluy 1985, Katz et al. 2005).

Considering the treatment of depression secondary to an illness, Pilkington et al (2005) identified one poor quality RCT for the treatment of depression secondary to chronic fatigue syndrome (Awdry et al 1996). This study is more appropriately reported in the evidence summary for Chronic Fatigue Syndrome, and thus is not summarised here.

Conclusion: There is insufficient evidence, from one moderate quality systematic review of two poor quality RCTS, of 71 individuals with different types and causes of primary depression, to reach a conclusion about the safety or effectiveness of homeopathy for the treatment of primary depression (Grade D).

Methodological assessment of the key evidence

Validity issue	Comment: Pilkington et al (2005)
The review question (PICO)	P: depression, expressive depressive disorders, expressive dysthymia, mood or affective disorders. I: homeopathy (not defined other than as individualised or complex) C: any (not defined) O: rating scales and performance measures
Is it unlikely that that important, relevant studies were missed?	Yes. The following databases were searched up to May 2004: MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Central, Cochrane Library, MEDLINE, PubMed, TRIP, DARE; and of specialist complementary and alternative medicine (CAM) databases: AMED, CISCOM, Cochrane complementary medicine field registry, and Hom-Inform, Cochrane CCDAN review group trial register was conducted. Efforts were made to identify unpublished and ongoing research using relevant sources and experts in the field. Clinical commentaries were obtained for studies reporting clinical outcomes. Search terms were text based.
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are basic but clearly stated. Whilst all study designs were included, only the randomised control trials are reported in this data extraction to provide the highest quality evidence.
Were the included studies sufficiently valid for the type of question asked?	Unclear. RCTs were evaluated using specified criteria including method of randomisation, allocation concealment, level of blinding, method of dealing with missing values, loss to follow up or withdrawals, measures of compliance and outcome measures reported. Neither study met all the methodological criteria. Studies were not excluded based on quality.
Were the results similar from study to study?	No. Studies are heterogeneous. As reported by the review authors: "the evidence for the effectiveness of homeopathy in depression is limited due to lack of clinical trials of high quality...the highly individualised nature of much homeopathic treatment and the specificity of response may require innovative methods of analysis of individual treatment response." (p. 153).
How are the results presented?	A summary for each included study was provided in table one "Summary of studies" (p. 159). This included study design, sample, inclusion criteria, treatment, control treatment, outcome measures, results, methodology comments and clinical comments. Meta-analysis was not conducted due to heterogeneity of study samples, interventions and outcome measures.
Main conclusion of review authors	Pilkington et al. (2005) concluded "the evidence for the effectiveness of homeopathy in depression is limited due to a lack of clinical trials of high quality...the adverse effects reported in the studies were congruent with the literature on the safety of homeopathy, suggesting that homeopathic medicines may provoke adverse effects but these are relatively rare, mild and transient, although there is probably under-reporting." (p. 158).

Other issues	Overall there was restricted impact of homeopathy treatment for depression

EVIDENCE STATEMENTS AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Evidence statement

Rating of D more appropriate: The above table states that nether study met all the methodological criteria, and that studies were not excluded on the basis of quality. 'Review method is sound' is not correct.

Key question	Rating	Justification
Evidence Base	C	The review method is sound but there are only two relevant included studies of poor quality
Consistency	D	See above comment on heterogeneity
Clinical impact	D	see 'Other issues' above

Included primary literature

- Huelluy (1985) in an unpublished study translated from French, reports an RCT (non-blinded) of 60 subjects under consultation for depression, postmenopausal involution or thymo-effective dystonia. Non-individualised *L72* (constituents not specified) (20 drops 4 times daily for 31 days dose increased if required) was the intervention, compared to Diazapam. This was a poor quality study as the method of allocation concealment was not reported, nor was blinding or loss to follow up. Jadad score 1/5
    - *Outcomes:* L72 was as effective as diazepam on all outcome measures. There were two cases of drowsiness on L72 and two for diazepam.
- Katz et al. (2005) is an RCT pilot (triple arm parallel group, double blind, double dummy) with 11 subjects with major depressive episode of moderate severity and duration of four or more weeks. A limited list of 30 remedies was prescribed by a trained homeopath using decision support software. Jadad score 1/5
    - *Outcomes:* Were not reported due to low numbers recruited (N=11) and completing (n=6).

References

Included systematic reviews

Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J. 2005. Homeopathy for depression: a systematic review of the research evidence. *Homeopathy* 94, 153-163.

Primary included studies

Heulluy B. 1985. Random trial of L.72 with Diazepam 2 in cases of nervous depression. Essai randomise ouvert de L 72 (specialite homopathique) contre diazepam 2 dans les etats anxiodepressifs. *Metz: Laboratoires Lehning*, Unpublished study [translation obtained by Pilkington et al. (2005)]

Katz T, Fisher P, Katz A, Davidson J, Feder G. 2005. The feasibility of a randomised, placebo-controlled clinical trial of homoeopathic treatment of depression in general practice. *Homeopathy* 94(3), 145-152.

- RCT evidence related to the management of depression secondary to an illness (reported in the evidence summary for chronic fatigue syndrome)
    - Awdry R. Homoeopathy and chronic fatigue—the search for proof. *Int J Alternat Complement Med* 1996: 19–21.
        - (same RCT also reported in Awdry R. Homoeopathy may help ME. *Int J Alternat Complement Med* 1996: 12–16).

Dermatological conditions

Executive summary

Two systematic reviews were identified (Category 3), which investigated the effectiveness of homeopathic treatments for dermatology.

- Simonart et al. (2011) focused on the efficacy of homeopathy for a range of dermatological conditions (warts, seborrhoeic dermatitis, atopic eczema, minor recurrent aphthous ulceration, leg ulcers / varicose veins, uraemic pruritus, candidiasis)
- Altunc (2007) reported on the management of warts in children with homeopathy, as part of a wider review into the effectiveness of homeopathy for childhood ailments.

Key systematic review: Because of its recency and its focus on a range of dermatological conditions, the Simonart et al. (2011) review was considered to be the key evidence source. This review included 11 relevant primary studies relating to a number of dermatological conditions:

- one RCT and two comparative trials for atopic eczema (Siebenwirth et al. 2009, Keil et al. 2008, Witt et al. 2009) (Total 277 children and adolescents; comprising 24 subjects 14-18 years, 118 subjects aged younger than 17 years, 135 children aged 1-14 years)
- one RCT for leg ulcers/ varicose veins (Garrett et al. 1997) (N=23 older adults)
- one RCT for minor recurrent aphthous ulceration (Mousavi et al. 2009a) (N=100 adults)
- one RCT for seborrhoeic dermatitis (Smith et al. 2002) (N=41 adults)
- one RCT for uraemic pruritus (Cavalcanti et al. 2003) (N=28 individuals, age not specified)
- three RCTs for warts (Labrecque et al. 1992, Kainz et al. 1996, Villeda et al. 2001) (N=260 adults and children)
- one comparative trial for candidiasis (Witt et al. 2009) (N=150 individuals)

Other systematic review: Altunc et al (2007) considered the effectiveness of homeopathic treatment for a broad group of childhood ailments which included one dermatological condition (warts). Other conditions considered in this review included adenoid vegetation, ADHD, asthma, otitis media, conjunctivitis, diarrhea, post-operative pain and URTI. Altunc (2007) included only one primary study relevant to this condition (Kainz et al. 1996), which was also included in Simonart et al. (2011). Therefore, Altunc (2007) included limited supporting evidence for this evidence summary on the effectiveness of homeopathy for one dermatological condition in children (warts).

Conclusion: There is no convincing evidence presented in one comprehensive, recent systematic review, of the effectiveness of homeopathy for seven dermatological conditions (11 experimental studies) (number of subjects per condition reported in relevant studies above) (Grade C).

Methodological assessment of the key evidence

Validity issue	Comment: Simonart (2007)
The review question (PICO)	P: cutaneous diseases in children and adults I: homeopathy (not defined) C: any (not defined) O: any
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely. Data was retrieved from January 1962 until April 2011 from MEDLINE (National Library of Medicine), PubMed, Current Contents, HomInform (Glasgow) (database of references to journal articles and books on homoeopathy), reference lists, homoeopathic textbooks, contacts with homoeopathic manufacturers and follow-up suggestions from these contacts. There was no restriction on language. The search terms included homeop*, homeopathy, homeopathic, homotoxicology, alternative medicine, dermatology, skin, skin disease(s), cutaneous, acne, atopic, atopy, carcinoma, dermatitis, eczema, melanoma, molluscum contagiosum, mollusca contagiosa, pruritus, psoriasis, urticaria, verruca, wart(s).
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. Comparative controlled trials were sought
Were the included studies sufficiently valid for the type of question asked?	Yes. Study quality was assessed by concealment of allocation, blinding of outcome assessment and handling of withdrawals and dropouts. Authors considered sample size adequacy, comparability of treatment groups at baseline, overall quality of reporting, and data handling. Studies were not excluded based on quality.
Were the results similar from study to study?	No. Studies were heterogeneous in terms of diagnosis, outcomes and interventions. As reported by the review authors: "a very limited number of trials investigating homoeopathic treatments for cutaneous diseases. Overall, of the 12 trials with interpretable results, nine trials indicated no positive effects of homoeopathy. The three trials showing a positive effect were of low methodological quality" (p. 897).
How are the results presented?	A summary for each included study was provided in Table 1 "Details of included placebo controlled trials" (p. 899). This table included drug, duration and treatment duration, participants and dropouts (age), study design, study outcomes, p value and comments.
Main conclusion of review authors	The authors concluded that "Reviewed trials of homoeopathic treatments for cutaneous diseases were highly variable in methods and quality. We did not find sufficient evidence from these studies that homoeopathy is clearly efficacious for any single dermatological condition" (p. 897).
Other issues	The authors identified no comparative (controlled) trials investigating the efficacy of homoeopathy in a range of common skin diseases, such as acne, mollusca contagiosa, psoriasis, urticaria, melanoma or nonmelanoma skin cancers. Thus this review did not report on the effectiveness of homeopathy for these conditions

Summary findings

	Study findings	*Interpretation*
Warts	No differences between groups	Homeopathy = placebo (3 studies)
Seborrhoeic dermatitis	Significant improvement favouring homeopathic group	Homeopathy > placebo (1 study)
Atopic eczema	No significant differences	Homeopathy=placebo (1 study) Homeopathy=conventional therapy (2 studies)**NB clinicians rated improvement as significant, although parents did not, in one study
Minor recurrent aphthous ulceration	Significant differences favouring homeopathy, for ulcer size and pain	Homeopathy> placebo (1 study)
Leg ulcers / varicose veins	No significant differences	Homeopathy = placebo (1 study)
Uraemic pruritus	Slightly better findings in the homeopathic group in reduction in pruritus score (but not significant between groups)	Homeopathy> placebo (1 study)
Candidiasis	Significant differences in culture-free status, and discomfort, favouring conventional therapy	Homeopathy < conventional therapy (1 study)

Evidence statement NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review method is sound, however, the 11 relevant included studies are of variable quality and deal with a range of dermatological conditions and homeopathic interventions.
Consistency	B	The findings are generally consistent within and between conditions, with homeopathy consistently providing scant evidence of effectiveness. Uncertainties can be explained by constrained study quality and small numbers of included studies per condition. See comments above on heterogeneity in the summary table of findings.
Clinical impact	D	Please see sections '*Main conclusion of authors*', '*how are the results presented?*' and '*Other issues*' above.

Included primary literature

Seborrhoeic dermatitis

- Smith et al. (2002) applied homoeopathic mineral therapy (*potassium bromide 1X, sodium bromide 2X, nickel sulphate 3X, sodium chloride 6X*) for 10 weeks in a RCT to 41 adults, in a study plagued by high dropouts in both groups. Jadad score 3/5
    - *Outcome:* Significant improvement in symptoms favouring homeopathic group

Atopic eczema

- Siebenwirth et al. (2009) applied individually selected homoeopathic remedies for 32 weeks, compared with placebo, for 24 young adults (18–35 years) with atopic eczema using a RCT, challenged by a high percentage of ineligible patients and high proportion of dropouts. Moderate Risk of Bias
    - *Outcome:* No significant differences between groups in symptom scores, quality of life, coping, global assessment of treatment success
- Keil et al. (2008) applied individually selected homoeopathic remedies for 12 months for 118 children (<17 years), in a prospective multicentre comparative observational nonrandomised study, compared with conventional therapy. Quality score not given.
    - *Outcome:* There was no significant difference between groups in eczema signs and symptoms as assessed by parents, although there were significant findings when clinicians compared outcomes between groups
- Witt et al. (2009) applied individually selected homoeopathic remedies for 12 months, compared with conventional medicine, in a prospective multicentre comparative observational nonrandomised study, on 135 children (1-14 years). High Risk of Bias
    - *Outcome:* No difference between groups

Minor recurrent aphthous ulceration

- Mousavi et al. (2009a) applied a moderate quality single-blind randomised clinical trial testing individually selected homoeopathic remedies with placebo to 100 individuals (>18 years), with 1-5 aphthous ulcers of less than 24 hours duration. Moderate Risk of Bias
    - *Outcome:* significant differences between groups, favouring homeopathy, for ulcer size and pain

Leg ulcers / varicose veins

- Garrett et al. (1997) applied *sulphur, silica and carbo-vegetabilis 6 cH* to 23 adults (53-87 years) in an open trial, compared with placebo. Study quality was poor, with no blinding, poor randomization, small number of patients, non- homogeneous groups and variable treatment duration. Moderate Risk of Bias
    - *Outcome:* no significant difference in ulcer size

Uraemic pruritus

- Cavalcanti et al. (2003) applied individually selected homoeopathic remedies for 2 months to 28 patients with uraemic pruritus using a randomised controlled trial design. The quality was constrained by older mean age and higher dialysis group in the control group. Moderate Risk of Bias
    - *Outcomes:* There were no significant differences between groups; however, the reduction in pruritus score was slightly better in the homeopathic group.

Candidiasis

- Witt et al. (2009) used a prospective, randomised trial to compare individually selected homoeopathic remedies with conventional therapy for 12 months in 150 individuals with

candidiasis. The study quality is uncertain with high drop-out rate, and uncertain blinding techniques. High Risk of Bias

- *Outcomes:* significant differences between groups in culture-free status, and discomfort, favouring conventional therapy

Warts

- Labrecque et al. (1992) used a RCT to investigate the effectiveness of *Thuya 30 cH* plus *antimony crudum 7 cH* plus *nitricium acidum 7 cH* for duration of 6 weeks in 174 adults and children with ordinary warts on their feet. Jadad score 4/5.
  - *Outcome:* There was no difference between groups in reducing the number and spread of warts
- Kainz et al. (1996) used a parallel arm RCT of moderate quality to investigate individualised homeopathic remedies in 60 children (8-9 years) with ordinary warts on the back of their hands, compared with placebo. Jadad score = 4/5
  - *Outcome:* there were no differences between groups in reducing the size and spread of warts. There was one adverse effect reported in homeopathic group and two in the placebo group.
- Villeda et al. (2001) used a double blind clinical trial of 26 adults and children to compare *Thuya 6 cH* applied for one month, with placebo, to ordinary warts anywhere on the body (quality constrained by lack of evidence of randomisation). Quality score not stated.
  - *Outcomes:* There were no significant differences in outcomes between groups

References

Included systematic reviews

Altunç U, Pittler MH, Ernst E. 2007. Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic proceedings. Mayo Clinic* 82, 69-75.

Simonart T, Kabagabo C, De Maertelaer V. 2011. Homoeopathic remedies in dermatology: a systematic review of controlled clinical trials. *British Journal of Dermatology* 165, 897-905.

Primary included studies

Cavalcanti AM, Rocha LM, Carillo R Jr et al. 2003. Effects of homeopathic treatment on pruritus of haemodialysis patients: a randomised placebo-controlled double-blind trial. *Homeopathy* 92, 177–81.

Garrett B, Harrison PV, Stewart T, Porter I. 1997. A trial of homoeopathic treatment of leg ulcers. *J Dermatolog Treat* 8, 115–17.

Kainz JT, Kozel G, Haidvogl M, Smolle J. 1996. Homoeopathic versus placebo therapy of children with warts on the hands: a randomized, double-blind clinical trial. *Dermatology* 193, 318–20.

Keil T, Witt CM, Roll S et al. 2008. Homoeopathic versus conventional treatment of children with eczema: a comparative cohort study. *Complement Ther Med* 16, 15–21.

Labrecque M, Audet D, Latulippe LG, Drouin J. 1992. Homeopathic treatment of plantar warts. *CMAJ* 146, 1749–53.

Mousavi F, Mojaver YN, Asadzadeh M, Mirzazadeh M. 2009a. Homeopathic treatment of minor aphthous ulcer: a randomized, placebo controlled clinical trial. *Homeopathy* 98, 137–41.

Siebenwirth J, Lu¨dtke R, Remy W et al. 2009. Wirksamkeit einer klassischhomoeopathischen Therapie bei atopischem Ekzem. Eine randomisierte, placebokontrollierte Doppelblindstudie. *Forsch Komplementmed* 16, 315–23.

Smith SA, Baker AE, Williams JH. 2002. Effective treatment of seborrheic dermatitis using a low dose, oral homeopathic medication consisting of potassium bromide, sodium bromide, nickel sulfate, and sodium chloride in a double-blind, placebo-controlled study. *Altern Med Rev* 7, 59–67.

Villeda LL, Dorantes GL, Gonzalez FB. 2001. Thuja occidentalis homeopatica vs placebo en verrugas vulgares. *Dermatol Rev Mex* 45, 14–18

Witt A, Kaufmann U, Bitschnau M et al. 2009. Monthly itraconazole versus classic homeopathy for the treatment of recurrent vulvovaginal candidiasis: a randomised trial. *BJOG* 116, 1499–505.

Witt CM, Brinkhaus B, Pach D et al. 2009. Homoeopathic versus conventional therapy for atopic eczema in children: medical and economic results. *Dermatology* 219, 329–40.

Fibromyalgia

Executive Summary

Seven systematic reviews were identified in Categories 1-3, which investigated the effectiveness of homeopathic treatments for fibromyalgia. Five reviews were published since 2009.

- One Category 1 review (Perry 2010) focused specifically on the effectiveness of homeopathic treatment on fibromyalgia.
- Four Category 2 reviews (Baranowsky 2009, De Silva 2010, Holdcraft 2003, Porter 2010) considered the effectiveness of CAM interventions for fibromyalgia.
- Two Category 3 reviews investigated homeopathy for multiple psychiatric conditions (Davidson 2011), and arthro-rheumatic diseases (Bellavite et al. 2011)

Key systematic review: The Perry review was deemed to be the key evidence source for this condition, as it was the only one to focus entirely on studies of homeopathy as a treatment for fibromyalgia. It included four randomised controlled trials reported in five publications (Fisher 1986, 1989, Bell 2004a,b, Relton 2009).

Other systematic reviews

Category 2 reviews

a) Baranowsky et al. (2009) investigated the effectiveness of complementary and alternative medicines (CAM) on fibromyalgia, using RCTs. The authors searched Embase, Medline, Pubmed, PsychInfo, Cochrane central register of controlled trials and Cambase up until June 2007. Inclusion criteria were studies which assessed fibromyalgia patients diagnosed by the American College of Rheumatology (ACR) criteria, and confirmation of diagnosis by these criteria included in the study protocol, randomisation performed (excluding studies with a within-subject design), at least one of the interventions could be attributed to the CAM field and between-group analysis on post-treatment results was reported. A range of CAM interventions was investigated. For homeopathy, only the Bell (2004a) study was identified (which had been identified in the key review). The authors concluded that "These results show homeopathy to be a promising option in the treatment of fibromyalgia. Yet, further clinical trials are needed to confirm these findings with bigger sample sizes and follow-ups and to create an eventual evidence-based basis for homeopathic treatment in fibromyalgia" (p. 11).

If Bell 2004a is already identified in Perry (key review), this report should not be used as results are being duplicated.

b) De Silva et al. (2010) investigated the effectiveness of complementary and alternative medicines (CAM) on fibromyalgia, using RCTs identified in searches to 2009, from EMBASE Ovid MEDLINE, Allied and Complementary Medicine, EBM Reviews, and DARE. Methodological quality was assessed using the Jadad scale. Three relevant studies for homeopathy were identified (Fisher 1986, Fischer et al. 1989, Bell et al. 2004a), all of which were identified in the key review. The authors concluded that there was insufficient evidence for any CAM intervention to make a conclusion on efficacy regarding treatment of fibromyalgia.

If Fisher 1986, Fisher et al 1989 and Bell 2004a are already identified in Perry (key review), this report should not be used as results are being duplicated.

Holdcraft et al (2003) reported 'CAM therapies have neither well designed studies nor positive results and are not currently recommended for FMS treatment'

c) Holdcraft et al. (2003) investigated the effectiveness of CAM interventions on fibromyalgia. These authors sought English language articles from a search until 2002 of Medline, Biosis, Embase, Cinahl, Alternative Medicine Alert, and the Cochrane central register of controlled trials. They sought studies applying CAM, acupuncture, traditional Chinese medicine, reiki, massage, chiropractic, osteopathy, ayurveda, botanical medicine, plant medicine, plant, energy therapy, biofeedback, relaxation and hypnotherapy. These authors identified Fisher et al. (1989) as the only eligible study on homeopathy, this study already being identified in the key review. The authors suggested that on the basis of this one study, the evidence for homeopathy was limited, but should be further investigated.

If Fisher et al 1989 is already identified in Perry (key review), this report should not be used as results are being duplicated.

d) Porter et al. (2010) reviewed the current literature related to alternative and complementary treatments for Chronic Fatigue Syndrome and fibromyalgia. The authors searched MEDLINE, Psych INFO, PubMed, Social Science Citation index, and the Cochran database of systematic reviews for randomised and non-randomised controlled trials regarding adults and children. Quality assessment of included studies was by the Jadad scale. This review identified two studies (Fisher et al. 1989, Bell et al. 2004a) which had also been identified by the key review. It identified one new RCT (Teitelbaum et al. 2001). The review authors concluded that "treatment types are often heterogeneous between studies and between individuals within studies. Given the limited number of studies and mixed outcomes, no conclusions can be offered on this treatment type, although the mainly positive results suggest potential for future research" (p.241).

If Fisher et al 1989 and Bell 2004a are already identified in Perry (key review), only the new RCT (Teitelbaum et al 2001) should be used to prevent results being duplicated.

Porter et al concluded: ....*Due to methodological inconsistencies across studies and the small body of evidence, no firm conclusions can be made at this time. Regarding alternative treatments, acupuncture and several types of meditative practice show the most promise for future scientific investigation. Likewise, magnesium, l-carnitine, and S-adenosylmethionine are nonpharmacological supplements with the most potential for further research. Individualized treatment plans that involve several pharmacological agents and natural remedies appear promising as well.*

Category 3 reviews

e) Davidson (2011) investigated homeopathy interventions (individualised, formulaic (unnamed) or *Argentium nitricum)* for psychiatry. Fibromyalgia was one of a number of conditions for which the effectiveness of homeopathy was tested, the others being sleep problems, stress and anxiety, ADHD, PMS, mild TBI, functional somatic symptoms described as chronic fatigue. Davidson (2011) searched from database inception to 2010 in the follow databases: PubMed, CINAHL, PsycInfo, HomInform, Cochrane CENTRAL, Clinical Trials.gov and the Nation Centre for Complementary and Alternative Medicine Grantee Publications Database. Davidson (2011) identified three primary studies relevant to the review question (Fisher 1986, Fisher et al. 1989, Bell 2004a), all of which had been identified in the key review. Davidson (2011) concluded that despite a limited number of studies of homeopathy and placebo in psychiatry, the results do not preclude the possibility of some benefit. For fibromyalgia specifically, there was marginal evidence of effectiveness.

If Fisher 1986, Fisher et al 1989 and Bell 2004a are already identified in Perry (key review), this report should not be used as results are being duplicated.

f) Bellavite et al. (2011) conducted a comprehensive search of the past 30 years of research into the effectiveness of individualised homeopathy, and ailment-specific homeopathic remedies and complexes, for arthro-rheumatic diseases. These authors identified all four primary studies which were also included in the key evidence source. These authors reported positive evidence for individualised homeopathy in fibromyalgia (Fisher et al. 1989, Bell et al. 2004, Relton et al. 2009) and no evidence of effectiveness for fibromyalgia *Arnica, RHUS TOX* or *BRYONIA* 6C (Fisher 1986).

Summary of location of primary papers in reviews

	Perry (2010)	Baranow-sky 2009	De Silva (2010)	Holdcraft 2003	Porter 2010	Davidson 2011
Fisher 1986	√		√			
Fisher 1989	√		√	√	√	√
Bell 2004a	√	√	√		√	√
Bell 2004b	√					
Relton 2009	√					
Teitelbaum et al 2001					√	

Typographical error: Bellavite 2011 not included here

Conclusion: One good quality recent key systematic review which focused on homeopathy and fibromyalgia, and six recent secondary systematic reviews which had broader foci than simply homeopathy and fibromyalgia, reported on five moderate quality experimental studies (reported in six papers) (including up to 265 individuals with fibromyalgia). The total study numbers are unclear because of mixed sample with Chronic Fatigue Syndrome and Fibromyalgia, in Teitelbaum et al. (2001), *which was included in the review by Porter et al. (2010).*

The term 'encouraging evidence' is not defined in this report. There are inconsistencies as to how it is interpreted.

There is encouraging evidence to suggest that homeopathy may have benefits in the treatment of fibromyalgia. However further research is required to clarify the benefits, and it should attempt to address the biases identified in the primary studies included in the reviews (Grade C).

EXPERT COMMITTEE HAS NOT ADVISED ON THE CONCLUSION ABOVE

This conclusion is flawed - see Evidence Statement. Given the Evidence Statement may have been rated C, D, D, there is a likelihood that this conclusion would differ from that above, and that the grading would be closer to a 'D' than a C. This conclusion admits that there are biases in the evidence and that further research is needed to clarify the benefits

There are really only six primary studies contributing to this outcome, variations of combinations of these make up the systematic reviews described above.

There is a risk that the conclusion reached by Perry is being amplified unnecessarily and incorrectly by the Contractor's method of presenting the authors' conclusions of the seven systematic reviews above. It would be more correct to report only on Perry (2010) and add any significant outcomes from the Teitelbaum (2001) study.

The CEBM appraisal below does just focus on Perry (2010).

Methodological assessment of the key evidence source

Validity issue	Comment: Perry (2010)
The review question (PICO)	P: fibromyalgia (not defined) I: homeopathy (not defined) C: any (not defined) O: rating scales and performance measures
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely The following databases were searched up to August 2009; MEDLINE, EMBASE and PSYCHINFO via the OVID interface, CINAHL and AMED via the EBSCO interface and CENTRAL via the Cochrane library Search terms were MeSH and text based
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. Included studies were RCTs.
Were the included studies sufficiently valid for the type of question asked?	Unclear. RCT quality was evaluated using the Jadad score, reported for the included studies listed above, as 3,3,4,2. Studies were not excluded based on quality.
Were the results similar from study to study?	No. Studies were heterogeneous and plans for meta-analysis were abandoned due to this (p. 458)
How are the results presented?	A summary for each included study was provided in Table 1 "Results Table" (p. 460). This included sample size, participant groups, treatment schedules, assessment schedules, type of analysis and measure, main results.
Main conclusion of review authors	Perry et al. (2006) concluded "None of the (included) trials was without serious flaws. Invariably, their results suggested that homoeopathy was better than the control interventions in alleviating the symptoms of FM. Independent replications are missing. Even though all RCTs suggested results that favour homoeopathy, important caveats exist. The effectiveness of homeopathy as a symptomatic treatment for fibromyalgia remains unproven" (p. 457).
Other issues	All studies included in this systematic review reported evidence supporting the effectiveness of homoeopathy compared to placebo or to usual care. However, the quality of the studies varied and therefore it is feasible that there were Type 1 errors in interpretation of the findings.

Evidence statement EVIDENCE STATEMENTS AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review methods are sound but the included studies are of variable quality. Unclear risk of bias. Studies were not excluded based on quality.
Consistency	C	Heterogeneity of studies suggests some inconsistency reflecting genuine uncertainty around clinical question
Clinical impact	C	see 'Main conclusion of review authors' and 'Other issues' above

CONSISTENCY : This should be a 'D', given the CEBM assessment reports 'studies were heterogeneous and plans for any meta-analysis were subsequently abandoned'. According to the FORM matrix, this should be classified as 'evidence is inconsistent' and rated 'D'

CLINICAL IMPACT : this refers the reader to the systematic review authors' conclusion rather than the Contractor undertaking any synthesis and interpretation themselves.

Given Perry has stated that '*important caveats exist. The effectiveness of homeopathy as a symptomatic treatment for fibromyalgia remains unproven*' , a grading of D: slight or restricted clinical impact seems more appropriate (as opposed to a 'moderate' or 'satisfactory' clinical impact).

University of South Australia

Primary included studies

- Fisher (1986) tested 24 adults in an RCT with active homeopathic interventions (*Arnica 6c or Bryonia 6 or Rhus tox 6c)*, or placebo. It was a moderate quality study (Jadad score 3/5)
    - Outcomes: "Analysis of the differences between groups in terms of pain and sleep measured by visual analogue scales (VAS) showed no significant effects: p=0.19, p=0.078, respectively. However, when broken down to distinguish between well-indicated remedies as opposed to poorly indicated remedies there were significant differences (p<0.05) in pain scores and in sleep scores (at 2 and 3 months) for those participants whose remedies were optimal fits. There was no significant difference in tender spot counts between groups and analgesic consumption results were not reported" (p. 458).
- Fisher et al. (1989) tested 60 individuals in a cross-over design trial with either *Rhus tox 6c* or placebo. It was a moderate quality study (Jadad score 3/5)
    - *Outcomes:* "At the end of the treatment period, the number of tender points in the placebo group was significantly higher than in the experimental group (p<0.005). Improvements in pain and sleep, measured by a combined VAS, was also significantly greater for the rhus tox group compared to the placebo group (p=0.0052). A re-analysis of Fisher's data was published by Colquon (1991). Distribution-free randomisation tests were applied separately to the scores of pain, sleep and tender points and no significant treatment effects after the first treatment period was found" (p. 459).

      Reference: Colquhoun D (1990) Re-anaylsis of clinical trial of homeopathic treatment in fibrositis. Lancet 336:441–442
- Bell (2004 a, b) tested 62 individuals with *LM1* daily dose of individual remedy, increasing to *LM2, LM3* as necessary, or placebo. It was a high quality study (Jadad score 4-5/5)
    - *Outcomes:* Positive effect on symptoms. "When adjusted for baseline depression and anger/hostility scores, there was a significant reduction in tender point count, tender point pain on palpation in homoeopathic group. FM scores improved significantly, as did global health rating after receiving homoeopathic treatment compared to placebo" (Table 1 p. 460).
- Relton (2009) tested 47 individuals with individualised homeopathy, or placebo. It was a low quality study (Jadad score 2/5).
    - *Outcomes:* Significant greater reduction in the FIQ total score in the homoeopathic care group compared to usual care Non-significant difference in pain score.
- Teitelbaum et al (2001) considered the effectiveness of multiple homeopathic agents for mixed chronic fatigue syndrome and fibromyalgia in 72 individuals. The study was of good quality (Jadad score 5/5)
    - *Outcomes:* Positive effect of on symptoms

References

Included systematic reviews

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Davidson JR, Crawford C, Ives JA, Jonas WB. 2011. Homeopathic treatments in psychiatry: a systematic review of randomized placebo-controlled studies (Provisional abstract). *Journal of Clinical Psychiatry* [Online]. Available: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12011004329/frame.html.

De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ, Arthrit Res, U. K. W. G. C., Arthritis Research, U. K. W. G. O. C., Alternative, M. & On Behalf Of The Arthritis Research, U. K. W. G. O. C. 2011. Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. *Rheumatology (Oxford, England),* 50, 911-920.

Holdcraft LC, Assefi N, Buchwald D. 2003. Complementary and alternative medicine in fibromyalgia and related syndromes. *Best Pract Res Clin Rheumatol,* 17, 667-83.

Perry R, Terry R, Ernst E. 2010. A systematic review of homoeopathy for the treatment of fibromyalgia (Provisional abstract). *Clinical Rheumatology* [Online]. Available: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12010005641/frame.html.

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. *Journal of Alternative & Complementary Medicine,* 16, 235-249.

Primary included studies

Fisher P. 1986. An experimental double-blind clinical trial method in homeopathy. Use of a limited range of remedies to treat fibrositis. *Br Homeopath J* 75(3), 142.

Fisher P, Greenwood G, Huskisson EC, Turner P, Belon P. 1989. Effects of homeopathic treatment on fibrositis (primary fibromyalgia). *Br Med J* 299, 365–366.

Bell IR, Lewis DA II, Brooks AJ. 2004a. Improved clinical status in Fibromyalgia patients treated with individualised homeopathic medicines versus placebo. *Rheumatology* 43(5), 577–582.

Bell IR, Lewis DA II, Brooks AJ, Schwartz GE, Lewis SE, Caspi O, Scott A et al. 2004b. Individual differences in response to randomly assigned active individualized homeopathic and placebo treatment in fibromyalgia: implications of a double-blinded optional crossover design. *J Altern Complement Med* 10(2), 269–283.

Relton C, Smith C, Raw J, Walters C, Adelbajo AO, Thomas KJ, Young TA. 2009. Healthcare provided by a homeopath as an adjunct to usual care for Fibromyalgia (FMS): results of a pilot randomised controlled trial. *Homeopathy* 98, 77–82.

Teitelbaum JE, Bird B, Greenfield RM, et al. 2001. Effective treatment of chronic fatigue syndrome and fibromyalgia: A randomized double-blind, placebo-controlled, intent-to-treat study. *J Chron Fatigue Syndr* 8, 3–28.

Hay fever, allergic rhinitis, pollinosis

Executive summary

Three systematic reviews were identified in Categories 1- 3 which investigated the effectiveness of homeopathic treatments for hay fever, pollinosis or allergic rhinitis.

- One Category 1 review (Ernst 2011), reported on the effectiveness of *Galphimia glauca* for hay fever.
- One Category 2 review (Passalacqua 2006) reported on the effectiveness of CAM (including homeopathy) for allergic rhinitis and asthma (the findings for asthma are reported elsewhere).
- One Category 3 review (Bellavite et al. 2011) which had been used as key evidence source for the evidence summary for asthma, considered the effectiveness of homeopathic treatment for groups of conditions which included allergic rhinitis, hay fever and pollinosis.

Key evidence sources: Ernst (2011) and Bellavite (2011) were identified as key evidence sources because of the comprehensive focus taken on searching the literature for evidence for homeopathy for allergic rhinitis, hay fever and pollinosis.

- Ernst (2011) identified four relevant experimental studies (Wiesenauer, Häussler & Gaus 1983, Wiesenauer & Gaus 1985, Wiesenauer, Gaus & Häussler 1990, Wiesenauer & Lüdtke 1995).
- Bellavite et al. (2011) considered the past 30 years of research into the effectiveness of homeopathic medicines for the treatment of respiratory allergies, common upper respiratory tract infections, otorhinolaryngologic complaints, and rheumatic diseases. This work supersedes the Bellavite 2006a and b, and the 2008 reviews. It identified 22 relevant studies, three of which had also been identified by Ernst (2011) (See study summary table below).

Other evidence source: The Passalacqua review (2006) was reported for validation purposes, as this review contained all the references reported by the key evidence sources. Medline and the Cochrane Library were searched to March 2005, using key words: Asthma [OR] Rhinitis, [AND] Complementary [OR] Alternative Medicine, [OR] Herbal, [OR] Acupuncture, [OR] Homeopathy, [OR] Alternative Treatment). The methodological quality of studies was assessed with the Jadad scale. This study identified seven experimental studies relevant to allergic rhinitis, all of which been identified by either Ernst (2011) or Bellavite (2011).

Passalacqu et al concluded that "Some positive results were described in rhinitis with homeopathy in good-quality trials, but an equal number of negative studies counterbalance the positive ones. Therefore it is not possible to provide evidence-based recommendations for the use of homeopathy to treat allergic rhinitis, and further randomized controlled trials are needed." (p. 1060)

Conclusion: Of the adult studies, 15 studies of 1684 individuals indicated positive results favouring homeopathy (9 RCTs, 4 prospective observational studies, 1 case series). Seven studies of 1677

individuals reported equivocal results between homeopathy and control (2 RCTs, 3 non-randomised controlled trials, one non-randomised controlled clinical trial). Of the two experimental studies on children, one RCT (N=73) showed adverse effects of homeopathy, and one non-randomised controlled trial (N=70) found positive effects favouring homeopathy.

Thus, from two good quality systematic reviews reporting on 22 primary experimental, observational and case series studies of 3415 adults, and two experimental studies of 143 children, there is inconclusive and equivocal evidence regarding the effectiveness of homeopathy for the treatment of hay fever, pollinosis and allergic rhinitis (Grade C).

Summary of sources of primary evidence

	N	Design	*Ernst 2011a*	*Passalacqua 2006*	*Bellavite 2011*
Aaabel, Laerum et al. 2000	66	RCT		√	√
Aabel 2000	73 Children	RCT		√	√
Aabel 2001	51	RCT			√
Ammerschlager, Klein et al. 2005	739	Non-randomised clinical trial			√
Connert & Maiwald 1991	26	Prospective observational			√
Colin 2006	147	Case series			√
Gassinger 1981	53	Non-randomised controlled trial			√
Goossens, Laekeman et al. 2009	46	Prospective observational			√
Hardy 1984	70	RCT			√
Kim et al 2005	40	RCT		√	√
Maiwald 1988	170	Non-randomised controlled trial			√
Micciché, Trapani et al. 1998	70 Children	Non-randomised controlled trial			√
Nolleveaux 1992	108	Prospective observational			√
Reilly et al 1986	144	RCT		√	√
Schmiedel and Klein 2006	397	Non-randomised clinical trial			√
Sprenger 1989	65	Prospective observational			√
Taylor et al 2000	50	RCT		√	√
Weiser, Gegenheimer et al. 1999	146	Non-randomised controlled trial		√	√
Wiesenauer & Gaus 1985	164	RCT	√	√	√
Wiesenauer Haussler, Gaus 1983		RCT	√		
Wiesenauer, Gaus,		RCT	√		

Häussler 1990					
Wiesenauer & Lüdtke 1987	132	RCT			√
Wiesenauer & Lüdtke 1995	115	RCT	√		√
Witt, Keil et al. 2005	178	Non-randomised controlled trial			√

Methodological assessment of the key evidence sources

Validity issue	**Comment: Ernst (2011a)**	**Comment: Bellavite et al. (2011)**
The review question (PICO)	P: individuals with hay fever I: *Galphimia glauca* (GG) C: any (not defined) O: any symptoms	P: adults and children with allergic rhinitis/ pollinitis, hay fever I: homeopathically prepared remedies C: any (not defined) O: any symptoms
Is it unlikely that that important, relevant studies were missed?	Unclear. This is an update review of a 1997 meta-analysis. Searching included an electronic literature search in January 2010 (using MEDLINE and EMBASE), as well as consultations with experts in the field, a check of bibliographies of other reviews of homeopathy, and a hand-search of reference lists and private files of the author Only studies which reported on this one homeopathic intervention were included	Yes, it is unlikely. The review sought experimental research on humans, published between 1978 and 2010. Data came from "current reading of major complementary and alternative medicine journals, screening of the Hominform Information Service databases (British Homeopathic Library, http://hominform.soutron.com/), literature searches using Medline, the Cochrane Database of Systematic Reviews, and cross-referencing between published papers" (p. 1364). The authors also "consulted previously published systematic reviews and meta-analyses that have covered trials of immunoallergology" (p. 1364). "All forms of homeopathic therapy were included in the review, namely: a) classical individualised homeopathy, b) ailment-specific remedies and complexes, c) isotherapy where indicated" (p. 1364).
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. Randomised control trials were sought.	Yes. The selection criteria are clearly stated. "Analysis included controlled clinical trials (with and without randomisation), observational studies and case series, but excluded single case reports" (p. 1364).
Were the included studies sufficiently valid	Yes There were only four studies which met the inclusion criteria,	Unclear. The included studies were not assessed for methodological quality, only described by

Sample sizes small - apart from two studies with N=397 and 739, the rest of the studies had N < 200, and 11 studies < 100 participants.

for the type of question asked?	which were assessed using the Jadad score (in chronological order 5,5,4,4). Studies not excluded based on quality. However Intention to treat analysis did not occur in any study (Table 1, p. 201).	experimental design, evidence source and study population. All studies assessed classical individualised homeopathy using experimental designs which variably including randomisation and controlling.
Were the results similar from study to study?	No. Findings differed depending on the dilution of homeopathic intervention, and outcome measures	No. Studies are heterogeneous in terms of populations and interventions, and outcomes.
How are the results presented?	Characteristics of included studies are included in Table 1 (p. 201), reporting study design, sample size, Jadad score, experimental and control interventions, intention to treat analysis, outcomes, main results and comments.	Characteristics of included studies are included in Table 1 (p. 1366), reporting authors, study design, participant type and N, treatment, outcomes and key results. Study findings are summarised in Table 4 (p. 1381) as strength of the body of evidence per condition, with the study name and type, and peer-reviewed journal source identified
Main conclusion of review authors	"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" (p. 202-203).	"The best evidence of effectiveness is related to *Galphimia glauca* in allergic oculorhinitis, classical individualized homeopathy in allergic complaints and *Euphorbium compositum* in rhinitis-synusitis" (p. 1380). In Table 4 (p. 1381) the authors conclude there is conflicting evidence for homeopathic immunotherapy of allergic rhinitis
Other issues	"All RCTs were conducted and published by the same research group. Even though findings of the review seem to suggest efficacy, important caveats prevent any firm conclusions being made; it also casts doubt on the reliability of the conclusion of the published meta-analysis" (p. 200).	The authors indicate that "Pragmatic equivalence trials suggest that, in primary care, homeopathic treatment is not inferior to conventional treatment. A larger number of observational studies and of clinical trials-- conducted in a methodologically correct manner without altering the treatment setting-- are needed before sure conclusions concerning the application of homeopathy for specific diseases can be drawn." (p. 1363).

NOT CONFIRMED BY EXPERT COMMITTEE

Evidence statement Evidence base score more likely a C: there are a variety of study designs, and the risk of bias is poorly reported so it is unclear as to the quality of the studies.

Key question	Rating	Justification
Evidence Base	B	The review methods are sound, and report on 24 primary studies of variable quality
Consistency	D	See above comment on heterogeneity

No mention of heterogeneity by the Contractor - just referring to CEBM criteria. No analysis

Clinical impact	C-D	see answers to all questions above

CLINICAL IMPACT should be a D: ('slight or restricted') given the statements above that there are important caveats preventing reaching any firm conclusions and that there are doubts about the published meta-analysis. Bellavite also suggests more and higher quality observational studies need to be conducted

Summary of primary included studies

Adults

- Aabel, Laerum et al. (2000) conducted a RCT of 66 individuals with allergic rhinitis with Homeopathic birch pollen *Betula* 30c vs. placebo. Jaded score 4/5.
    - *Outcomes:* slightly less symptoms after 10 days, minor adverse events initially in verum group.
- Aabel (2000) treated 51 individuals with allergic rhinitis in an RCT using Homeopathic birch pollen *Betula* 30c vs. placebo. Jaded score 4/5.
    - *Outcome:* Verum and placebo had similar improvement.
- Ammerschlager, Klein et al. (2005) in a non-randomised clinical trial of 739 individuals with rhinitis or sinusitis, applied Low-dilution homeopathic complex formulation *Euphorbium compositum*, nasal spray vs. xylometazoline. High risk of Bias score.
    - *Outcomes:* equivalence between groups.
- Colin (2006) in a case series of 147 individuals with respiratory allergies, treated with classical homeopathy. High risk of Bias score.
    - *Outcome*: improvement in 90% cases (uncontrolled).
- Connert & Maiwald (1991) in a prospective observational study of 26 individuals with rhinitis and nasal obstruction, applied *Euphorbium compositum.* Jadad score 3/5.
    - *Outcome:* Decrease of symptoms in most patients (uncontrolled).
- Gassinger (1981) in a non-randomised controlled trial of 53 individuals with acute rhinitis, applied *Eupatorium perfoliatum* 2x vs. aspirin. Quality score not stated.
    - *Outcome*: equivalence between groups.
- Goossens, Laekeman et al. (2009) conducted a prospective, observational, multicentre study of 46 individuals with allergic rhinitis with classical homeopathy. Quality score not stated.
    - *Outcomes*: Major improvement in symptoms between 3-4 weeks.
- Hardy (1984) in a RCT of 70 individuals with Allergic oculorhinitis (house dust) treated with Homeopathic immunotherapy (H.I.T.) made with house dust potencies. Quality score not stated.
    - *Outcomes*: HIT better than placebo.
- Kim, Riedlinger et al. (2005) used an RCT for 40 individuals with allergic rhinitis, with H.I.T. prepared from individual allergen vs. placebo. Jadad score 5/5.
    - *Outcomes:* Better clinical changes in verum group compared with placebo.
- Maiwald (1988) in a non-randomised controlled trial of 170 individuals with acute rhinitis, applied Homeopathic complex *Grippheel* vs. aspirin. High Risk of Bias score.
    - *Outcome*: equivalence between groups.
- Nolleveaux (1992) treated 108 individuals with Allergic oculorhinitis in a prospective observational study with *Pollen* 30c, *Apis* 15c, *Lunghistamine* 15c. Quality score not given.
    - *Outcomes*: most patients improved (uncontrolled).

- Reilly et al. (1986) conducted a RCT of 144 individuals with Allergic oculorhinitis (hay fever), treated them with *Pollens* 30c (H.I.T.) vs. placebo. Jadad score 5/5.
    - *Outcomes*: HIT group better outcome than placebo (so statistical information).
- Schmiedel and Klein (2006) in a prospective observational study of 397 individuals with acute rhinitis, applied Homeopathic complex *Engystol* vs. conventional treatment. Quality score not given.
    - *Outcome*: equivalence between groups.
- Sprenger (1989) in a prospective observational study of 65 individuals with acute and chronic rhinitis, applied low-dilution homeopathic complex formulation *Euphorbium compositum*, nasal spray. Moderate Risk of Bias score.
    - *Outcome:* Decrease of symptoms in 83% patients (uncontrolled).
- Taylor, Reilly et al. (2000) conducted a RCT of 50 individuals with allergic rhinitis with individual allergen 30c vs. placebo (HIT). Jadad score 5/5.
    - *Outcomes:* slightly better outcomes in verum group (no statistical data).
- Wiesenauer, Hausler et al. (1983) conducted a RCT of 207 individuals with hay fever treated with *Galphimia glauca* (GG-D4); dosage individualised. Duration: 39 days on average compared with placebo. Jadad score 5/5.
    - *Outcomes:* Significant differences between groups favouring homeopathy.
- Wiesenauer and Gaus (1985) in a RCT of 121 individuals with Allergic oculorhinitis treated with individualised doses of *Galphimia glauca D6* versus placebo (GG diluted by factor 10-6) or placebo. Jadad score 5/5.
    - *Outcomes*: Trend to better improvement in homeopathic group, but not significantly different between groups.
- Wiesenauer and Ludtke (1987) treated 132 individuals with allergic oculorhinitis in a RCT, with *Galphimia glauca* 2c vs. placebo. High Risk of Bias score.
    - *Outcomes:* significantly less symptoms in verum group.
- Wiesenauer, Gaus, Hausler et al. (1990) conducted a good quality RCT of 243 individuals with individualised dosage of *Galphimia glauca C2* versus placebo. Jadad score 3/5.
    - *Outcome:* statistically significant differences favouring homeopathy.
- Wiesenauer and Ludtke (1995) treated 164 individuals with allergic oculorhinitis with allergic oculorhinitis in a RCT, with *Galphimia glauca* 2 vs. placebo. High Risk of Bias score.
    - *Outcomes:* Significant relief in verum group.
- Weiser, Gegenheimer et al. (1999) conducted a non-randomised open trial of 146 individuals with allergic rhinitis with low-dilution homeopathic complex formulation *Luffa compositum* vs. chromolyn sodium. Quality score not stated.
    - *Outcomes:* equivalence between verum and allopathic groups.
- Witt, Keil et al. (2005) in a non-randomised clinical trial, of 178 individuals with Allergic diseases including rhinitis and asthma, with classical homeopathy versus conventional care. High Risk of Bias score.
    - *Outcomes:* better in the homeopathic group.

Children

- Aabel (2000) treated 73 children with allergic rhinitis in an RCT using Homeopathic birch pollen *Betula* 30c vs. placebo. Jadad score 4/5.

- *Outcome:* Verum had significantly worse effects than placebo.

- Micciché,Trapani et al.(1998) conducted a non-randomised controlled trial of 70 children with Allergic oculorhinitis with Homeopathic protocol based on three low-dilution drugs vs. conventional therapy. Quality score not stated.
  - *Outcome:* Trend to better improvement in the homeopathy group.

References

Included systematic review

Bellavite P, Marzotto M, Chirumbolo S, Conforti A. 2011. Advances in homeopathy and immunology: a review of clinical research. *Frontiers in Bioscience,* S3, 1363-1389.

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 on Alternative & Complementary Therapies* 16(3), 200-203.

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, 1054-62.

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Micciché G, Trapani GF, Lucamante M, Lanza C, Tanga L, Gallese A, Grasso RM, Totino T. 1998. Le oculoriniti allergiche in età pediatrica. *Cahiers de Biotherapie* 1(2), 13-18.

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Taylor MA, Reilly D, Lyewellyn-Jones RH, McSharry C, Aintchison T. 2000. Randomised controlled trial of homeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *BMJ* 321, 471-6.

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Wiesenauer M, Gaus W. 1985. Double-blind trial comparing the effectiveness of the homeopathic preparation Galphimia potentiation D6, Galphimia dilution 10(-6) and placebo on pollinosis. *Arzneimittelforschung* 35, 1745-7.

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Witt C, Keil T, Selim D, Roll S, Vance W, Wegscheider K, et al. 2005. Outcome and costs of homeopathic and conventional treatment strategies: a comparative cohort study in patients with chronic disorders. *Complement Ther Med* 13, 79–86.

Headache

Executive Summary

Three systematic reviews were identified in Categories 1-2, which investigated the effectiveness of homeopathic treatments for headaches.

- Two Category 1 reviews (Ernst 1999a, Owen 2004) both focused specifically on the effectiveness of homeopathy as a treatment for mixed headache types.
- One Category 2 review (Vernon 1999) considered the effectiveness of CAM for non-migrainous headache (i.e. excluding migraine, cluster and organic headaches).

Key systematic reviews: The two Category 1 reviews are considered together because of the diagnostic uncertainty regarding headache type classification. Neither is recent, with Ernst (1999a) being published over 10 years ago, and Owen (2004) eight years ago. The component studies in the reviews are listed below. There were no new experimental studies identified in the Owen (2004) review from the earlier Ernst (1999a) review. However Owen included two prospective observational studies (Muscari-Tomaioli 2001, Walach 2001). Only the experimental studies are summarised in this evidence review.

Typographical error: Muscari-Tomaioli (2001) and Walach (2001) should read Muscari-Tomaioli et al (2001) and Walach et al (2001)

Prospective observational studies represent level II study design - that is a good quality study design. Unsure why the Contractor excluded Muscari-Tomaioli (2001) and Walach et al (2001) based on study design.

Other systematic review: Vernon (1999) evaluated RCTs of complementary/alternative (CAM) therapies in the treatment of non-migrainous headache (i.e. excluding migraine, cluster and organic headaches). MEDLINE, PsycInfo and CINHAL databases were searched to 1998. RCTs for CAM therapies of the treatment of non-migrainous headache were identified and quality scored. The Walach (1997) study which had been identified in the key reviews was the only one included. The authors concluded on the basis of this trial that there was no evidence of effectiveness of homeopathy for headache of non-migranous type.

A summary of the sources of the included primary studies is provided below.

	Ernst (1999a)	Owen (2004)	Vernon (1999)
Brigo (1991)	√	√	
Straumsheim (1997)	√	√	
Whitmarsh (1997)	√	√	
Walach (1997)	√	√	√
Muscari-Tomaioli (2001)		√	
Walach (2001)		√	

Conclusion: There is no convincing evidence from two non-recent good quality key systematic reviews reporting on four RCTs of variable quality, on 284 individuals with migraine, or mixed migraine and tension-type headache, that homeopathy is effective (Grade C).

Inconsistencies in how the Contractor refers to dates of studies. There is an over-emphasis on Owen (2004) being a 'non-recent' review, for example in the review of Fibromyalgia, Holdcraft (2003) was not referred to in this way.

The CONSISTENCY element of the FORM matrix appears incorrect and should have a 'D' rating (see comment on p89). This would impact the grading of this conclusion and downgrade it to a D (given the other two FORM elements are graded C and D)

Methodological assessment of the Ernst and Owen reviews

Validity issue	Comment: Ernst (1999a)	Comment: Owen (2004)
The review question (PICO)	P: Migraine or tension-type headache I: homeopathy (not defined) C: placebo (not defined) O: any	P: three common types of headache, as determined by the International Headache Society (tension type headache, cervicogenic headache and migraine headache) I: homeopathy (not defined) C: placebo (not defined) O: any
Is it unlikely that that important, relevant studies were missed?	Unclear. The following databases were searched Medline, Embase, CISCOM, and the Cochrane Library (inception to August 1998). Search terms were text	Unclear Pre-MEDLINE/MEDLINE, MANTIS, Cochrane library, AMED to May 2002 Search terms were text
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. The review included randomised, placebo-controlled double-blind clinical trials of homeopathic treatments for headache	Yes. The selection criteria are clearly stated. The review included randomised, placebo-controlled double-blind clinical trials of homeopathic treatments for headache
Were the included studies sufficiently valid for the type of question asked?	Unclear. The included studies were evaluated using the five score Jadad tool. Studies were of variable quality (respectively 2,4,3,5). Studies were not excluded based on quality, but they were excluded if they were trials of one homeopathic potency against another, or trials of homeopathy versus other types of treatment.	Unclear The included studies were evaluated for quality using a 14 criteria tool modified from a tool published by Bronfort et al (2001) (quality ranging from 25% to 63% of total). Studies that used homeopathic preparations containing multiple homeopathic remedies or potencies, in single remedy dose, introduced other CAM therapies and/or introduced additional medical therapy for patients in the homeopathic treatment groups were excluded
Were the results similar from study to study?	No. There was one report of increased effectiveness of homeopathy versus placebo, two of no within- or between-group differences, and one of within-group differences but no between-group difference.	No. Only the findings of the experimental studies are considered for the purpose of this review. These were the same as reported in Ernst (1999a).
How are the results presented?	A summary for each included study was provided in Table 1 "Homeopathic Trials in Migraine and Headaches" (p. 355). This included sample size, Jadad score, description of patients,	A summary of each included study was provided in Table 2 "Clinical Trials of Homeopathy for Headache" (p. 47). This table reports headache type, study design, sample size, duration, intervention, outcomes.

Prospective observational studies represent level II study design - that is a good quality study design. Unsure why the Contractor excluded Muscari-Tomaioli (2001) and Walach et al (2001) based on study design.

	homeopathic treatments, drop outs, follow-up, outcome variables and results. Meta-analysis was not conducted.	Meta-analysis was not conducted.
Main conclusion of review authors	Ernst (1999a) concluded that "the trial data available to date do not suggest that homeopathy is effective in the prophylaxis of migraine or headache beyond a placebo effect." (p. 353).	Owen (2004) concluded "There is insufficient evidence to support or refute the use of homeopathy for tension type headache, cervicogenic headache and migraine headache" (p. 51).
Other issues	Headaches included in this review were of mixed type (three studies only of migraine, and one of migraine and tension-type headaches).	As for Ernst, including the definitional issue noted for Walach (1997)

Evidence statement

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

CONSISTENCY should be downgraded to D.

The CEBM appraisal on pp88 &89 states studies were not similar, reporting inconsistent directions of effect. It does not offer any explanations for the inconsistency.

Key question	Rating	Justification
Evidence Base	C	The review methods were sound but the included studies were of variable quality.
Consistency	B	Most studies are constant in reporting no effect, and inconstancy may be explained by elevated risk of bias in some primary studies.
Clinical Impact	D	Slight or restricted as indicated in the section on study result similarity, and the matter raised in 'Other issues'.

Summary of included primary studies

- Brigo (1999) conducted a poor quality RCT (Jadad score 2/5) on 60 people with migraine (not further defined), treating them with four single doses of 30C potencies of a choice of 6 remedies given orally in 2-week intervals.
  - *Outcomes*: significant improvement favouring homeopathy
- Straumsheim (1997) conducted a moderate-good quality RCT (Jadad score 4/5) on 63 individuals with migraine according to the IHS criteria, treated with a choice of 60 remedies in D30, D200, and 1M potencies prescribed individually at monthly consultations with a homeopath
  - *Outcome*: No intergroup differences in frequency, intensity, or duration of attacks or analgesic consumption. Only indication of difference (p=0.05) was neurologist's assessment of attack frequency
- Whitmarsh (1997) treated 63 individuals with migraine according to IHS criteria in a moderate quality study (Jadad score 3/5) with a choice of 11 remedies (all 30C) prescribed individually, 2 tablets twice weekly for 3 months.
  - *Outcome*: both groups improved, favouring homeopathic group, however differences not significant
- Walach (1997) assessed 98 individuals with migraine or tension headache in a high quality study (Jadad score 5/5) using a free choice of individualised remedies for 12 weeks
  - *Outcome*: improvements in both groups, no intergroup differences

References

Included systematic reviews

Ernst E. 1999. Homeopathic prophylaxis of headaches and migraine: a systematic review (Structured abstract). *Journal of Pain and Symptom Management* [Online]. Available: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11999002258/frame.html.

Owen JM, Green BN. 2004. Homeopathic Treatment of Headaches: A Systematic Review of the Literature. *Journal of Chiropractic Medicine,* 3, 45-52.

Vernon H, McDermaid CS, Hagino C. 1999. Systematic review of randomized clinical trials of complementary/alternative therapies in the treatment of tension-type and cervicogenic headache. *Complement Ther Med,* 7, 142-55.

Primary included studies

RCTs

Brigo B, Serpelloni G. 1991. Homeopathic treatment of migraine: A sixty case, double-blind, controlled study (homeopathic remedy vs. placebo). *Berlin J Research Homeo* 1, 98–102.

Straumsheim P, Borchgrevink C, Mowinckel P, Kierulf H, Hafslund C. 2000. Homeopathic treatment of migraine: a double blind, placebo controlled trial of 68 patients. *Br Hom J* 89, 4–7.

Walach H, Haeusler W, Lowes T, et al. 1997. Classical homeopathic treatment of chronic headaches. *Cephalgia* 17, 119–26.

Prospective observational studies (findings not considered in this review)

Muscari-Tomaioli G, Allegri F, Miali E, et al. 2001. Observational study of quality of life in patients with headache, receiving homeopathic treatment. *Br Hom J* 90, 189–97.

Walach H, Lowes T, Mussbach W, et al. 2001. The long-term effects of homeopathic treatment of chronic headaches: one year follow-up and single case time series analysis. *Br Hom J* 90, 63–72.

Whitmarsh T, Coleston-Shields D, Steiner T. 1997. Double-blind randomized placebo-controlled study of homeopathic prophylaxis of migraine. *Cephalgia* 17, 600–4.

Prospective observational studies represent level II study design - that is a good quality study design.

Unsure why the Contractor excluded Muscari-Tomaioli et al (2001) and Walach et al (2001) based on study design.

HIV

Executive Summary

One systematic review was identified (Category 2), which investigated the effectiveness of CAM treatments (including homeopathy) for HIV/ AIDS.

Mills et al. (2005) reported on two non-recent relevant studies (Rastogi 1999, Struew 1993). This review was deemed to be the key evidence source, because of its review methodology.

Conclusion: There is insufficient evidence from one moderate-quality review, reporting on two old methodologically-flawed experimental studies of 112 individuals, to reach a conclusion on the effectiveness of homeopathic treatment for HIV (Grade D).

One of these 'old' studies falls within the required publication date range of the search strategy

Methodological assessment of the key review

Validity issue	Comments: Mills et al. (2005)
The review question (PICO)	P: HIV I: homeopathy (not defined) (as part of CAM interventions) C: any (not defined) O: any
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely. English and non-English articles were searched to April 2004: AltHealthWatch, AMED, CinAHL, Cochrane Controlled Trials, e-Pysch, MedLINE, PychInfo. Search terms were text based.
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. RCTs were sought. Studies that were unpublished were excluded, as were trials of antioxidant and vitamin therapy, trials to improve antiretroviral adherence, exercise and pharmacokinetic trials.
Were the included studies sufficiently valid for the type of question asked?	Yes. Quality assessments of bias were made on allocation concealment, sequence generation, blinding, sample size determination, ethical procedures Studies were not excluded based on quality.
Were the results similar from study to study?	Unclear. Only two studies were identified, which reported on different interventions and outcome measures
How are the results presented?	A comprehensive descriptive summary of each included study per CAM type was provided Table 1, p. 396
Main conclusion of review authors	"Data (on homeopathy for HIV) are insufficient for demonstrating effectiveness" p. 395
Other issues	Serious methodological issues of included primary studies, different interventions and outcome measures

Evidence statement EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	D	The review methods were sound but the two included studies were old and methodologically-flawed
Consistency	D	Studies were methodologically flawed and tested different interventions in different ways, with different outcome measures. Determination of consistency was not possible
Clinical impact	D	Questionable and restricted effect of homeopathic intervention, as indicated from the individual study details

No mention of risk of bias results

Included primary studies

- Rastogi (1999) reported on a randomised controlled trial of high methodological bias, of 100 patients (71 men, 29 women), with a homeopathic intervention or placebo. There were 50 individuals each in an asymptomatic strata or a persistent generalised lymphadenopathy (PGL) strata.
    - *Outcomes:* In PGL group there was a significant difference in CD4 cell count before and after treatment. There was no change in the placebo group, and asymptomatic HIV infection.
- Struew (1993) assessed 12 patients (7 withdrew) in a methodologically-flawed randomised controlled trial of dronabinol or placebo.
    - *Outcome:* increased body fat, decreased symptom distress in verum group compared with placebo, no significant differences.

References

Included systematic review

Mills E, Wu P et al. 2005. Complementary therapies for the treatment of HIV: in search of the evidence. *International Journal of STD & AIDS* 16(6), 395-403.

Primary included studies

Rastogi DP, Singh VP, Singh V, Dey SK, Rao K. 1999. Homeopathy for HIV infection: a trial report of double blind placebo controlled study. *Br. Homeopath J* 88, 49-57

Struwe M, Kaempfer SH, Geiger CJ et al. 1993. Effect of dronabinol on nutritional status in HIV infection. *Ann Pharmacother.* 27, 827-831

Inducing labour

Executive summary

One systematic review (Cochrane review) was identified (Smith 2010, Category 1), which investigated the effectiveness of homeopathic treatments for inducing labour. This review focussed specifically on the effectiveness of homeopathy for third trimester cervical ripening or induction of labour.

Key systematic review: This review was nominated as the key evidence source. It included two non-recent randomised control trials of 133 women (Beer 1999, Dorfman 1987). Both were randomised controlled trials of unclear methodological quality, investigating the use of homeopathy for the inducement of labour. Given the lack of current evidence Smith et al. (2010) concluded the lack of good quality empirical evidence precluded the support of homeopathy for the inducement of labour.

Conclusion: One good quality Cochrane review, of two RCTs of unclear methodology, including 133 women, found no evidence that homeopathy was effective for inducing labour (Grade D).

The grading of this conclusion could be upgraded to a 'C', if the Expert Committee agreed with the comments about improving the rating of CONSISTENCY to a B. (Three elements would then be rated as C, B and D, offering the possibility of a 'C' grading.) This would strengthen the conclusion reached by the Contractor.

AS MENTIONED, THIS REPORT AND ITS FINDINGS HAVE NOT BEEN CONFIRMED BY THE EXPERT COMMITTEE

Methodological assessment of the key evidence source

Validity issue	Comment: Smith (2010)
The review question (PICO)	P: women requiring inducement of labour I: Homeopathy (unstated) or *caulophyllum* C: placebo (not defined) O: vaginal delivery not achieved within 24 hours, uterine hyperstimulation, with fetal heart rate changes, caesarean section, serious neonatal morbidity or perinatal death (eg. Seizures, birth asphyxia defined by trialists, neonatal encephalopathy, disability in childhood), serious maternal morbidity or death.
Is it unlikely that that important, relevant studies were missed?	Unclear. The following databases were searched up to December 2009: Cochrane pregnancy and childbirth group's trials register. Search terms were text and MeSH based.
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. Only randomised controlled trials were included.
Were the included studies sufficiently valid for the type of question asked?	Unclear. Methodological quality was assessed by generation of random sequence and concealment of allocation. The risk of bias for both included studies was unclear. Neither study demonstrated a sample size calculation.
Were the results similar from study to study?	Yes. Studies were homogeneous and meta-analysis was able to be conducted (p. 12-16). There was no evidence of significant effect for homeopathic interventions.
How are the results presented?	A summary of each included study was provided in "characteristics of studies" (p. 10). This included methods, participants, interventions, outcomes, notes and risk of bias. Meta-analysis was conducted with forest plots provided for caesarean section, vaginal delivery within 24 hours, instrumental delivery, augmentation with oxytocin, length of labour, difficult labour.
Main conclusion of review authors	Smith (2010) concluded that: "There is insufficient evidence to recommend the use of homoeopathy as a method of induction. It is likely that the demand for complementary medicine will continue and women will continue to consult a homoeopath during their pregnancy. Although *caulophyllum* is a commonly used homoeopathic therapy to induce labour, the treatment strategy used in the one trial in which it was evaluated may not reflect routine homoeopathy practice. Rigorous evaluations of individualised homeopathic therapies for induction of labour are needed." (p. 1).
Other issues	

Evidence statement EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review methods are sound, however there are only two relevant included studies which are not recent, and have unclear methods.
Consistency	C	Studies are generally consistent in demonstrating no effect of homeopathy compared to placebo on study outcome measures, and inconstancies need

CEBM appraisal indicates some studies may have been missed in the search

CONSISTENCY could be graded as a B, given the CEBM appraisal clear about homogeneous studies

University of South Australia

		furtherexplaination.
Clinical impact	D	Meta-analysis indicates slight clinical impact for all measures of outcome.

Summary of included primary studies

- Beer (1999) involved 40 women in their first pregnancy with a pre-labour rupture of membranes, randomised to *caulophyllum* or placebo. Risk of bias was unclear due to information not being reported on allocation concealment
    - *Outcomes*: "Vaginal delivery not achieved within 24 hours was reported for one woman in the control group (1/20) and no women in the treatment group (risk ratio (RR) 0.33, 95% confidence interval (CI) 0.01 to 7.72). Data on uterine hyper-stimulation were not recorded. Two women in the group given caulophyllum had caesarean sections compared with no women in the placebo group (RR 5.0, 95% CI 0.26 to 98.00). No data were presented on fetal heart rate changes although the author describes that slight but not significant differences were noted. No data were reported on serious maternal or neonatal morbidity such as; meconium-stained liquor; Apgar score less than seven at five minutes; neonatal intensive care unit admission; postpartum haemorrhage; or serious maternal complications (e.g. intensive care unit admission, septicaemia)" (p. 6).
- Dorfman (1987) involved 93 women reporting mean length of labour and difficulty of labour, receiving homeopathic therapy (caulophyllum, arnica, actea racemosa, pulsatilla and gerenium, with three granules administered morning and evening from 36 weeks' gestation verses placebo). Risk of bias was unclear due to information not being reported on allocation concealment
    - *Outcomes:* 'The mean length of labour for women receiving the homoeopathic therapy was 5.1 hours compared with 8.48 hours in the placebo group (P less than 0.001). Data could not be entered into the meta-analysis due to the absence of data on standard deviation. A difficult labour was reported for six women (11.3%) in the treatment group and 16 (40%) in the placebo group (RR 0.28, 95%CI 0.12 to 0.66).Mode of delivery was not reported by study group' (p.7).

References

Included systematic reviews

Smith, C. A. 2003. Homoeopathy for induction of labour. *Cochrane Database of Systematic Reviews*.

Primary included studies

Beer AM, Heiliger F. 1999. Randomized, double blind trial of caulophyllum D4 for induction of labour after premature rupture of membranes at term. *Gerburtshilfe und Frauenheilkunde* 59, 431–5.

Dorfman P, Lasserre M, Tetau M. 1987. Homoeopathic preparation for labour: two fold experiment comparing a less widely known therapy with a placebo. *Cahiers de Biotherapie* 94, 77–81.

Low back pain

Executive Summary

One systematic review was identified (Category 2), which investigated the effectiveness of CAM treatments (including homeopathy) for low back pain (Quinn et al 2005). Although Quinn et al. (2005) reported on only one relevant study (Stam, Bonnet & Haselen 2001), it was deemed to be the key review because of its review methodology.

Conclusion: There is insufficient evidence from one moderate-quality systematic review, reporting on one methodologically-sound RCT of 161 individuals, reporting on an equivocality study of two active arm interventions, to reach a conclusion on the effectiveness of homeopathic treatment of low back pain (Grade C).

Methodological assessment of the key review

Validity issue	Comments: Quinn et al 2005
The review question (PICO)	P: low back pain I: homeopathy (not defined) (as part of CAM interventions) C: any (not defined) O: any
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely. The following databases were searched Pubmed, Medline, AMED, Cinahl and The Cochrane Central Register for Controlled Trials 4th quarter, from beginning to 2005. The review was undertaken using QUORUM guidelines. Search terms were text based.
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. RCTs were sought. Chronicity of low back pain was not an exclusion criterion.
Were the included studies sufficiently valid for the type of question asked?	Yes. The van Tulder methodological quality criterion was applied (19 criteria), and included study quality was reported in full in Table 2, p. 110. Studies were not excluded based on quality.
Were the results similar from study to study?	NA. Only one study was identified.
How are the results presented?	A comprehensive descriptive summary of the included studies per CAM type was provided in the paper. P. 113 provides a descriptive summary of homeopathy for low back pain and Table 3, p. 111 provides statistical information
Main conclusion of review authors	Quinn et al. (2005) concluded "One study was identified which investigated the efficacy and safety of a homeopathic gel in the treatment of LBP. This (study) was of high methodological quality. The homeopathic gel (*Spiroflor SRL*) was compared to (a standard capsicum-based product) *Cremor Capsici Compositus* (CCC), and pain was scored

	using a VAS. The trial concluded that SRL and CCC are equally effective in the treatment of LBP; however, SRL has a lower risk of adverse effects." (p. 113).
Other issues	"As only one or two RCTs were found for each area of CAM (including the homeopathic intervention described in this evidence summary), it is impossible to draw definitive conclusions regarding the effectiveness of any one therapy from this systematic review" p. 115

Evidence statement

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review methods were sound and the single included study was of good methodological quality and had robust study numbers
Consistency	NA	Only one relevant study
Clinical impact	C	Moderate effect of homeopathic intervention, and comparator, as indicated from the individual study detail, no significant difference between them, fewer adverse effects of homeopathic gel

No mention of results of risk of bias assessment

CLINICAL IMPACT should only be a 'D' given it can only support one study of 161 participants, and that the results are inconclusive.

Included primary studies

- Stam et al. (2001) reported on an RCT of 161 individuals testing the homeopathic gel (*Spiroflor SRL*) compared to (a standard capsicum-based product) *Cremor Capsici Compositus* (CCC). The study was of high methodological quality (scoring 16/19 on the van Tulder quality scale)
    - *Outcome:* Both products equally effective but homeopathic gel had less adverse effects

References

Included systematic review

Quinn F, Hughes C, et al. 2006. Complementary and alternative medicine in the treatment of low back pain: a systematic review. *Physical Therapy Reviews* 11(2), 107-116.

Primary included studies

Stam C, Bonnet MS, Haselen RA. 2001. The efficacy and safety of a homeopathic gel in the treatment of acute low back pain: a multi-centre, randomised, double-blind comparative clinical trial. *Br Homeopath J* 90, 21–8.

Menopausal symptoms

Executive summary

Two systematic reviews (Category 2) were identified, which investigated the effectiveness of homeopathic treatments for menopausal symptoms (Seidl 1998, Rada et al. 2010). Neither review focused solely on homeopathy for the treatment of menopausal symptoms, and both reviews took different approaches to reviewing the literature. Because of their different populations, both were classified as key evidence sources for the purpose of this evidence review.

Key systematic reviews

a) Seidl et al (1998) reviewed the literature on common alternative remedies for treatment of symptoms attributed to menopause (suffered by healthy women). This review found no relevant studies for homeopathy.
b) Rada et al (2010) in a Cochrane review, assessed the efficacy of non-hormonal therapies in reducing hot flushes in women with a history of breast cancer. It identified two relevant studies (Jacobs 2005, Thompson 2005).

Conclusion: *Healthy women:* There is no available evidence from one 14 year old, poor-quality systematic review to support any conclusion about the effectiveness of homeopathy for the treatment of menopausal symptoms in *healthy women*.

Women with a history of breast cancer: There is no convincing evidence from one recent high quality review of two variable quality experimental studies of 124 women, that homeopathic remedies are effective in reducing hot flushes in women with a history of breast cancer (Grade C).

Methodological assessment of the key evidence sources

Validity issue	Comment: Seidl et al (1998)	Comment: Rada et al (2010)
The review question (PICO)	P: (healthy) menopausal women with any symptoms attributed to this condition I: alternative therapies C: any comparison O: reduction in symptoms	P: women with current or a history of breast cancer, suffering menopausal hot flashes I: non-hormonal therapy C: any O: reduced in frequency and disturbance of hot flushes
Is it unlikely that that important, relevant studies were missed?	Unclear. Peer-reviewed articles were identified from MEDLINE, CINAHL, and HEALTH databases from 1966 to mid-1997 seeking English-language articles. Test-based search terms were used to identify articles reporting on symptoms commonly attributed to menopause (hot flashes), to the effects of changing estrogen levels (irregular menses, vaginal dryness), and side effects of treatments.	Yes, it is unlikely. A range of databases with no language or publication restrictions was searched up to May 2010; Cochrane Breast Cancer Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL which includes Medline and Embase), CINAHL, PsycINFO, LILACS, WHO International Clinical Trials Registry Platform (ICTRP) Search Portal. Grey literature and conference presentations were searched and hand searching was also attempted. Studies with any of the keywords 'hot flush', 'hot flushes', 'hot flash', 'hot flashes', 'vasomotor symptoms', 'non-hormonal therapy', 'non hormonal therapy', 'selective serotonin reuptake inhibitors' or 'SSRI' were extracted for consideration.
Were the criteria used to select articles for inclusion appropriate?	Unclear. The methods do not state article type sought, however the results section for homeopathy indicates that no double blind placebo-controlled trials were found. There was no assessment of study quality	Yes. Randomised controlled trials were sought, describing women with breast cancer, comparing non-hormonal treatments with placebo or no treatment.
Were the included studies sufficiently valid for the type of question asked?	NA No studies were identified	Yes Study quality was assessed using the Cochrane criteria and found to have low to moderate risk of bias.
Were the results similar from study to study?	NA No studies were identified	Yes. (considering the homeopathic studies). Neither study found differences between homeopathy and control arms.
How are the results presented?	Qualitatively	Qualitatively
Main conclusion of review authors	There is no conclusion that can be made about homeopathy because	"No differences between the different study groups were found for the studies

	no relevant studies were found. "....scientific data are insufficient to indicate that these remedies (homeopathic) are superior to placebo" (p. 13).	with homeopathy" (p. 13)
Other issues	Well-controlled studies are needed to prove that specific physical approaches to obtaining relief from menopausal symptoms are safe and effective. Although some scientific evidence about the safety and efficacy of alternative treatments was found in this review (NB not homeopathy), that evidence was usually inconclusive.	

No evidence statement can be made for healthy women (no relevant studies)

NOT CONFIRMED BY EXPERT COMMITTEE

Evidence statement for women with a history of breast cancer

Key question	Rating	Justification
Evidence Base	C	The key review method is recent and sound, and the two included primary studies are relatively recent, have low to moderate risk of bias and deal with homogenous samples.
Consistency	B	See above comment on heterogeneity, and main conclusions of authors
Clinical impact	D	Inconclusive and restricted for individualised homeopathy for reduction in severity and frequency of hot flushes for women with a history of breast cancer

There is no 'above comment' on heterogeneity.

This is the first mention of risk of bias in the evidence statements in this report

Included primary literature

- Jacobs (2005) used a parallel group triple blind placebo-controlled experimental study with low risk of bias, comparing two forms of homeopathy with placebo in 83 women (79 assessable, mean age 55.5 years) with a history of carcinoma in situ or Stage I - III breast cancer who had completed all surgery, chemotherapy and radiotherapy, and who experienced hot flushes. Interventions were individualised homeopathy (single medicine given once monthly or bimonthly), *Hyland's Menopause*, a proprietary combination homeopathic medicine (*Amyl Nitrate 3x, Sanguinaria canadensis 3x* and *Lachesis 12x)* given three times a day. Jadad score 5/5.
    - *Outcomes:* There were no statistical differences among comparisons for the frequency or severity of hot flushes.
- Thompson (2005) using a parallel group design experiment of moderate risk of bias investigated 53 women (45 assessable) who had breast cancer with more than 3 hot flushes per day (Mean age 52 years) who received a tailored homeopathic prescription or placebo. Two active arms consisted of single homeopathic remedy or combination homeopathic remedy (Hyland's menopause). The placebo looked the same as the active interventions. Jadad score 1/5.

- *Outcomes:* There were no significant effects observed in self-rated symptoms of severity or frequency of hot flushes, activities of daily living and general well-being.

References

Included systematic reviews

Rada G, Capurro D, Pantoja T, Corbalán J, Moreno G, Letelier LM, Vera C. 2010. Non-hormonal interventions for hot flushes in women with a history of breast cancer. *Cochrane Database of Systematic Reviews*, Issue 9. Art. No. CD004923.

Seidl MM, Stewart DE. 1998. Alternative treatments for menopausal symptoms *Can Fam Physician* 44, 1299-1308.

Included primary studies

Jacobs J, Herman P, Heron K, Olsen S, Vaughters L. 2005. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled trial. *Journal of Alternative and Complementary Medicine* 11(1), 21–7.

Thompson EA, Montgomery A, Douglas D, Reilly D. 2005. A pilot, randomized, double-blinded, placebo-controlled trial of individualized homeopathy for symptoms of estrogen withdrawal in breast-cancer survivors. *Journal of Alternative and Complementary Medicine* 11(1), 13–20.

Nocturnal Enuresis (bed wetting)

Executive summary

One systematic review was identified (Category 2), which investigated the effectiveness of homeopathy for nocturnal enuresis (bed wetting) in children. This review (Huang et al 2009, an updated Cochrane review) considered the effectiveness of complementary and miscellaneous interventions for this condition. It was designated as the key review.

Key systematic review: The Huang et al (2009) systematic review was the only secondary evidence found regarding the treatment of childhood nocturnal enuresis (bed wetting) with homeopathy. No primary research evidence relevant to homeopathy for this condition was found by in this review, thus there is no current information regarding the effectiveness of homeopathic interventions for this condition.

Conclusion: One good quality Cochrane systematic review which undertook comprehensive searching found no relevant literature about the effectiveness of homeopathy for the treatment of bed wetting in children.

Methodological assessment of the evidence source

Validity issue	Comment: Huang et al (2009)
The review question (PICO)	P: nocturnal enuresis I: complementary and miscellaneous interventions C: placebo or any other treatment O: symptoms
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely. Authors searched PubMed (1950 to June 2010), EMBASE (1980 to June 2010), the Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS) (1984 to June 2010), Chinese Biomedical Literature Database (CBM) (1975 to June 2010), China National Knowledge Infrastructure (CNKI) (1979 to June 2010), VIP database (1989 to June 2010), and the reference lists of relevant articles, all last searched 26 June 2010. No language restriction was used. Search terms were text based.
Were the criteria used to select articles for inclusion appropriate?	Yes. All randomised or quasi-randomised trials of complementary and other miscellaneous interventions for nocturnal enuresis in children were included except those focused solely on daytime wetting.
Were the included studies sufficiently valid for the type of question asked?	NA No eligible studies were found
Were the results similar from study to study?	NA No eligible studies were found
How are the results presented?	NA No eligible studies were found
Main conclusion of review authors	The Huang et al. (2009) review concluded that "for homeopathy versus no treatment or placebo or another treatment, no trials were found which addressed this comparison." (p.12)
Other issues	

Evidence statement EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

This review found no relevant primary studies with which to answer the specific review question relevant to the effectiveness of homeopathy for childhood bed wetting. Thus it was not possible to construct a table of the strength of the body of evidence.

'Thus it was not possible to develop an Evidence Statement' would be a preferred sentence here .
The UNiSA sentence is not incorrect, just clumsy.

References

Included systematic review

Huang T, Shu X, Huang YS, Cheuk DKL. 2011. Complementary and miscellaneous interventions for nocturnal enuresis in children. *Cochrane Database of Systematic Reviews*, Issue 12. Art. No.: CD005230.

Obesity

Executive summary

One systematic review was identified in Category 2, which investigated the effectiveness of homeopathic treatments for obesity in a larger review of the effectiveness of complementary therapies for reducing body weight (Pittler & Ernst 2005). It included two relevant primary experimental studies (Werk and Galland 1994, Schmidt et al 2002).

As this review did not focus on homeopathy as the sole intervention for obesity it not considered as a key evidence source.

Conclusion: There is no convincing evidence from one moderate quality seven-year old systematic review of complementary therapies for the management of obesity, reporting on two relevant moderate-quality primary studies of homeopathy for 377 overweight individuals, to support a conclusion about the effectiveness of homeopathy for the treatment of obesity (Grade D).

Reference to age of systematic review is not warranted. The 2005 review is well within the publication date inclusion criteria.

Methodological assessment of evidence source

Validity issue	Comment: Pittler & Ernst (2005)
The review question (PICO)	P: overweight/ obese adults I: Complementary therapies (incl homeopathy) C: any O: weight reduction
Is it unlikely that that important, relevant studies were missed?	Unclear. Library databases of Medline, Embase, Amed and the Cochrane Library were searched until January 2004. Hand-searches of relevant medical journals, conference proceedings and reference lists occurred. Search terms included complementary medicine, alternative medicine, acupuncture, hypnotherapy, homeopathy, homoeopathy, herbal medicine, phytotherapy, dietary supplements, overweight, obesity, weight loss, slimming and derivatives
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. Randomised controlled trials were included, as well as systematic reviews and meta-analyses (if based on RCTs)
Were the included studies sufficiently valid for the type of question asked?	Yes. Methodological quality was assessed by the Jadad quality appraisal tool.
Were the results similar from study to study?	No. Only two studies were found relevant to homeopathy for weight loss. Study findings were inconsistent (Werk 1994 showing a significant difference, and Schmidt 2002 showing no difference).
How are the results presented?	A summary of each included study was provided in Table 2 (p. 1034). This included design/ risk of bias (Jadad score), intervention, regimen, control, duration, number of subjects, results for body weight, adverse events, control of lifestyle factors).
Main conclusion of review authors	"Our findings suggest that for most complementary therapies, the weight of the evidence for reducing body is not convincing. Hypnotherapy, E. sinica and other ephedrine-containing dietary supplements may lead to small reductions in body weight" (p. 1030).
Other issues	The small evidence-base precluded making any determination on effectiveness of homeopathy for weight loss. No adverse events were reported

Evidence statement

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	D	The review methods are sound, however only two studies are included, of moderate study quality, and which are at least 10 years old.
Consistency	D	See above comment on heterogeneity
Clinical impact	D	Resitricted

There is no 'above comment on heterogeneity'

Included primary literature

- Werk and Galland (1994) in a double-blind RCT used *Helianthus tuberosus D1* for 12 weeks with 166 individuals (102 completers) for weight loss. Jadad score 3/5
    - *Outcome*: There was a significant difference between groups, with homeopathy group showing greater weight loss than placebo group
- Schmidt et al. (2002) in a double-blind RCT used *Thyroidinum 30cH* compared with placebo for 211 individuals (208 completers) Jadad score 3/5.
    - *Outcomes:* No intergroup difference in weight loss

References

Included systematic review

Pittler MH, Ernst E. 2005. Complementary therapies for reducing body weight: a systematic review. *International Journal of Obesity* 29: 1030–1038.

Included primary studies

Werk W, Galland F. 1994. Helianthus-tuberosus-Therapie bei Ùbergewicht. *Therapiewoche*; 44, 34–39.

Schmidt JM, Ostermayr B. 2002. Does a homeopathic ultramolecular dilution of Thyroidinum 30cH affect the rate of body weight reduction in fasting patients? A randomized placebo-controlled double-blind clinical trial. *Homeopathy*; 91, 197–206.

Osteoarthritis

Executive summary

Three systematic reviews were identified in Categories 1 -3, which investigated the effectiveness of homeopathic treatments for osteoarthritis.

- One Category 1 review (Long & Ernst 2001) focussed specifically on the effectiveness of homeopathic treatment on osteoarthritis.
- One Category two review (De Silva et al. 2011) considered the effectiveness of CAM for the treatment of osteoarthritis.
- One Category 3 review (Bellavite et al. 2011) considered the effectiveness of homeopathic interventions for a range of conditions including the treatment of osteoarthritis.

Key systematic review: The Long and Ernst (2001) review was the only systematic review to focus entirely on studies of homeopathy as a treatment for osteoarthritis. It included four randomised control trials (Nahler et al. 1998 (knee arthritis), Shealy et al. 1998 (knee arthritis), Shipley et al. 1993 (hip and knee osteoarthritis), van Haselen & Fisher 2010 (knee osteoarthritis)). This review was designated as the key evidence source.

Other systematic reviews:

a) De Silva et al. (2011), who assessed the evidence regarding the efficacy of homeopathy in the treatment of osteoarthritis as part of a larger review of the efficacy of complementary and alternative medicines. Study criteria were clearly outlines. De Silva et al. (2011) searched Allied and Complementary Medicine, EMBASE, Ovid, MEDLINE, EBM Reviews-ACP Journal Club, EBM Reviews-Cochrane Central Register of Controlled Trials, and EBM Reviews-Database of Abstracts of Reviews of Effects. . The methodological quality of included studies was scored using the Jadad scale. Study findings were reported descriptively. These authors found three of the trials identified in the key review (Shealy et al. 1998, Shipley et al. 1983, van Haselen & Fisher 2000)). The authors concluded that there was no difference in effect between homeopathic interventions and placebo for this condition.

b) Bellavite et al. (2011) reported on the evidence for homeopathy as a treatment for respiratory allergies, common Upper Respiratory Tract Infections, otorhinolaryngologic complains and rheumatic diseases. The review sought experimental or prospective observational research on humans, published between 1978 and 2010. Data came from "current reading of major complementary and alternative medicine journals, screening of the Hominform Information Service databases (British Homeopathic Library, http://hominform.soutron.com/), literature searches using Medline, the Cochrane Database of Systematic Reviews, and cross-referencing between published papers" (p. 1364). The authors also "consulted previously published systematic reviews and meta-analyses that have covered trials of immunoallergology" (p. 1364). "All forms of homeopathic therapy were included in the review, namely: a) classical individualised homeopathy, b) ailment-specific remedies and complexes, c) isotherapy where indicated" (p. 1364). This review identified all four primary experimental studies identified by Long and Ernst (2011) and also identified two further relevant studies (Birnesser, Klein et al.

2003 (controlled clinical trial of knee osteoarthritis) and Pomposelli, Codecà et al.2003 (prospective observational study of osteoarthritis and back pain)).

The included primary research sources are outlined below.

	Long & Ernst (2001_	De Silva et al. (2011)	Bellavite et al 2011
Birnesser, Klein et al. 2003			√
~~Nahler et al.~~ 1996	√		√
Pomposelli, Codecà et al.2003			√
Shipley et al. 1983	√	√	√
Shealy et al. 1998	√	√	√
van Haselen and Fisher 2000	√	√	√

Typographical error: incorrect date of Nahler publication. Should be 1998

Conclusion: *Three good quality systematic reviews, reporting on six studies (total N=957), four* moderate quality RCTs of 310 individuals, one controlled clinical trial of 592 individuals and one prospective observational study of 55 individuals, found no convincing evidence of the effectiveness of homeopathy for osteoarthritis (Grade C).

Conclusion refers to the three systematic reviews, but the Contractor chose to do a CEBM appraisal just on the key review (Long & Ernst 2001).

Given the Evidence Statement just reflects this appraisal,the Contractor should have separated comments here in the Conclusion on the key review (Long & Ernst 2001), and the other two systematic reviews. (The grading of C just relates to the Long and Ernst analysis.)

Methodological assessment of the key evidence source

Typographical error: incorrect date of Long & Ernst publication. should be 2001

Validity issue	Comment: Long & Ernst (2011)
The review question (PICO)	P: patients with osteoarthritis I: homeopathic medicine C: any active drug or placebo O: self-rating scales of pain and stiffness, and performance measures and physiotherapy assessment.
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely The following databases were searched up to August 2000: MEDLINE, EMBASE, AMED, Biosis, CIRARL and the Cochrane Library. Manual searching through bibliographies and reviews located in the computer search, and through the authors own files were also conducted, and experts and manufacturers in the field were approached to provide unpublished and published materials. Search terms were text and MeSH based
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. A number of studies were excluded and exclusion criteria are reported. Types of study: "all RCTs of homeopathic treatment of osteoarthritis." (p. 38)
Were the included studies sufficiently valid for the type of question asked?	Unclear. RCTs evaluated using CRD tool (methodological quality score reported for the included studies listed above (3, 3, 4, 3)). Studies not excluded based on quality.
Were the results similar from study to study?	No. Studies are heterogeneous.
How are the results presented?	A summary for each included study was provided in Table 1 "RCTs of homeopathic remedies in the treatment of OA" (p. 39). This included quality score, joint involved with OA, sample size, design, intervention and control, duration of treatment, primary outcome measures and main results.
Main conclusion of review authors	Long and Ernst (2001) concluded that "the small number of randomised controlled clinical trials conducted to date, although favouring homeopathic treatment, do not allow firm conclusions as to the effectiveness of homeopathic remedies in the treatment of patients with osteoarthritis" (p. 37).
Other issues	

The Contractor could have been clearer here about the implications for risk of bias

Evidence statement

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review methods are sound but the included studies are relatively small and of variable quality, and addressed osteoarthritis at different locations.
Consistency	C	There were some inconsistencies in the findings between the studies reflecting genuine uncertainty around the clinical question.
Clinical	C-D	Restricted. See section on 'How were the results presented' and the

No mention of results of any risk of bias assesment

If restricted, then this grading of Clinical Impact should be a 'D'.

impact		determination of Consistency

Summary of primary studies

- Birnesser et al. (2003) conducted a non-randomised controlled clinical trial of 592 individuals with knee arthritis and tested the effectiveness of *Zeel compositum-N versus*. COX-2 inhibitors (no quality score)
    - *Outcome*: Equivalence of homeopathic and allopathic medicines
- Nahler et al. (1998) conducted a multicentre, patient-blind equivalence trial with two parallel arms on 121 patients with primary knee osteoarthritis. It was a moderate quality study (Jadad score 3/5). Intervention was Ten injections of *Zeel compositum* (two 2 ml intraarticular injections per week) or five injections of yalart (one 2 ml intraarticular injection per week) for 5 weeks.
    - *Outcome*: Symptomatic improvements in both treatment groups. Tolerance was good for both groups, with no significant differences in outcome.
- Pomposelli et al. (2003) conducted a non-randomised, prospective observational study of 55 individuals with osteoarthritis and back pain, using either individualised homeopathic prescription or conventional therapy. No quality score available.
    - *Outcome*: "homeopathic therapy (associated with physiotherapy and if necessary with pharmacological therapies) might give better results than conventional therapy alone, and points to the need for a randomised trial comparing homogeneous groups of patients" (p. 1378)
- Shealy et al. (1998) conducted a double-blind, placebo controlled randomised control trial on 69 patients with knee osteoarthritis oral administration of either 10 drops of a homeopathic preparation (*Rhus toxicodendron, Causticum and Lac Vaccinum*) and placebo capsules 4 times daily or a liquid placebo and paracetamol capsules (daily dose of 2600mg paracetamol) four times daily. Moderate Risk of Bias score
    - *Outcome*: Improvement in pain in both groups, no significant differences between groups
- Shipley et al. (1983) conducted a double-blind, placebo controlled crossover study on 36 patients suffering from either knee or hip osteoarthritis, or both. It was a moderate quality study (Jadad score 4/5). Treatment regimens consisted of (1) placebo capsules and placebo drops (2) fenoprofen capsules and placebo drops or (3) placebo capsules and *Rhus toxicodendron* drops
    - *Outcome*: No significant differences were observed between *Rhus toxicodendron* and placebo treatment phases. Treatment with fenoprofen produced highly significant pain relief compared with both *Rhus toxicodendron* and placebo treatment phases.
- van Haselen & Fisher (2000) in a moderate quality RCT (Jadad score 3/5) tested 184 subjects with topical application of 1 g 0.5% piroxicam gel or SRL1 (containing *Symphytum officinale* (comfrey), *Rhus toxicodendron* (poison ivy) and *Ledurn palustre* (marsh-tea) to knees three times daily.
    - *Outcomes*: There was a difference (non-significant) between the two groups for pain favouring homeopathic treatment.

References

Included systematic reviews

Bellavite P, Marzotto M, Chirumbolo S, Conforti A. 2011. Advances in homeopathy and immunology: a review of clinical research. *Frontiers in Bioscience,* S3, 1363-1389.

De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ, Arthrit Res U. K. W. G. C., Arthritis Research, U. K. W. G. O. C., Alternative, M. & On Behalf Of The Arthritis Research, U. K. W. G. O. C. 2011. Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. *Rheumatology (Oxford, England),* 50, 911-920.

Long L, Ernst E. 2001. Homeopathic remedies for the treatment of osteoarthritis: a systematic review (Structured abstract). *British Homoeopathic Journal* [Online]. Available: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12001003447/frame.html.

Primary included studies

Birnesser H, Klein P, Weiser M. 2003. A modern homeopathic medication works as well as COX 2 Inhibitors. *Der Allgemeinartz* 25, 261-264.

Nahler G, Metelmann H, Sperber H. 1998. Treating osteoarthritis of the knee with a homeopathic preparation. *Biomedical Therapy,* XVI, 186-191.

Pomposelli R, Codecà G, Bergonzi R, Andreoni C, Salvi G, Costini G, Piasere V, Bellavite P. 2003. Terapia omeopatica in pazienti con patologia artroreumatica. *Medicina Naturale* 13, 44-50.

Shealey CN, Thomlinson RP, Cox RH, Borgmeyer V. 1998. Osteoarthritic pain: a comparison of homeopathy and acetaminophen. *American journal of Pain Management,* 8, 89-91.

Shipley M, Berry H. 1983. Controlled trial of homeopathic treatment of osteoarthritis. *Lancet,* I, 97-99.

Van Haselen RA, Fisher PAG. 2000. A randomised controlled trial comparing topical piroxicam gel with a homeopathic gel in osteoarthritis of the knee. *Rheumatology,* 39, 714-719.

Otitis media

Executive summary

Two relevant Category 3 systematic reviews were identified, which discussed the effectiveness of homeopathy for otitis media in children (Altunc 2007, Bellavite 2011). Neither review focused solely on otitis media and homeopathy. This comment differs from what the CEBM appraisal results state

- Altunc et al. (2007) considered a number of childhood ailments including adenoid vegetation, ADHD, asthma, otitis media, conjunctivitis, diarrhea, post-operative pain, upper respiratory tract infections and warts.
- Bellavite et al. (2011) explored the past 30 years of research in respiratory allergies, common upper respiratory tract infections, otorhinolaryngologic complains and rheumatic diseases.

Freise et al 1996 and 1997 are the same study

Key systematic review: The Bellavite et al (2011) review reported on six primary experimental studies (seven papers) of varying design and quality, relevant to this condition (Frei and Thurneysen 2001, Freise et al 1996, 1997, Haidvogl et al 2007, Jacobs et al 2001, Kruse et al 1998, Riley et al 2001). The review was of high methodological quality and conducted a comprehensive search. Thus the Bellavite et al (2011) review was considered to be the key evidence source for the effectiveness of homeopathy for otitis media in children.

Query use of term 'positive evidence' . There are no justification or details provided.

Other systematic review: The evidence presented in the Altunc et al (2007) review was not included in this evidence summary, as it did not ask a focused clinical question in a comprehensive manner, and identified only one primary study (Jacobs et al 2001) which was also included in the Bellavite et al (2011) review.

Conclusion: One good quality, recent, comprehensive key systematic review reporting on six primary experimental studies (seven papers) of varying design and quality, reporting on at least 562 children with otitis media, indicates that there is consistent positive evidence that individualised homeopathy is effective for the treatment of otitis media in children (Grade C).

Of the six studies, there were two that did not look at otitis media. Haidvogel et al (2007) is reported by Bellavite to have focused on 'upper respiratory tract infections' and Riley et al (2001) reported to have focused on 'respiratory tract complaints or ear complaints' in Table 1 on page 1366- 1368.

As such, the Bellavite systematic review, which forms the basis of this conclusion reported on only four primary studies with 562 participants

The Contractor makes this observation on page 120 , but does not report it here

Disagree that the PICO is clear: Bellavite does not stipulate children with otitis media as the sole population group.

Methodological assessment of the key evidence source

The Comparator is described as conventional therapy, usually antibiotics mucolytics and antipyretics

The Interventions are varied and include a range of homeopathic remedies

Validity issue	Comment: Bellavite et al. (2011)
The review question (PICO)	P: children with otitis media I: classical individualised homeopathy C: any (not defined) O: symptoms (primary outcomes), healing, adverse events
Is it unlikely that that important, relevant studies were missed?	No. The review sought experimental research on humans, published between 1978 and 2010. Data came from 'current reading of major complementary and alternative medicine journals, screening of the Hominform Information Service databases (British Homeopathic Library, http://hominform.soutron.com/), literature searches using Medline, the Cochrane Database of Systematic Reviews, and cross-referencing between published papers' (p. 1364). The authors also 'consulted previously published systematic reviews and meta-analyses that have covered trials of immunoallergology' (p. 1364). 'All forms of homeopathic therapy were included in the review, namely: a) classical individualised homeopathy, b) ailment-specific remedies and complexes, c) isotherapy where indicated' (p. 1364).
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. 'Analysis included controlled clinical trials (with and without randomisation), observational studies and case series, but excluded single case reports' (p. 1364).
Were the included studies sufficiently valid for the type of question asked?	Unclear. The included studies were not assessed for methodological quality, only described by experimental design, evidence source and study population. All studies assessed classical individualised homeopathy using experimental designs which variably including randomisation and controlling.
Were the results similar from study to study?	Yes. Studies were homogenous in terms of population, interventions. The same outcome measures were reported, and outcome differences between groups were reported as equivalent to control, or better, for homeopathy.
How are the results presented?	Characteristics of included studies are included in Table 1 (p. 1366), reporting authors, study design, participant type and N, treatment, outcomes and key results. Study findings are summarised in Table 4 (p. 1381) as strength of the body of evidence per condition, with the study name and type, and peer-reviewed journal source identified
Main conclusion of review authors	The authors concluded the strength of the body of evidence for a range of conditions in Table 4 (p. 1381). For individualised homeopathy for children with otitis media, the authors concluded all primary studies demonstrated 'good positive evidence of effectiveness'.
Other issues	The authors indicate that 'while there are significant effects in otitis media, a larger number of observational studies and clinical trials -- conducted in a methodologically correct manner without altering the

There is no mention of the study designs

Risk of bias not commented on

Confounding factor in the Haidvogel study of possible bias: 81% of the homeopathic participants stated they have a preference for homeopathy

	treatment setting-- are needed before sure conclusions concerning the application of homeopathy for specific diseases can be drawn' (p. 1363)

Evidence statement EVIDENCE STATEMENTS AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review methods are sound, although the six included studies are of variable experimental designs, and unknown study quality.
Consistency	B	See above comment on homogeneity
Clinical impact	C	Although effectiveness was reported by the review authors as similarly positive and good, using the same outcome measures, the individual study findings suggest that treatment effects are in general, small.

Only four studies - see comments in Executive Summary.

No mention of risk of bias.

There is no 'above comment on homogeneity'

Low sample sizes - 562 participants across the four studies

CLINICAL IMPACT should be graded as a D, given the conclusions are based on only 562 children, and noting the comments from the CEBM assessment by Bellavite (see 'Other issues above')

Evidence base should not be graded as C

Included primary literature: FORM matrix definitions, the clinical impact is slight (D), not moderate (C)

The Bellavite et al (2011) review identified and analysed seven relevant experimental papers (reporting on six trials) which tested the effectiveness of classical individualised homeopathy for the treatment of otitis media in children:

- Frei and Thurneysen 2001 (non-randomised, non-controlled trial) N=230, Jadad score 5/5
  - *Outcomes:* Improvement in 39% of intervention patients after 6 hours, another 33% after 12 hours
- Freise et al 1996 and 1997(non-randomised controlled trial reported in two papers) N=131, quality score not given
  - *Outcomes:* Homeopathy slightly better than conventional therapy
- Haidvogl et al 2007 (non-randomised controlled trial) investigating otitis media among other upper respiratory conditions N=1557, quality score = Low Risk of Bias
  - *Outcomes:* Homeopathic treatment not inferior to the allopathic and best tolerated
- Jacobs et al 2001 (randomised controlled trial) N=75, Jadad score 5/5
  - *Outcomes:* Less failure in verum group, not significant; little and significant decrease of symptoms in verum group
- Kruse et al 1998 (non-randomised, non-controlled trial) N=126, quality score not given
  - *Outcomes:* Equivalent efficacy
- Riley et al 2001 (non-randomised, controlled trial investigating otitis media among other upper respiratory conditions) N=456, Cochrane quality score= High Risk of Bias
  - *Outcomes:* Improvement in 82.6% of homeopathic patients, 68% of allopathic

Considering the four trials which reported only on children with otitis media, the total sample was 562. It was not possible to identify how many children with otitis media only, were included in the other two studies.

References

Included systematic reviews

Bellavite, P, Marzotto, M, Chirumbolo, S, Conforti, A. 2011. Advances in homeopathy and immunology: a review of clinical research. *Frontiers in Bioscience,* S3, 1363-1389.

Altunç, U, Pittler, MH, Ernst, E. 2007. Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic proceedings. Mayo Clinic,* 82, 69-75.

Included primary studies

Frei H, Thurneysen A. 2001. Homeopathy in acute otitis media in children: treatment effect or spontaneous resolution? *Br Homeopath J* 90, 180–2.

Friese KH, Kruse S, Ludtke R, Moeller H. 1997. The homoeopathic treatment of otitis media in children: comparisons with conventional therapy. *Int J Clin Pharmacol Ther* 35,296–301.

Friese KH, Kruse S, Moeller H. 1996. Acute otitis media in children. Comparison between conventional and homeopathic therapy. *HNO* 44, 462-466.

Haidvogl M, Riley DS, Heger M, Brien S, Jong M, Fischer M, Lewith GT, Jansen G, Thurneysen AE 2007. Homeopathic and conventional treatment for acute respiratory and ear complaints: a comparative study on outcome in the primary care setting. *BMC Complement Altern Med* 7, 7.

Jacobs J, Springer DA, Crothers D. 2001. Homeopathic treatment of otitis media in children: a preliminary randomised placebo-controlled trial. *Pediatr Infect Dis J* 20, 177-183.

Kruse S. 1998. Otitis media bei kindern, Stuttgart: *Hippokrates Verlag*, Edition Forschung.

Riley D, Fischer M, Singh B, Haidvogl M, Heger M. 2001. Homeopathy and conventional medicine: an outcomes study comparing effectiveness in a primary care setting. *J Altern Complement Med* 7, 149-159.

Pre-menstrual syndrome

Executive Summary

One systematic review was identified (Category 2), which investigated the effectiveness of CAM treatments (including homeopathy) for pre-menstrual syndrome (PMS) (Stevinson et al. 2001). This review reported on only one relevant study (Chapman et al 1994), however Stevinson et al was deemed to be the key review because of its review methods.

Conclusion: There is insufficient evidence from one moderate-quality systematic review reporting on one old, methodologically-biased RCT of 10 women, to reach a conclusion on the effectiveness of homeopathic treatment of pre-menstrual syndrome (PMS) (Grade D).

Methodological assessment of the key review

Validity issue	Comment: Stevinson & Ernst (2001)
The review question (PICO)	P: pre-menstrual syndrome (PMS) I: homeopathy (not defined) C: any (not defined) O: any
Is it unlikely that that important, relevant studies were missed?[6]	Yes, it is unlikely. The following databases were searched MEDLINE, EMBASE, BIOSIS, CINAHL, PsychoINFO, The Cochrane Library (up to October 2000), and CISCOM (up to December 1998). The reference lists of articles were checked and experts in complementary medicine, and manufacturers of herbal preparations were asked for any additional trials Search terms were text based.
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. RCTs were sought. Trials on other pre-menstrual conditions/ syndromes other than PMS were excluded.
Were the included studies sufficiently valid for the type of question asked?	Unclear. Comments were made on each study regarding patient recruitment, trial design, and statistical analysis. Studies were not excluded based on quality.
Were the results similar from study to study?	NA. Only one study was identified.
How are the results presented?	A summary of the included studies (CAM incl homeopathy) was provided in Table 1 (including information on Design (No. recruited /analysed), Diagnostic methods, Intervention (control), Dose (duration), Primary outcome measures, Reported superiority of intervention over control, No. of AEs in intervention/control, Comments) (p. 228). Meta-analysis was not conducted.

[6] It is not possible to be certain that important studies were not missed by these two reviews given the similarity of publication date and different included study numbers.

Main conclusion of review authors	Stevinson and Ernst concluded "There was only one published RCT investigating the efficacy of homeopathic 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, but a placebo response of 47% in the pre-treatment 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." (p. 230).
Other issues	Only one relevant study published nearly 20 years ago precludes construction of a comprehensive evidence statement

Evidence statement EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY THE EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	D	The review methods were sound but the one included study was old and had significant methodological concerns moderate to poor quality.
Consistency	NA	Only one relevant study
Clinical impact	D	Slight or restricted as indicated from the individual study details.

No mention of risk of bias

Included primary studies

- Chapman et al. (1994) reported on a double-blind parallel arm study of 10 women (whom all completed) testing homeopathy (non-defined) compared with placebo, three doses per month for four cycles
    - *Outcome:* no difference between intervention and placebo arms

References

Included systematic review

Stevinson C, Ernst E. 2001. Complementary/alternative therapies for premenstrual syndrome: A systematic review of randomized controlled trials. *Am J Obstet Gynecol* 185, 227-35.

Primary included studies

Chapman EH, Angelica J, Spitalny G, Strauss M. 1994. Results of a study of the homeopathic treatment of PMS. J *Am Inst Homeopath* 87, 14-21.

Postoperative ileus

Executive summary

One meta-analysis was identified (Category 1), which investigated the effectiveness of homeopathic treatments for postoperative ileus. Barnes et al. (1997) focused specifically on the effectiveness of homeopathy as a treatment for postoperative ileus.

Key systematic review: The Barnes et al (1997) review was of good quality and included six primary RCTs (Castelin 1979, Valero 1981, Chevrel 1984, Aulagnier 1985, GRECHO 1989 (Groupe de Recherches et d'Essais Cliniques en Homéopathie), Dorfman 1992).

Conclusion: One good quality, non-recent meta-analysis of six primary RCTs of 1082 subjects provides encouraging evidence of the effectiveness of homeopathy in reducing time to first flatus in postoperative patients when administered immediately after surgery. There is no indication of which homeopathic medicines are most appropriate (Grade C).

The term 'encouraging evidence' is not defined in this report. There are inconsistencies as to how it is interpreted.

Methodological assessment of the key evidence source

Validity issue	Comment: Barnes et al (1997)
The review question (PICO)	P: patients who had undergone abdominal or gynaecologic surgery I: homeopathic medicines (see above) C: placebo O: time to first flatus
Is it unlikely that that important, relevant studies were missed?	Yes, it is unlikely. The following databases were searched up to March 1996: The European Homeopathic Research Group's list of more than 350 references of published reports of homeopathy (compiled by hand-searching relevant journals and from searches of nine databases: MEDLINE, EMBASE, BIOSIS, PsychInfo, CINAHL, Science Citation Index, British Library Stock Alert Service, Sigle, AMED); the systematic review by Kleijnen et al.; articles cited in the bibliographies of retrieved studies; the CISCOM database (Research Council for Complementary Medicine, London). Search terms were text based.
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. Exclusion criteria are reported. Types of study: human placebo controlled trials with data presented in a way that allowed meta-analysis.
Were the included studies sufficiently valid for the type of question asked?	Unclear. A criteria-based evaluation of the studies was conducted (characteristics of patients, number analysed, randomisation, intervention, double blinding, measurement of effect, presentation of data) and scored out of 100, >55 indicating a high quality study (scores for above articles 20, 80, 58, 75, 90, 50). Studies were not excluded based on quality.
Were the results similar from study to study?	Yes. Meta-analysis conducted to determine the effect of homeopathic treatment over that of placebo. There was a consistent and positive effect of homeopathic medicines on time to first flatus in the high quality trials, and in weighted combined analysis.
How are the results presented?	A summary for each included study was provided in Table 2 "Results of individual studies". This included treatment, number of participants and mean time to first flatus and first faeces, separated into control or therapy groups. Meta-analysis was presented descriptively and in forest plot (Fig 1, p 10-11).
Main conclusion of review authors	Barnes et al. (1997) concluded that "The WMD in the time to first flatus between homeopathy and placebo was shown to be -7.4 hours in favour of homeopathy (95% CI -4.0 to -10.8 hours). This effect is statistically significant ($p < 0.05$) and also likely to be clinically relevant. Excluding low-quality studies from a second meta-analysis produced slightly reduced WMDs for time to first flatus of -6.11 hours, respectively (95% CI -2.31 to -9.91 hours; n = 676), but did not alter the statistical significance of the results. Meta-analyses of the four studies comparing homeopathic treatment of <12C potency (i.e., dilutions likely to contain molecules of the "mother

Unclear what WMD refers to

	tincture") with placebo indicated a statistically significant difference ($p < 0.05$) in favour of homeopathy for time to first flatus (WMD, -6.6 hours; 95% CI, -2.6 to -10.5 hours; n = 660). Meta-analyses of the studies comparing a homeopathic remedy of >=12C potency ("immaterial dilutions") with placebo did not indicate a statistically significant difference between the two groups for time to first flatus (WMD, -3.1 hours; 95% CI, -7.5 to 1.3 hours; n = 416)". (p.11-12)
Other issues	The authors indicate that although meta-analysis is less prone to investigator bias, it may still be prone to bias due to methodological issues in the included primary studies. Three of the included studies were not peer reviewed, and had poor-moderate quality scores, thus, in combination with the large standard deviation, generated concern regarding their quality. The authors have therefore recommended that "Several drawbacks inherent in the original studies and in the methodology of meta-analysis preclude a firm conclusion...However, these meta-analyses do produce a rationale and provide a background for future, more rigorously designed, randomized trials"

These comments suggest a significant risk of bias.

Evidence statement EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The review methods are sound but the included studies are relatively small and of variable quality. Note comment on possible risk of bias above
Consistency	B	Evidence around the effectiveness of homeopathy was consistent and inconsistency may be explained by primary study size and quality
Clinical impact	C	Moderate effect as indicated in meta-analysis of the higher quality studies Fig 1 p 630 A 'D' grade more appropriate - see below

CLINICAL IMPACT : dispute grading of C (moderate) given authors of meta-analysius stated that whilst there is some evidence of an effect.....
However, several caveats preclude a definitive judgment. These results should form the basis of a randomized controlled trial to resolve the issue.

Summary of included primary references

- Aulagnier (1985) assessed 206 postoperative patients (not specified) *opium, raphanus sativus* and *arnica Montana* against placebo. Quality score- Low Risk of Bias.
  - *Outcome:* A significant positive effect favouring homeopathy, to first time flatus.
- Castelin (1979) assessed 20 patients (not specified) who had undergone abdominal surgery using *opium* against placebo. Quality score- High Risk of Bias.
  - *Outcome:* A positive effect favouring homeopathy (non-significant), to first time flatus.
- Chevrel (1984) assessed 96 postoperative patients (not specified) using *opium* against placebo. Quality score- Moderate Risk of Bias.
  - *Outcome:* A significant positive effect favouring homeopathy, to first time flatus.
- Dorfman (1992) assessed 80 patients postoperatively using *Raphanus sativus, Arnica Montana* and *China regia* against placebo. Quality score- Low Risk of Bias.
  - *Outcome:* A significant positive effect favouring homeopathy, to first time flatus.
- GRECHO (1989) (Groupe de Recherches et d'Essais Cliniques en Homéopathie) conducted two arms testing *opium* alone against placebo, and testing *opium* in conjunction with

Raphanus sativus against placebo on a total of 600 patients (not specified) postoperatively using *opium,* and *opium + Raphanus sativus* against placebo. Quality score- Low Risk of Bias.
    - *Outcome:* Equivocality of groups, to first time flatus.
- Valero (1981) assessed 80 patients (not specified) postoperatively using *Raphanus sativus* against placebo. Quality score- Low Risk of Bias.
    - *Outcome:* Equivocality of groups, to first time flatus.

References

Included systematic reviews

Barnes J, Resch KL, Ernst E. 1997. Homeopathy for Postoperative Ileus?: A Meta-analysis. *Journal of Clinical Gastroenterology* 25, 628-633.

Primary included studies

Aulagnier G. 1985. Action d'un traitement homéopathique sur la reprise du transit post-opératoire. *Homéopathie* 6, 42-5.

Castelin T. 1979. Etude de l'action homéopathique de Raphanus sativus niger 5 CH et d'Opium 15 CH sur la reprise du transit en chirurgie digestive post-opératoire (dissertation). Bordeaux: Université de Bordeaux II.

Chevrel JP, Saglier J, Destable MD. 1984. Reprise du transit intestinal en chirurgie digestive. Action homéopathique de l'Opium. *Presse Med* 13, 833.

Dorfman P, Amodéo C, Riccioti F, Tetau M, Véroux G. 1992. Iléus post-opératoire et homéopathie: bilan d'une évaluation clinique. *Cahiers de Biothérapie* 114, 33-9.

GRECHO (Groupe de Recherches et d'Essais Cliniques en Homéopathie). 1989. Evaluation de deux produits homéopathiques sur la reprise du transit après chirurgie digestive. Un essai contrôlé multicentrique. *Presse Med* 18, 59-62.

Valero EM. 1981. Etude de l'action préventive de: raphanus sativus 7 CH, sur le temps do reprise du transit intestinal post-opératoire (à propos de 80 cas)-Pyrogenium 7 CH sur les infections post-opératoire (à propos de 128 cas) (dissertation). Grenoble: Université Scientifique et Médicale de Grenoble.

Rheumatic Diseases

Executive Summary

One good quality, recent systematic review was identified (Bellavite et al 2011, Category 2), which investigated the effectiveness of homeopathic treatments for arthro-rheumatic diseases. This was considered as the key review for this condition. This evidence summary deals with three rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis and chronic polyarthritis). Fibromyalgia and osteoarthritis (also reported in this review) are considered separately in the condition-specific evidence summaries for these conditions, reported later in this report.

Key systematic review: Bellavite et al (2011) discussed clinical questions regarding homeopathic treatments in arthro-rheumatic diseases. Bellavite et al (2011) reviewed the past 30 years of research for a range of conditions (respiratory allergies, common upper respiratory tract infections, otorhinolaryngologic complaints and arthro-rheumatic diseases). The Bellavite et al (2011) review was of high methodological quality (although it did not provide methodological quality scoring for the included studies). It conducted a comprehensive search, included 16 relevant primary studies for arthro-rheumatic diseases, and reported on the effectiveness of individualised homeopathy, and ailment-specific homeopathic remedies and complexes.

The Bellavite et al. (2011) review included six relevant primary studies (experimental studies) pertaining to the three rheumatic diseases:

- rheumatoid arthritis (Andrade et al. 1991, Fisher and Scott 2001, Gibson et al. 1978, Gibson et al. 1980)
- anklyosing spondylitis (Schirmer et al. 2000)
- chronic polyarthritis (Weisenauer & Gaus 1991)

Conclusion: There is no convincing evidence from one good quality systematic review of six experimental studies published since 1990, regarding the effectiveness of homeopathy for the treatment of rheumatoid arthritis (four primary studies, total N=398), anklyosing spondylitis (one primary study, N=104) or chronic polyarthritis (one primary study, N=111) (Grade D).

Methodological assessment of the key evidence source

Validity issue	Comments: Bellavite et al (2011)
The review question (PICO)	P: adults arthro-rheumatic diseases I: homeopathically prepared remedies C: any (not defined) O: symptoms (any)
Is it unlikely that that important, relevant studies were missed?	No. The review sought experimental research on humans, published between 1978 and 2010. Data came from "current reading of major complementary and alternative medicine journals, screening of the Hominform Information Service databases (British Homeopathic Library, http://hominform.soutron.com/), literature searches using Medline, the Cochrane Database of Systematic Reviews, and cross-referencing between published papers" (p. 1364). The authors also "consulted previously published systematic reviews and meta-analyses that have covered trials of immunoallergology" (p. 1364). "All forms of homeopathic therapy were included in the review, namely: a) classical individualised homeopathy, b) ailment-specific remedies and complexes, c) isotherapy where indicated" (p. 1364).
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. "Analysis included controlled clinical trials (with and without randomization), observational studies and case series, but excluded single case reports" (p. 1364).
Were the included studies sufficiently valid for the type of question asked?	Unclear. The included studies were not assessed for methodological quality, only described by experimental design, evidence source and study population. All studies assessed classical individualised homeopathy using trials which variably including randomisation and controlling.
Were the results similar from study to study?	No. Studies are heterogeneous in terms of populations and interventions.
How are the results presented?	Characteristics of included studies are included in Table 3 (p. 1377), reporting authors, study design, participant type and N, treatment, outcomes and key results. Study findings are summarised in Table 4 (p. 1381) as strength of the body of evidence per condition, study name and type, and peer-reviewed journal source
Main conclusion of review authors	Table 4 (p. 1381) (paraphrased) There is equivocal evidence for individualised homeopathy for rheumatoid arthritis (2 studies positive, two no evidence). There is no evidence for the effectiveness of *Formica Rufa* 6X in anklyosing spondylitis from 1 study, or for homeopathic complex *Luffa+Cinnabaris+Kalium Bichromicum* for chronic polyarthritis
Other issues	The authors indicate that "Pragmatic equivalence trials suggest that, in primary care, homeopathic treatment is not inferior to conventional treatment. A larger number of observational studies and of clinical trials -- conducted in a methodologically correct manner without altering the treatment setting-- are needed before sure conclusions concerning the application of homeopathy for specific diseases can be drawn." (p. 1363).

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITEE

Evidence statement

Key question	Rating	Justification
Evidence Base	C	The key review methods are sound, however the six included primary studies are of unknown quality, contained subject numbers ranging from 45-195 individuals, and are generally old (four published prior to 2000). The primary studies also dealt with three different rheumatic-type diseases
Consistency	D	See above comment on heterogeneity, and main conclusions of authors
Clinical impact	D	Inconclusive and restricted evidence for individualised or formulaic homeopathic interventions for rheumatoid arthritis, ankylosing spondylitis or chronic polyarthritis

no mention of risk of bias

Included primary literature (extracted from Table 3 p. 1376)

Rheumatoid arthritis

- Andrade, Ferraz et al. (1991) applied a randomised controlled trial to 45 individuals, testing individualised prescription versus placebo, for 6 months.
  - *Outcome*: Slight (not significant) differences favouring verum group over placebo
- Fisher and Scott (2001) used a randomised controlled trial to test 112 individuals with NSAIDS + individualized prescription versus NSAIDS+ placebo
  - *Outcome*: No effect of homeopathy over placebo
- Gibson, Gibson et al. (1978) conducted a controlled clinical trial of 195 individuals, testing individualised prescription versus salicylate and placebo for 12 months
  - *Outcome:* Better relief in the homeopathic group compared to the allopathic and placebo. There was a high incidence of drop-out.
- Gibson, Gibson et al. (1980) tested 46 individuals with individualised prescription control placebo, using a randomised controlled trial
  - *Outcome*: Better relief in the homeopathic group versus placebo (non-significant)

Chronic polyarthritis

- Wiesenauer and Gaus (1991) applied a randomised controlled trial design to 111 individuals, testing homeopatic preparation "*Rheumaselect*" or placebo, for 12 weeks
  - *Outcome:* non-significant differences, favouring verum group

Ankylosing spondylitis

- Schirmer, Fritz et al. (2000) tested 104 individuals with *Formica rufa* 6x and re-injection of patient own blood versus placebo, using a randomised controlled trial
  - No differences between intervention and placebo outcomes

References

Included systematic reviews

Bellavite P, Marzotto M, Chirumbolo S, Conforti A. 2011. Advances in homeopathy and immunology: a review of clinical research. *Frontiers in Bioscience,* S3, 1363-1389.

Primary included studies

Andrade LE, Ferraz MB, Atra E, Castro A, Silva MS. 1991. A randomized controlled trial to evaluate the effectiveness of homeopathy in rheumatoid arthritis. *Scand J Rheumatol* 20, 204-208.

Fisher P, Scott DL. 2001. A randomized controlled trial of homeopathy in rheumatoid arthritis. *Rheumatology (Oxford)* 40, 1052-1055.

Gibson R. G., Gibson S. L., MacNeill A. D., Buchanan W. W. 1980. Homoeopathic therapy in rheumatoid arthritis: evaluation by double- blind clinical therapeutic trial. *Br J Clin Pharmacol* 9, 453-459.

Gibson RG, Gibson SL, MacNeill AD, Gray GH, Dick WC, Buchanan WW. 1978. Salicylates and homoeopathy in rheumatoid arthritis: preliminary observations. *Br J Clin Pharmacol* 6, 391-395.

Schirmer KP, Fritz M, Jackel WH. 2000. Effectiveness of Formica rufa and autologous blood injection in patients with ankylosing spondylitis: a double-blind randomized study. *Z Rheumatol* 59, 321-329.

Wiesenauer M, Gaus W. 1991. Wirksamkeitsnachweis eines Hom÷opatikums bei chronischer Polyarthritis. Eine randomised Doppelblindstudie bei niedergelassen Arzten. *Akt Rheumatol* 16, 1-9.

Sleep disorders

Executive Summary

Three systematic reviews were identified in Categories 1 and 2, which investigated the effectiveness of homeopathic treatments for sleep disorders.

- Two recent Category 1 reviews (Cooper and Relton 2010, Ernst 2011b) focused specifically on the effectiveness of homeopathy as a treatment for sleep disorders.
- One recent Category 1 review (Sarris and Byrne 2011) considered the effectiveness of CAM for insomnia.

Error: Sarris and Byrne 2011 is a Category 2 review - see below

Key systematic reviews: Cooper and Relton (2010) identified four RCTs and Ernst (2011b) identified the same four RCTs, plus another two RCTs. Both systematic reviews were of good methodological quality and focussed specifically on the effectiveness of homeopathic treatment on insomnia, therefore these reviews were considered to be key evidence sources for this question.

	Cooper & Relton 2010	***Ernst 2011b***
Carlini et al. 1987	√	√
Ciadella et al. 2001	√	√
Wolf 1992	√	√
Kolia-Adam et al. 2008	√	√
La Pine et al. 2006		√
Naude et al. 2010		√

Other systematic review: Sarris and Byrne (2011) conducted a systematic review of insomnia and complementary medicine, including herbal and nutritional medicine, acupuncture, acupressure, yoga, tai chi, massage, aromatherapy and homeopathy. It was a Category 2 review as it did not focus only on homeopathy and sleep disorders. The review authors searched from database inception to late 2009 in the follow databases: PubMed, CINAHL, PsycInfo, Cochrane library. Only RCTs were included and these were excluded if they had an inadequate control condition or a sample size of less than 30. No homeopathy studies met the inclusion criteria in this review.

Conclusion: There is no convincing evidence from two good quality systematic reviews, reporting on six primary experimental studies of poor to moderate quality, of 263 individuals with sleep disorders, that homeopathy is effective for the treatment of sleep disorders (Grade C).

Methodological assessment of the key reviews

Validity issue	Comment: Cooper and Relton (2010)	Comment: Ernst (2011b)
The review question (PICO)	P: Insomnia as a primary condition. I: homeopathy (not defined other than as individualised or complex) C: any (not defined) O: self-reported sleep duration, latency and quality and the clinical global impression improvement scale	P: Insomnia, sleep disorders. I: homeopathy (any form) C: other interventions (placebo or no treatment) O: self-reported sleep duration, latency, the sleep impairment index and quality and the clinical global impression improvement scale
Is it unlikely that that important, relevant studies were missed?[7]	Yes, it is unlikely. The following databases were searched up to July 2009: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE), Science Citation Index, and BIOSIS Previews. Searches were also undertaken of the Allied and Complementary Medicine (AMED) database and homeopathy-specific databases including Hom-Inform, ReferenceWorks and a further database of trials of homeopathy Search terms were text and MeSH based.	Yes, it is unlikely. The following databases were searched up till June 2010: MEDLINE, EMBASE, AMED, CINAHL, Cochrane central register. Search terms were text.
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated.	Yes. The selection criteria are clearly stated.
Were the included studies sufficiently valid for the type of question asked?	Unclear. RCTs evaluated using CRD tool. There were Significant problems with withdrawal, or failure to take account of withdrawals, absent information on statistical power comparability between groups not reported. Studies were not excluded based on quality.	Unclear. RCTs evaluated using Cochrane criteria (sequence generation, allocation concealment, blinding, completeness of outcome data and other sources of bias (scored from 0-12 [poor 0-4, moderate 5-8, good 9-12])). Quality rating of the included studies was poor-moderate.
Were the results similar from study to study?	Yes. Study samples were similar and within-group change was similar	Yes. No significant intergroup differences were reported in five studies, although

[7] It is not possible to be certain that important studies were not missed by these two reviews given the similarity of publication date and different included study numbers.(Author's footnote)

	across component studies.	Naude (2010) reported change in hours of sleep favouring homeopathy.
How are the results presented?	A summary for each included study was provided in table one "Homeopathic medicines: Characteristics and results of included studies" (p. 332). This included study type, population, intervention and N, control, results and quality/ methodology/ clinical comments. Meta-analysis was not conducted.	A summary for each included study was provided in table one "RCTs of homeopathy for insomnia and sleep related disorders" (p. 197). This included study design, sample size, intervention, control, main outcome measures, main results, quality ratings and comment. Meta-analysis was not conducted.
Main conclusion of review authors	Cooper and Relton (2010) concluded that "The limited evidence available does not demonstrate a statistically significant effect of homeopathic medicines for the treatment of insomnia. Existing RCTs were of poor quality and were likely to have been underpowered." (p. 329).	Ernst (2011b) concluded that "Evidence from RCTs does not show homeopathy to be an effective treatment for insomnia and sleep related disorders" (p. 195).
Other issues	Cooper and Relton sought studies of homeopathic medicines and studies of treatment by a homeopath. All four included RCTs related to homeopathic medicines, no RCTs were identified for treatment by a homeopath.	

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Evidence statement

Key question	Rating	Justification
Evidence Base	C	The review methods were sound but the included studies were of moderate to poor quality.
Consistency	B	Most studies are consistent in reporting no effect, and inconstancy may be explained by biases in primary study design.
Clinical impact	D	Slight or restricted as indicated in the section on study result similarity, and on the details extracted from the individual studies.

Bias does not contribute to Consistency - it is the heterogeneity of studies that is important here

CLINICAL IMPACT: study results were similar - strengthening the consistency as mentioned above. The Contractor has confused consistency and clinical impact here.

Included primary studies

- Carlini et al. (1987) conducted a crossover RCT using 44 patients with severe insomnia (age not reported), using Individualised homeopathic medicine as the intervention. The study was of poor quality, biased by 41% withdrawal rate. Jadad score 3/5
  - *Outcomes:* Both groups showed significant improvement from baseline by day 15 and at all time points until 3 months, on all outcomes. No consistent differences between patients starting on intervention or placebo, although difficult to analyse due to crossover design.
- Cialdella et al. (2002) conducted an RCT using 96 patients with insomnia (mean age 54) having received low dose benzodiazepines for three months or more. Intervention was Formulaic

homeopathic medicines: *Homeogene-46a or Sedatif-PC*, compared with placebo. The study was of poor quality, biased by 36% withdrawal rate, subjects who were not included in analysis. Unknown Risk of Bias

  - *Outcomes:* No significant difference between groups

- Kolia-Adam et al. (2008) conducted an RCT of 30 people (mean age 32.5) with insomnia, lasting a year or more, with difficulty falling asleep due to nervous excitability. Intervention was Formulaic homeopathic medicine: *Coffea cruda 200c*. Study was of poor quality (High Risk of Bias), biased by unstated withdrawals and lack of information on comparability between groups.
  - *Outcomes:* Significant increase in sleep duration in both groups; no significant differences between groups
- La Pine et al. (2006) conducted a double-blinded cross-over trial with 34 participants. The study was of moderate quality. The intervention was formulaic *No-Shift-Lag* applied for 1 week compared with (unstated) placebo. Quality score not stated.
  - *Outcomes:* No significant intergroup differences
- Naude et al. (2010) conducted a parallel double-blinded experimental design study, with 30 participants, applying individualised homeopathy for 4 weeks compared with placebo (unstated). The study was of moderate quality, but had a High Risk of Bias.
  - *Outcomes:* Change in total hours of sleep/week favoured homeopathy, not significant
- Wolf (1992) used an RCT to study 29 patients with difficulties falling asleep or staying asleep (age range 19-73). Intervention was Formulaic homeopathic medicine *Requiesana*. Study was poor quality, biased by lack of information on allocation concealment and comparability between groups. Quality score not stated.
  - *Outcomes:* 57% patients reported improvement in homeopathy group; 29% in placebo group (difference between groups non-significant)

References

Included systematic reviews

Cooper KL, Relton C. 2010. Homeopathy for insomnia: A systematic review of research evidence. *Sleep Medicine Reviews* 14, 329-337.

Ernst E. 2011b. Homeopathy for insomnia and sleep-related disorders: a systematic review of randomised controlled trials. *Focus on Alternative & Complementary Therapies* 16, 195-199.

Sarris J, Byrne GJ. 2011. A systematic review of insomnia and complementary medicine. *Sleep Medicine Reviews* 15, 99-106.

Primary included studies

Carlini EA, Braz S, Troncone LR, Tufik S, Romanach AK, Pustiglione M, et al. 1987. [Hypnotic effect of homeopathic medication and placebo. Evaluation by double-blind and crossing technics]. Revista Da Associacao Medica. (translated from Portuguese) *AMB Rev Assoc Med Bras* 33, 83–8.

Cialdella P, Boissel JP, Belon P. 2001. [Homeopathic specialties as substitutes for benzodiazepines: double-blind vs. placebo study]. *Therapiewoche* 56(4), 397–402. (translated from French)

Kolia-Adam N, Solomon E, Bond J, Deroukakis M. 2008. Double-blind placebo controlled study with coffea for insomnia. *Simillimum* 21 [Winter/ Spring].

La Pine MP, Malcomson FN, Torrance JM, Marsh NV. 2006. Night shift: can a homeopathic remedy alleviate shift lag? *Dimens Crit Care Nurs* 25, 130–6.

Naudé DF, Marcelline I, Couchman S, Maharaj A. 2010. Chronic primary insomnia: efficacy of homeopathic simillimum. *Homeopathy* 99, 63-68

Wolf J. 1992. Schlafstorungen ohne Hang-over behandeln. *Natura Med* 7(9), 586–9. (translated from German)

Upper Respiratory Tract Infections (URTI) (incl. bronchitis, sinusitis, tonsillitis, pharangitis, influenza, common cold and miscellaneous otorhinolaryngologic complaints)

Executive summary

Two systematic reviews were identified (Category 3), which investigated the effectiveness of homeopathic treatments for URTI and related conditions (Altunc 2007, Bellavite et al. 2011). There was no Category 1 review which focused solely on homeopathy for URTI, and no Category 2 review which reported on the effectiveness of CAM (including homeopathy) for URTI.

Key systematic review: Bellavite et al. (2011) considered the past 30 years of research into the effectiveness of homeopathic medicines for the treatment of respiratory allergies, common upper respiratory tract infections, otorhinolaryngologic complaints, and rheumatic diseases. This work supersedes the Bellavite 2006 and 2008 reviews. Bellavite et al. (2011) identified 21 relevant primary (experimental) studies which tested the effects of homeopathy for URTI (various diagnoses). See summary table below, with references grouped by URTI conditions. Bellavite et al. (2011) was included in other evidence summaries in this report, as a key evidence source, because of its comprehensive search. Bellavite et al. (2011) reports on a high quality search and contains a comprehensive reference list for a range of respiratory conditions (83 included references for allergic and infections conditions). It includes both studies identified by Altunc (2007). Thus Bellavite et al. (2011) was considered as the key evidence source for URTI conditions.

Other systematic review: Altunc et al. (2007) investigated the effectiveness of homeopathy for a number of childhood conditions, namely adenoid vegetation, ADHD, asthma, otitis media, conjunctivitis, diarrhea, post-operative pain, URTI and warts. The authors searched a range of databases to identify relevant literature, including MEDLINE, EMBASE, AMED, CINAHL, Cochrane Central, British Homeopathic Library, ClinicalTrials.gov, and the UK National Research Register up to January 2006. Considering the effectiveness of homeopathy for URTI, Altunc et al. (2007) found two relevant primary (experimental) studies, both of which were included in Bellavite et al. (2011). The authors concluded that "the evidence from rigorous clinical trials of any type of therapeutic or preventative intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition" (p 74).

Summary of primary studies, conditions, N and source review

Study	***Condition***	***N*** (adults unless otherwise stated)	***Bellavite 2011***	***Altunc 2007***
Bordes and Dorfman 1986	Cough	60	√	
Casanova and Gerard 1988	Influenza-like symptoms	300	√	
Ferley et al. 1989	Influenza-like symptoms	478	√	
Heilmann 1994	Common 'flu and cold'	102	√	
Papp et al. 1998	Influenza-like symptoms	372	√	

Adler 1999	Acute sinusitis	119	√	
Wiesenauer et al. 1989	Sinusitis	152	√	
Weiser and Clasen 1994	Chronic sinusitis	155	√	
Zabolotnyi, Kneis et al. 2007	Maxilliary sinusitis	113	√	
de Lange de Klerk et al. 1994	Pharangitis and tonsillitis	170 children	√	√
Trichard, Chaufferin et al.2005	Acute rhinopharangitis	499 children	√	
Wiesenauer 1998	Acute tonsillitis	107	√	
Zenner and Metelmann 1990	Pharyngitis and tonsillitis	594	√	
Haidvogl, Riley et al. 2007	Upper respiratory tract infections	1557	√	
Lecoq 1985	Upper respiratory tract infections	60	√	
Rabe, Weiser et al. 2004	Mild upper respiratory tract infections	485	√	
Ramchandani 2010	Upper respiratory tract infections	30 children	√	
Riley, Fischer et al. 2001	Respiratory tract complaints or ear complaints	456	√	
Steinsbekk, Bentzen et al. 2005a	Upper respiratory tract infections	251 children	√	√
Steinsbekk, Fonnebo et al. 2005b	Upper respiratory tract infections	169 children	√	
Steinsbekk, Lewith et al. 2007	Upper respiratory tract infections	208 children	√	

Conclusion: Children: Of six studies of total 1327 children, there is no convincing evidence to support the effectiveness of homeopathy for the treatment of any manifestation of upper respiratory tract infections (URTIs) (Grade D)

Adults: Of 15 studies of total 5050 adults, homeopathy has variable effectiveness dependent on the diagnosis, as outlined below (Grade C)

Cough (N=60) (one study which favours homeopathy)

Influenza (N=1252) (four studies, three favouring homeopathy, one equivalent)

URTI (N=2558) (four studies, two favouring homeopathy, two equivalent)

Sinusitis (N=539) (four studies, two favouring homeopathy, two equivalent)

Tonsillitis (N=701) (two studies, both favouring homeopathy)

Methodological assessment of the key evidence source

Validity issue	Comments: Bellavite et al (2011)
The review question (PICO)	P: adults and children with conditions collectively termed URTI I: homeopathically prepared remedies C: any (not defined) O: any reported
Is it unlikely that that important, relevant studies were missed?	No. The review sought experimental research on humans, published between 1978 and 2010. Data came from "current reading of major complementary and alternative medicine journals, screening of the Hominform Information Service databases (British Homeopathic Library, http://hominform.soutron.com/), literature searches using Medline, the Cochrane Database of Systematic Reviews, and cross-referencing between published papers" (p. 1364). The authors also "consulted previously published systematic reviews and meta-analyses that have covered trials of immunoallergology" (p. 1364). "All forms of homeopathic therapy were included in the review, namely: a) classical individualised homeopathy, b) ailment-specific remedies and complexes, c) isotherapy where indicated" (p. 1364).
Were the criteria used to select articles for inclusion appropriate?	Yes. The selection criteria are clearly stated. "Analysis included controlled clinical trials (with and without randomisation), observational studies and case series, but excluded single case reports" (p. 1364).
Were the included studies sufficiently valid for the type of question asked?	Unclear. The included studies were not assessed for methodological quality, only described by experimental design, evidence source and study population. All studies assessed classical individualised homeopathy using experimental designs which variably including randomisation and controlling.
Were the results similar from study to study?	No. Studies are heterogeneous in terms of populations and interventions.
How are the results presented?	Characteristics of included studies are included in Table 1 (p. 1366), reporting authors, study design, participant type and N, treatment, outcomes and key results. Study findings are summarised in Table 4 (p. 1381) as strength of the body of evidence per condition, with the study name and type, and peer-reviewed journal source identified.
Main conclusion of review authors	In Table 4 (p. 1381) the authors conclude that there is: • good positive evidence for the use of *Anas barbariae* 200k in therapy of influenza like-syndromes a. positive evidence reported by Casanova and Gerard 1988, Papp, Schuback et al. 1998, Ferley, Zmirou et al. 1989. b. evidence of little effect reported by Vickers and Smith 2009. • good evidence of effect of the use of *euphorbium compositum* in sinusitis (Weiser and Clasen 1994)

Poor commentary on quality of studies and risk of bias of primary studies

	• conflicting evidence in individualized homeopathy in upper respiratory tract infections, with *a.* positive evidence reported by Riley, Fischer et al. 2001, Steinsbekk, Fonnebo et al. 2005, Trichard, Chaufferin et al. 2005, Haidvogl, Riley et al. 2007, Witt, Ludtke et al. 2009, Ramchandani 2010. *b.* little evidence reported by de Lange de Klerk 1994. *c.* no evidence reported by Steinsbekk, Bentzen et al. 2005. • positive evidence for *engystol-n* in common cold and flu (Heilmann 1994, Schmiedel and Klein 2006). • no evidence for homeopathic complex *Luffa+Cinnabaris+Kalium Bichromicum* (Wiesenauer, Gaus et al. 1989).
Other issues	The authors indicate that "The evidence for individualised homeopathic therapy in the field of upper respiratory tract infections and for homeopathic immunotherapy in respiratory allergies is conflicting. Pragmatic equivalence trials suggest that, in primary care, homeopathic treatment is not inferior to conventional treatment. A larger number of observational studies and of clinical trials -- conducted in a methodologically correct manner without altering the treatment setting-- are needed before sure conclusions concerning the application of homeopathy for specific diseases can be drawn". (p. 1363)

Evidence statement

EVIDENCE STATEMENT AND CONCLUSIONS NOT CONFIRMED BY EXPERT COMMITTEE

Key question	Rating	Justification
Evidence Base	C	The key review method is sound. However despite their number, the included primary studies are of variable study design and quality, and they consider a range of conditions which are labelled as URTI, but may which reflect very different pathogens and manifestations
Consistency	C-D	See above comment on heterogeneity, and main conclusions of authors
Clinical impact	C-D	Slight or Restricted for homeopathy for URTI for children Moderate impact for some conditions for adults. The degree of impact indicated by the lack of homogeneity of primary study designs, interventions and differences in primary outcome measures between treatment groups

CONSISTENCY should be a 'D' rating as the CEBM appraisal clearly states that populations and interventions were heterogeneous.

The Contractor is confusing consistency (homogeneity) and clinical impact

Summary of primary included studies

Children

- De Lange de Klerk et al. (1994) used a RCT to study 170 children with pharangitis and tonsillitis (described by Altunc (2007) as having recurrent URTI), aged approximately 4 years old, using a moderate quality parallel experimental design trial (Jadad score = 3/5). Individualised homeopathic remedies were used.
  - *Outcomes:* No significant difference between groups.
- Ramchandani (2010), using a prospective observational study, tested 30 children with URTI using individualised homeopathy. Quality score not stated.

- *Outcomes:* Decrease in episodes of 6 months which favoured homeopathy

- Steinsbekk, Bentzen et al. (2005a) studied 251 children with parents-selected homeopathic medicines vs. placebo in a high quality parallel experimental design (Jadad score = 5/5).
  - *Outcome*: No effectiveness of homeopathy over placebo.
- Steinsbekk, Fonnebo et al. (2005b) studied 169 children aged approximately 3 years, with URTI (both reviewers agree on the diagnosis), in a non-randomised, controlled (open) trial. Standardised non-material homeopathy was used, for 12 weeks, compared with conventional care. Quality score- Moderate Risk of Bias.
  - *Outcomes:* There was a decrease of days with symptoms in homeopathic group but no overall differences between groups. There were no drop-outs due to adverse events.
- Steinsbekk, Lewith et al. (2007) used a RCT which studied 208 children with URTI with individualised vs. parents-selected medicines. Jadad score 3/5.
  - *Outcome*: No difference between the two methods of prescription.
- Trichard et al. (2005) studied 499 children with acute rhinopharangitis with homeopathic strategy vs. allopathic strategy (e.g. antibiotics) (case series). Quality score not stated.
  - *Outcome*: Various indexes significantly in favour of homeopathic strategy, lower medical costs (case series, uncontrolled).

<u>*Adults*</u>

Cough

- Bordes and Dorfman (1986) considered 60 adults in a RCT, investigating Low-dilution (3c) homeopathic complex in syrup (*Drosera*) vs. placebo. Quality score-Low Risk of Bias.
  - *Outcome*: Significantly better decrease of symptoms in treated patients.

Influenza-like symptoms

- Casanova and Gerard (1988) in 300 adults, used a RCT to investigate *Oscillococcinum* (*Anas barbariae* 200K) 1 dose in the morning and 1 in the evening for 3-4 days. Quality score-Low Risk of Bias.
  - *Outcome*: In the verum group faster temperature reduction, significantly less shivering and less myalgia after 4 days.
- Ferley et al. (1989) investigated in 478 adults in a RCT using *Oscillococcinum* (*Anas barbariae*200k) 5 doses, one every 12 h. Jadad score 5/5.
  - *Outcome*: Clinical healing after 48 hours and rate of temperature reduction better in the verum group.
- Heilmann (1994) investigated common 'flu and cold (presumed influenza-like symptoms) in a RCT of 102 adults using *Engystol-N vs.* placebo, i.v. injection. Quality score not stated.
  - *Outcome*: No changes of frequency of attacks; decrease of symptoms and their duration.
- Papp et al. (1998) in a RCT, investigated influenza-like symptoms in 372 adults using *Oscillococcinum* (*Anas barbariae* 200k) 1 dose for 3 time/day x 3 days. Jadad score 4/5.
  - *Outcome*: Statistically significant reduction of symptoms after 48 h in the verum group.

Upper respiratory tract infections

- Haidvogl, Riley et al. (2007) in a non-controlled, randomised open trial studied 1557 adults using homeopathic strategy vs. allopathic (e.g. anti-inflammatory drugs, antibiotics). Quality score-Low Risk of Bias.
    - *Outcomes:* Homeopathic treatment not inferior to the allopathic and best tolerated
- Lecoq (1985) in 60 adults, RCT investigating Homeopathic complex *L52* vs. placebo. Quality score-Moderate Risk of Bias.
    - *Outcome:* Patients rated more relief in symptoms in verum group
- Rabe, Weiser et al. (2004) 485 adults tested homeopathic complex *Grippheel*vs. Anti-inflammatory agents (non-randomised controlled open trial). Quality score not stated.
    - *Outcome:* equivalence between intervention and placebo.
- Riley, Fischer et al. (2001) (included ear complaints) in 456 adults applied individualized homeopathy vs. allopathy (non-randomised controlled clinical trial). Quality score-High Risk of Bias.
    - *Outcome*: Improvement in 82.6% of homeopathic patients, 68% of allopathic.

Sinusitis

- Adler (1999) investigated acute sinusitis in 119 adults using Homeopathic complex *Sinusitis PMD* in a prospective observational study. Quality score-High Risk of Bias.
    - *Outcome:* trended to positive (uncontrolled).
- Weiser and Clasen (1994) (Chronic sinusitis) (N=155)(RCT) investigated Euphorbium compositum vs. placebo. Jadad score 3/5.
    - *Outcome:* 21.1% improvement in the verum group, 14.4% in the placebo group, non-significant differences.
- Wiesenauer et al. (1989) (undefined sinusitis) investigated 152 adults with Low-dilution (3x-4x) homeopathic complex *Luffa*, *Cinnabaris*, *Kalium bichromicum* vs. placebo in a RCT. Quality score not stated.
    - *Outcome*: No effect over placebo in global symptoms.
- Zabolotnyi, Kneis et al. (2007) investigated 113 adults with maxiliary sinusitis in a RCT applying Homeopathic complex *Sinfrontal* vs placebo. Quality score not stated
    - *Outcomes*: significant improvement in homeopathic group

Acute tonsillitis

- Wiesenauer (1998) (prospective observational study) tested 107 individuals with Low-dilution homeopathic complex of *Phytolacca americana,Guajacum officinale,Capsicum annuum.* Quality score not stated.
    - *Outcome:* Decrease of symptoms in most patients (uncontrolled).
- Zenner and Metelmann (1990) (pharyngitis and tonsillitis) (N=594) investigated Low-dilution (3x-4x) homeopathic complex *Lymphomyosot* drops in a prospective observational study. Quality score not stated.
    - *Outcome*: Improvement in >90% of cases (uncontrolled).

References

Included systematic review

Altunç U, Pittler MH, Ernst E. 2007. Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic proceedings. Mayo Clinic* 82, 69-75

Bellavite P, Marzotto M, Chirumbolo S, Conforti A. 2011. Advances in homeopathy and immunology: a review of clinical research. *Frontiers in Bioscience* S3, 1363-1389.

Included primary studies

Adler M. 1999. Efficacy and safety of a fixed-combination homeopathic therapy for sinusitis. *Adv Ther* 16, 103–11.

Bordes LR, Dorfman P. 1986. Evaluation de l'activite´ antitussive du sirop Drosetux: Etude en double aveugle versus placebo. *Cahiers d'Otorhinolaryngologie* 21, 731–4.

Casanova P, Gerard R. 1988. Bilan de 3 années d'études randomisées multicentriques oscillococcinum/placebo. *Proposta Omeopatica* 6, 14-17.

De Lange de Klerk et al. 1994. Effect of homeopathic medicines on dailyburden of symptoms in children with recurrent upper respiratory tract infections. *BMJ* 309: 1329-1332.

Ferley JP, Zmirou D, D'Adhemar D, Balducci F. 1989. A controlled evaluation of a homoeopathic preparation in the treatment of influenza-like syndromes. *Br J Clin Pharmacol* 27, 329-335.

Haidvogl M, Riley DS, Heger M, Brien S, Jong M, Fischer M, Lewith GT, Jansen G, Thurneysen AE. 2007. Homeopathic and conventional treatment for acute respiratory and ear complaints: a comparative study on outcome in the primary care setting. *BMC Complement Altern Med* 7(1), 7.

Heilmann A. 1994. A combination injection preparation as a prophylactic for flu common colds. *Biol Ther* 7, 249-253.

Lecoq PL. 1985. L-52. Les voies the´rapeuthiques des syndromes grippaux. *Cah Biothe´r* 87, 65–73.

Papp R, Schuback G, Beck E, Burkard G, Bengel S, Lehr S, Belon P. 1998. Oscillococcinum in patients with influenza-like syndromes: a placebo controlled doubleblind evaluation. *Br Homeopath J* 87, 69-76.

Rabe A, Weiser M, Klein P. 2004. Effectiveness and tolerability of a homoeopathic remedy compared with conventional therapy for mild viral infections. *Int J Clin Pract* 58, 827-32.

Ramchandani NM. 2010. Homoeopathic treatment of upper respiratory tract infections in children: Evaluation of thirty case series. *Complement Ther Clin Pract* 16, 101-108.

Riley D, Fischer M, Singh B, Haidvogl M, Heger M. 2001. Homeopathy and conventional medicine: an outcomes study comparing effectiveness in a primary care setting. *J Altern.Complement Med* 7, 149-159.

Steinsbekk A, Bentzen N, Fonnebo V, Lewith G. 2005a. Self-treatment with one of three self selected, ultramolecular homeopathic medicines for the prevention of upper respiratory tract infections in children. A double-blind randomized placebo controlled trial. *Br J Clin Pharmacol* 59, 447–55.

Steinsbekk A, Fonnebo V, Lewith G, Bentzen N. 2005b. Homeopathic care for the prevention of upper respiratory tract infections in children: a pragmatic, randomised, controlled trial comparing individualised homeopathic care and waiting-list controls. *Complement Ther Med* 13, 231–8.

Steinsbekk A, Lewith G, Fonnebo V, Bentzen N. 2007. An exploratory study of the contextual effect of homeopathic care. A randomised controlled trial of homeopathic care vs. self-prescribed homeopathic medicine in the prevention of upper respiratory tract infections in children. *Prev Med* 45, 274-279.

Trichard M, Chaufferin G, Nicoloyannis N. 2005. Pharmacoeconomic comparison between homeopathic and antibiotic treatment strategies in recurrent acute rhinopharyngitis in children. *Homeopathy* 94, 3–9.

Weiser M, Clasen BP. 1994. Controlled double-blind study of a homoeopathic sinusitis medication. *Biol Ther* 13, 4–11.

Wiesenauer M, Gaus W, Bohnacker U, Haussler S. 1989. Efficiency of homeopathic preparation combinations in sinusitis. Results of a randomized double blind study with general practitioners. *Arzneimittelforschung* 39, 620–5.

Wiesenauer M. 1998. Comparison of solid and liquid forms of homeopathic remedies for tonsillitis. *Adv Ther* 15, 362–371.

Zabolotnyi DI, Kneis KC, Richardson A, Rettenberger R, Heger M, Kaszkin-Bettag M, Heger PW. 2007. Efficacy of a complex homeopathic medication (Sinfrontal. in patients with acute maxillary sinusitis: a prospective, randomized, double-blind, placebo controlled, multicenter clinical trial. *Explore (NY)* 3, 98-109.

Zenner S, Metelmann H. 1990. Therapeutic use of lymphomyosot, result of a multicentric use observation study on 3512 patients. *Biol Ther* 8, 49–69.

Vertigo

Executive summary

One meta-analysis was identified (Category 1), which investigated the effectiveness of homeopathic treatments for vertigo (Schneider et al 2005).

Key systematic review: Schneider et al. (2005) conducted a meta-analysis for the treatment of vertigo with homeopathy, however no details were provided of study selection, which studies were included or study details. This study did not score positively on any of the CEBM criteria, and did not provide any verifiable evidence to inform this overview review.

Conclusion: One poor quality review summarised four un-named primary studies. Despite the author's positive analysis of the data from the included studies, this review provided no details on primary studies which could be verified through independent analysis. The Contractor has omitted to include Evidence Statement grading of D

Methodological assessment of the key evidence

Validity issue	Comment: Schneider et al. (2005)
The review question (PICO)	No PICO was provided
Is it unlikely that that important, relevant studies were missed?	No search strategy was provided
Were the criteria used to select articles for inclusion appropriate?	No selection criteria was provided
Were the included studies sufficiently valid for the type of question asked?	Unclear. There was no quality scoring of the included studies, and no indication of how the included studies were identified.
Were the results similar from study to study?	No. Studies appear to be heterogeneous from the data presented in Table 2, and Figures 1 and 2. The included studies were not identified by name and therefore the data extraction cannot be verified
How are the results presented?	A summary for each included study was provided in Table 2 of treatment group, N, age mean +/SD, mean baseline episodes / day. Figures 1 and 2 report study outcome data. Meta-analysis appears to have been reported in Figures 3 and 4.
Main conclusion of review authors	Schneider et al. (2005) concluded "the meta-analysis supports the consistently demonstrated efficacy and tolerability of this homeopathic preparation, effects that seem to be at least as good as good as for standard therapies" (p. 29).
Other issues	This study may have lost important data in translation from German to English.

Evidence statement

Key question	Rating	Justification
Evidence Base	D	The review method is poor and it is not possible to evaluate the quality of the(unidentified) included studies
Consistency	D	See above comment on heterogeneity
Clinical impact	D	see answers to all questions above

References

Included systematic review

Schneider B, Klein P, Weiser M (2005): Treatment of vertigo with a homeopathic complex remedy compared with usual treatments. Arzneim.-Forsch./Drug Research 55(1): 23-29

Part 3: Summary of relevant Government Reports

Section A

Purpose of this report: This report summarises relevant international Government reports produced since 2000, on any aspect of the prescription, delivery and effectiveness of homeopathy. This report forms part of a larger project undertaken in 2012 for NHMRC entitled 'The Effectiveness of Homeopathy: An overview review of secondary evidence'.

Searching methods: For the purpose of the larger project, secondary evidence was identified from a number of sources, namely the reference lists of public submissions to NHMRC, directly from library databases, reference lists of relevant literature identified from the library databases and submissions, 'grey literature' which included government reports, and clinical guidelines. The grey literature search specifically targeted government reports. The reason for identifying these reports was twofold, to:

- summarise their key findings and recommendations
- identify systematic reviews in their reference lists which had not been identified by other searching methods undertaken in this project.

***Grey literature searching*:** Government reports were identified through a comprehensive and iterative search using Google, the World Health Organisation website, the UK National Health Service, and internationally-respected guideline sites (NHMRC, SIGN, NZGG and NICE).

Search terms included 'homoeopathy OR homeopathy AND report OR guide* OR review'.

Results: Six potentially-relevant Government reports were identified through the search strategy (See Table 6), and four reports were retained as relevant to this review. All were recent (published within the last five years). Of the two excluded articles, one was found via Google, and was a public information pamphlet (not a government report), and the other was a WHO report, which reported on drug safety practices.

Table 6. Sites searched, number of hits and retained Government reports

Site	Hits (relevant to project objectives)
NHMRC http://www.nhmrc.gov.au/	0
SIGN http://www.sign.ac.uk/guidelines/index.html	0
NHC http://www.nationalhealthcouncil.org/	0
NZGG http://www.nationalhealthcouncil.org/	0
NICE http://www.nice.org.uk/	0
NHS http://www.ic.nhs.uk/	0
Google http://www.google.com/webhp?hl=en	5 (4)
WHO http://www.who.int/en/	1 (0)

Government Report Conclusions

The four included Government reports provided answers to targeted and different questions posed by the British House of Commons, the Swiss Government's evaluation of complementary medicine evidence, and two Belgium Government reports (one conducted in response to the findings of the other). The reports differed in their conclusions, with two finding no evidence of homeopathy treatment effectiveness (UK, Belgium Federal Health Care Knowledge Centre) and two finding evidence for homeopathy treatment effectiveness (Swiss Government, Belgium Liga Medicorum Homeopathica Internationalis (LIGA)).

Search strategies differed between the reports, and the LIGA report was conducted on the grounds of concerns regarding the research methodology and findings of the Belgium Knowledge Care Centre report. LIGA conducted its own systematic review, and provided evidence tables of references published since 2000, and summary findings for many of the clinical conditions also reviewed in the NHMRC overview review. In many instances, the cited LIGA reviews were found by the methodologists for the NHMRC review in an independent search, although the conclusions are not universally replicated between the two reviews. There are also a number of instances where included secondary evidence in the LIGA report were excluded by the NHMRC methodologists because the evidence did not meet systematic review criteria, or were not the most recent secondary evidence source.

Government Report References

House of Commons Science and Technology Committee, Evidence Check 2: Homeopathy fourth report of session 2009-10.

Bornhoft & Matthiessen (eds.) Homeopathy in healthcare: Effectiveness, appropriateness, safety, costs. An HTA report on homeopathy as part of the Swiss Complementary Medicine Evaluation Program. 2011

Etat des lieux de l'homeopathie en Belgique (Homeopathy: the state of affairs in Belgium) a report published by the Belgium Federal Health Care Knowledge Centre 2011.

The research working group of the Liga Medicorum Homeopathica Internationalis (LMHI) about the clinical efficacy of homeopathy. 2011

U.S. Department of Health and Human Services, National Institute of Health and the National Centre for Complementary and Alternative Medicine. Homeopathy: an introduction. 2009.
Excluded- this is a public information pamphlet.

World Health Organisation, Safety issues in the preparation of homeopathic medicines, 2009.
Excluded- focus is on whether homeopathic medicine growth, collection, and delevopment meet drug safety standards

The included Government reports are summarised in Section B.

Section B

1. House of Commons Science and Technology Committee, Evidence Check 2: Homeopathy fourth report of session 2009-10.

The purpose of the evidence check programme was to examine evidence used by the British government to devise and review its policies. The comprehensive review provided in this report was undertaken in order to examine the scientific evidence base for the UK government's policies on the funding and provision of homeopathy through the National Health Service, and the licencing of homeopathic products and medicine through the Medicines and Healthcare products Regulatory Agency. The report collated a range of evidence from a range of sources, and included two invited submissions by eminent researchers in homeopathy (Edward Ernst, and Robert Mathie). Both of these submissions provided extensive reference lists. We cite the evidence summary in this Government report, and collate the reference lists provided by the eminent homeopath researchers as validation for the secondary evidence included in the NHMRC overview review.

In addition to the 74 potentially relevant secondary evidence outlined in Tables 7 and 8, this Government report referenced an additional 460 articles that were primary studies, opinion pieces, or background evidence on general research, legislation and licencing matters.

The evidence section of the report concluded that

> *"Systematic reviews of rigorous trials of homeopathy fail to demonstrate that homeopathic remedies have effects beyond those of placebo. Monitoring the development of the evidence over time we find that the overall evidence-base of homeopathy is becoming more and more negative. Confronted with such data, homeopaths tend to counter that the method of testing homeopathy in clinical trials is flawed and the hierarchy of evidence is of disputed value. Nowadays they frequently cite Sir Michael Rawlins (NICE) in support of this view who recently gave a lecture discussing that the evidence from randomised clinical trials should not be seen in isolation. Homeopaths fail to mention, however, that Sir Michael also made the following statement about homeopathy: "As far as homeopathy is concerned it breaks every rule in the evidential base! It is biologically implausible; it is almost always used to treat conditions where the natural history is unpredictable; and the signal to noise ratio is close to one!" (Rawlins 2009). (p. Ev 28)*

This overall report concluded that

> *"By providing homeopathy on the NHS and allowing MHRA licensing of products which subsequently appear on pharmacy shelves, the Government runs the risk of endorsing homeopathy as an efficacious system of medicine. To maintain patient trust, choice and safety, the Government should not endorse the use of placebo treatments, including homeopathy. Homeopathy should not be funded on the NHS and the MHRA should stop licensing homeopathic products." (p47)*

Supplementary memorandum submitted by Professor Edzard Ernst (HO 16a)

"In the document submitted on 5 November 2009, I stated that "systematic reviews or meta-analyses of the totality of the clinical trial data fail to show that homeopathic remedies generate clinical effects beyond those of placebo". This is an appendix substantiating this claim which I ask to be attached to my previously submitted evidence". (p. EV27)

Table 7: References cited by Ernst and their relevance to NHMRC project

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
Altunc U, PittlerMH, Ernst E. Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. Mayo Clin Proc 2007; 82(1):69–75.	Y Category 3		
Barnes J, Resch K L, Ernst E. Homeopathy for Postoperative Ileus. J Clin Gastroenterol 1997; 25:628–633.	Y Category 1		
Bornhoft & Matthiessen Homeopathy in healthcare: Effectiveness, appropriateness, safety, costs. An HTA report on homeopathy as part of the Swiss Complementary Medicine Evaluation Program. 2011	Y (Government Report)		
Cucherat M, Haugh M C, Gooch M, Boissel J-P. Evidence of clinical eYcacy of homeopathy. A metaanalysis of clinical trials. Eur J Clin Pharmacol 2000; 56:27–33.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Ernst E. Are highly dilute homoeopathic remedies placebos? Perfusion 1998; 11:291–292.			Y, reanalysis of data presented in Linde (1997)
Ernst E. Homoeopathic prophylaxis of headaches and migraine? A systematic review. J Pain Sympt Managem 1999; 18:353–357.	Y Category 1		
Ernst E. Classical homoeopathy versus conventional treatments: a systematic review. Perfusion 1999; 12:13–15.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Ernst E. Asystematic review of systematic reviews of homeopathy. Br J Clin Pharmacol 2002; 54:577–582.		Y (umbrella review)	
Ernst E. Weighing the homeopathic evidence. Homeopathy 2003; 92:67–68.			Y (methodological paper outlining quality appraisal of studies)
Ernst E, Barnes J. Are homoeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo-controlled trials. Perfusion 1998; 11:4–8.	Y Category 1		
Ernst E, Pittler MH. Effcacy of homeopathic arnica. A systematic review of placebo-controlled clinical trials. Arch Surg 1998;	Y Category 3		

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
133:1187–1190.			
Ernst E, Pittler M H. Re-analysis of previous meta-analysis of clinical trials of homeopathy. J Clin Epidemiol 2000; 53:1188.			Y (Reanalysis of previously-reported data, not SR or MA))
Ernst E, Pittler M H, Stevinson C, White A R. The Desktop Guide to Complementary and Alternative Medicine. 1st Edition. Edinburgh: Mosby. 2001.			Y
Ernst E, Pittler M H, Wider B, Body K. Homeopathy: is the evidence-base changing? Perfusion 2006; 19:1–3.			Y (methodological paper outlining changes over time in quality and findings of research)
Ernst E, Pittler M H, Wider B, Boddy K. The Desktop Guide to Complementary and Alternative Medicine. 2nd edition. Edinburgh: Elsevier Mosby. 2006.			Y
Jadad A R, Moore R A, Carrol D, Jenkinson C, Reynolds D J M, Gavaghan D J *et al*. Assessing the quality of reports of randomized clinical trials— is blinding necessary? Contr Clin Trials 1996; 17:1–12.			Y (methodological paper outlining quality appraisal of studies)
Jonas WB, Linde K, Ramirez G. Homeopathy and rheumatic disease. Rheum Dis Clin North Am 2000; 26:117–123.			Y, reanalysis of data already reported in Linde (1987)
Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV et al. Are the clinical eVects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 1997; 350:834–843.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Linde K, Jobst K A. Homeopathy for chronic asthma. The Cochrane Library 1998; 1:1–7.	Y, but excluded as there is an updated Cochrane review (McCarney 2008)		
Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: a state-of-the-art review. J Alt Complementar Med 1998; 4(371):388.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Linde K, Scholz M, Ramirez G, Clausius N, Melchart D, Jonas WB. Impact of study quality on outcome in placebo controlled trials of homoeopathy. J Clin Epidemiol 1999; 52:631–636.			Y Methodological paper
Long L, Ernst E. Homeopathic remedies for the treatment of osteoarthritis: a systematic review. Br Homeopath J 2001; 90:37–43.	Y Category 1		
Ludtke R,Wilkens J. KlinischeWirksambeitsstudien zu Arnica in homoeopathischen Zubereitungen. In: Company Report, Carstents Stiftung. Essen, German: 1999.		Y, excluded because no English language translation could be obtained	
Mathie R T. The research base for homeopathy: a fresh assessment of the literature. Homeopathy 2003; 92:80–87	Y, assigned as Category 4 and excluded from our		

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
	clinical review as did not have a focused clinical question		
Morrison B, Lilford R J, Ernst E. Methodological rigour and results of clinical trials of homoeopathic remedies. Perfusion 2000; 13:132–138.			Y Methodological paper
Rawlins M. As cited in Rose L, BMJ Rapid Response. BMJ Rapid Response 2009; 14 July.			Y primary paper
Shang A, Huwiler-Mu¨ntener K, Nartey L, Ju¨ ni P, Sterne J A C, Pewsner D *et al*. Are the clinical effectsof homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet 2005; 366:726–732.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Sterne J, Egger M, SmithGD. Investigating the dealing with publication and other biases. In: Systematic reviews in healthcare: meta-analysis in context. In: Egger M, Smith GD, Altman DG, editors. London: 2001. 189–208.			Y (Methodological paper)
Vickers A J, Smith C. Homeopathic oscillococcinum for preventing and treating influenza and influenzalike syndromes. The Cochrane Library 2001; 1:1–10.		Y, excluded as Cochrane review update in 2009 was never finished, and Cochrane Library indicated that earlier versions were out of date	

Table 8: References provided by Dr Robert Mathie

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
Altunc¸ U, Pittler MH, Ernst E (2007). Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic Proceedings*, **82**: 69–75.	Y Category 3		
Barnes J, Resch K-L, Ernst E (1997). Homeopathy for postoperative ileus? A meta-analysis. *Journal of Clinical Gastroenterology*, **25**: 628–633.	Y Category 1		
Behi R, Nolan M (1996). Quasi- experimental research designs. *British Journal of Nursing*, **5**:1079–1081.			Y primary paper
Bell IR, Lewis DA 2nd, Brooks AJ, *et al* (2004). Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. *Rheumatology*, **43**: 577–582.			Y primary paper
Bellavite P, Ortolani R, Pontarollo F, *et al*	Y, update review in		

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
(2006). Immunology and homeopathy. 4. Clinical studies— Part 2. *Evidence-based Complementary and Alternative Medicine: eCAM*, **3**: 397–409.	2011, therefore this review was considered redundant		
Bellavite P, Ortolani R, Pontarollo F, *et al* (2006). Immunology and homeopathy. 4. Clinical studies—Part 1. *Evidence-based Complementary and Alternative Medicine: eCAM*, **3**: 293–301.	Y, update review in 2011, therefore this review was considered redundant		
Boissel JP, Cucherat M, Haugh M, Gauthier E (1996). Critical literature review on the effectiveness of homoeopathy: overview of data from homoeopathic medicine trials. In: *Homoeopathic Medicine Research Group, Report of the Commission of the European Communities, Directorate-General XII—Science, Research and Development, Directorate E—RTD Actions: Life Sciences and Technologies*—Medical Research, Brussels, Belgium.			Y (methodological paper)
Bordet MF, Colas A, Marijnen P, *et al* (2008). Treating hot flushes in menopausal women with homeopathic treatment—results of an observational study. *Homeopathy*, **97**: 10–15.			Y primary paper
Bornhoft G, Wolf U, Ammon K, *et al* (2006). EVectiveness, safety and cost-eVectiveness of homeopathy in general practice—summarized health technology assessment. *ForschendeKomplementa¨rmedizin*, **13** Suppl 2: 19–29.			
Coulter MK, Dean ME (2007). Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder *(Cochrane Review)*. In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD005648.	Y updated review used (2009) Category 1		
Cucherat M, Haugh MC, Gooch M, Boissel JP (2000). Evidence of clinical efficacy of homeopathy—A meta-analysis of clinical trials. *European Journal of Clinical Pharmacology*, **56**: 27–33.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Ernst E (1999). Homeopathic prophylaxis of headaches and migraine? A systematic review. *Journal of Pain and Symptom Management*, **18**: 353–357.	Y Category 1		
Ernst E, Barnes J (1998). Are homoeopathic remedies effective for delayed-onset muscle soreness?—A systematic review of Placebo-controlled trials. *Perfusion (Nu¨rnberg)*, **11**: 4–8.	Y Category 1		
Ernst E, Pittler MH (1998). EYcacy of homeopathic arnica. A systematic review of placebo-controlled clinical trials. *Archives of Surgery*, **133**: 1187–1190.			Y methodological paper
Fisher P (1986). An experimental double-blind clinical trial method in homoeopathy. Use of a			Y Methodological paper

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
limited range of remedies to treat fibrositis. *British Homeopathic Journal*, **75**: 142-147.			
Friese K-H, Kruse S, Lu¨dtke R, Moeller H (1997). The homoeopathic treatment of otitis media in children—comparisons with conventional therapy. *International Journal of Clinical Pharmacology and Therapeutics*. **35**: 296–301.			Y primary paper
Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D (2003). Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. *Pediatric Infectious Disease Journal*, **22**: 229–234.			Y
Jonas WB, Linde K, Ramirez G (2000). Homeopathy and rheumatic disease. *Rheumatic Disease Clinics of North America*, **26**: 117–123.			Y, reanalysis of data already reported in Linde (1987) (Categpry 4)
Kainz JT, Kozel G, Haidvogl M, Smolle J (1996). Homoeopathic versus placebo therapy of children with warts on the hands: a randomized, double-blind clinical trial. *Dermatology*, **193**: 318–320.			Y primary paper
Kassab S, Cummings M, Berkovitz S, *et al* (2009). Homeopathic medicines for adverse effects of cancer treatments *(Cochrane Review)*. In: The Cochrane Library. Chichester, UK: JohnWiley & Sons, Ltd. CD004845, 2009.	Y Category 1		
Kleijnen J, Knipschild P, ter Riet G (1991). Clinical trials of homoeopathy *British Medical Journal*,**302**: 316–323.			Y, also not relevant
Klopp R, Niemer W, Weiser M (2005). Microcirculatory eVects of a homeopathic preparation in patients with mild vertigo: an intravital microscopic study. *Microvascular Research*, **69**: 10–16.			Y primary paper
Labrecque M, Audet D, Latulippe LG, Drouin J (1992). Homoeopathic treatment of plantar warts. *Canadian Medical Association Journal*, **146**: 1749–1753.			Y primary paper
Linde K, Clausius N, Ramirez G, *et al* (1997). Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet*, **350**: 834–843.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Long L, Ernst E (2001). Homeopathic remedies for the treatment of osteoarthritis: a systematic review. *British Homeopathic Journal*, **90**: 37–43.	Y Category 1		
Ludtke R, Hacke D (2005). On the effectiveness of the homeopathic remedy Arnica montana. *Wiener Medizinische Wochenschrift*, **155**: 482–490.			Y methodological paper
Ludtke R, Rutten ALB (2008). The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. *Journal of Clinical Epidemiology*, **61**: 1197–1204.			Y methodological paper

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
McCarney RW, Linde K, Lasserson TJ (2004). Homeopathy for chronic asthma *(Cochrane Review)*. In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD000353.	Y, updated 2008 review used Category 1		
McCarney R, Warner J, Fisher P, van Haselen R (2004). Homeopathy for dementia *(Cochrane Review)*. In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD003803.	Y Category 1		
Milazzo S, *et al* (2006). EYcacy of homeopathic therapy in cancer treatment. *European Journal of Cancer*, **42**: 282–289.	Y Category 1		
Owen JM, Green BN (2004). Homeopathic treatment of headaches: A systematic review of the literature. *Journal of Chiropractic Medicine*, **3**: 45–52.	Y Category 1		
Pilkington K, Kirkwood G, Rampes H, *et al* (2005). Homeopathy for depression: a systematic review of the research evidence. *Homeopathy*, **94**: 153–163.	Y Category 1		
Pilkington K, Kirkwood G, Rampes H, *et al* (2006). Homeopathy for anxiety and anxiety disorders: A systematic review of the research. *Homeopathy*, **95**: 151–162.	Y Category 1		
Rabe A, Weiser M, Klein P (2004). Effectiveness and tolerability of a homoeopathic remedy compared with conventional therapy for mild viral infections. *International Journal of Clinical Practice*, **58**: 827–832.			Y primary paper
Rahlfs VW, Mossinger P (1976). [On the treatment of irritable colon] *Arzneimittelforschung*, **26**: 2230–2234.			Y primary paper
Schneider B, Klein P, Weiser M (2005). Treatment of vertigo with a homeopathic complex remedy compared with usual treatments: a meta-analysis of clinical trials. *Arzneimittelforschung*, **55**: 23–29.	Y category 1		
Shang A, Huwiler-Muntener K, Nartey L, *et al* (2005). Are the clinical eVects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. *Lancet*, **366**:726–732.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Smith CA (2004). Homoeopathy for induction of labour *(Cochrane Review)*. In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD003399.	Y Category 1		
Taylor MA, Reilly D, Llewellyn-Jones RH, *et al* (2000). Randomised controlled trials of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *British Medical Journal*, **321**: 471–476.			Y
Thompson EA, Mathie RT, Baitson ES, *et al* (2008). Towards standard setting for patient-reported outcomes in the NHS homeopathic hospitals. *Homeopathy*, **97**: 114–121.			Y primary paper
Ullman D (2003). Controlled clinical trials			Y

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
evaluating the homeopathic treatment of people with human immunodeficiency virus or acquired immune deficiency syndrome. *Journal of Alternative and Complementary Medicine*, **9**: 133–141.			
Vickers A, Smith C (2006). Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes *(Cochrane review)*. In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD001957.		Y -excluded as Cochrane review update in 2009 was never finished, and Cochrane Library indicated that earlier versions were out of date	
Walach H, Jonas WB, Lewith GT(2002). The role of outcomes research in evaluating complementary and alternative medicine. *Alternative Therapies in Health and Medicine*, **8**: 88–95.			Y primary paper
White A, Ernst E (2001). The case for uncontrolled clinical trials: a starting point for the evidence base for CAM. *Complementary Therapies in Medicine*, **9**: 111–115.			Y primary paper
Wiesenauer M, Ludtke R (1996). A meta-analysis of the homeopathic treatment of pollinosis with Galphimia glauca. *Forschende Komplementa¨rmedizin und Klassische Naturheilkunde*, **3**: 230–236.		Y out of date range	

2. **Bornhoft & Matthiessen (eds.) Homeopathy in healthcare: Effectiveness, appropriateness, safety, costs. An HTA report on homeopathy as part of the Swiss Complementary Medicine Evaluation Program. 2011**

This comprehensive Health Technology Assessment (HTA) examines the efficacy and the real world effectiveness, as well as the appropriateness and cost effectiveness of an intervention (homeopathy). This HTA was conducted with the intent to inform the Swiss government on the future of homeopathy within the healthcare system following the provisional inclusion of complementary medicine in 1998.

The report concluded that

".....it can be said that there is sufficient evidence for the preclinical (experimental) effectiveness and the clinical efficacy of homeopathy and for its safety and economy compared to conventional treatment. It is a highly popular intervention. From the homeopathic point of view, the positive evidence with regard to its action and effectiveness is the more remarkable as most research studies violate its fundamental rules. In the interest of scientific recognition, external evidence is often sacrificed for the sake of internal validity which leads to the risk of false negative results. Future research methods must respect the unique qualities of homeopathy by attaching more weight to single case evaluations, by including practically and expertly applied homeopathic treatment into research and clinical practice in order to identify its real potential and limitations. The recently introduced outcome studies are promising in this respect as they do not focus on specific effect but on the overall practical treatment and patient care in homeopathy." (p203)

In addition to the 37 potentially relevant articles outlined in Table 9, this technical report contained an additional 491 articles that were primary studies, opinion pieces, or background evidence on general research and legislation matters.

Table 9: Relevant secondary evidence in Bornhoft and Matthiessen (2011)

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
Becker-Witt C, Lüdtke R, Weisshuhn TER, Willich SN (2004) Diagnoses and treatment in homeopathic medical practice. Forschende Komplementärmedizin und Klassische Naturheilkunde 11:98-103			Y - primary study
Barnes, J., Resch, K.L., & Ernst, E. (1997). Homoeopathy for postoperative ileus? A meta-analysis. *Journal of Clinical Gastroenterology*, 25: 628-633.	Y - Category 1		
Cucherat, M. & Linde, K. (2000). Evidence of clinical effectiveness of homeopathy: a meta-analysis of clinical trials. Eur J Clin Pharmacol 56: 27-33.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		

Dantas, F. & Rampes, H. (2000). Do Homeopathic Medicines Provoke Adverse Effects? A Systematic Review. British Homeopathic Journal; 89: 70-74	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Ernst, E. (1999b), 'Classical homoeopathy versus conventional treatments: a systematic review (Structured abstract)', *PERFUSION,* (1), 13-15.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Ernst, E. (2000). "The usage of complementary therapies by dermatological patients: a systematic review." British Journal of Dermatology **142**(5): 857-861		Y - review of surveys of CAM usage	
Ernst, E. (2002), 'A systematic review of systematic reviews of homeopathy', *British Journal of Clinical Pharmacology, 54 (6), 577-82.*		Y -Umbrella review	
Ernst, E. & Barnes, A. (1998). Are homeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo controlled trials. Perfusion, 11: 4-8.	Y - Category 1		
Ernst, E. and Pittler, M. H. (1998), 'Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials', Archives of surgery (Chicago, Ill. : 1960), 133 (11), 1187-90.	Y - Category 3		
Fisher, P., B. Berman, et al. (2005). "Are the clinical effects of homoeopathy placebo effects?" Lancet **366**(9503): 2082-2083; author reply 2083-2086			Y - letter to editor
Frei H, Everts R, von Ammon K, Kaufmann F, Walter D, Hsu Schmitz SF, Collenberg M, Fuhrer K, Hassink R, Steinlin M, Thurneysen A (2005) Homeopathic treatment of children with attention deficit hyperactivity disorder. Eur J Pediatr 164:758–767			Y - primary study
Friese, K.H. Kruse, S. Ludtke, R. Moeller, H. (1997). Homeopathic treatment of otits media in children: comparisons with conventional therapy. Int J Clin Pharmacol Ther; 35: 296-301.			Y
Grabia, S. and E. Ernst (2003). "Homeopathic aggravations: a systematic review of randomised, placebo-controlled clinical trials." Homeopathy **92**(2): 92-98.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Jacobs, J. Jonas, W.B. Jimenez-Perez, M. Crothers, D. (2003). Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. Pediatric Infectious Disease Journal, 22: 229-234.			Y

Jonas, W. B., R. L. Anderson, et al. (2001). "A systematic review of the quality of homeopathic clinical trials." BMC Complementary and Alternative Medicine **1**: 12.			Y- methodological paper
Jonas, W.B. (2003). A critical overview of homoeopathy. Ann Int Med 138: 393-399.			Y - not a SR
Kienle GS, Kiene H, Albonico HU (2006) Anthroposophische Medizin: Health Technology Assessment Bericht – Kurzfassung. Forschende Komplementärmedizin 13 [Suppl 2]:7–18		Y - not in English	
Linde K, Jonas W (2005) Are the clinical effects of homeopathy placebo effects? Lancet 366:2081–2082;			Y - letter to editor
Linde, K., M. Hondras, et al. (2001). Systematic reviews of complementary therapies - an annotated bibliography. Part 3: Homeopathy		Y -umbrella review	
Linde, K., Clausius, N., Ramirez, G., Melchart, D., Eitel, F., Hedges, L.V. & & Jonas, W.B. (1997). Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo controlled trials. Lancet, 350: 834-843.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Linde, K. & Melchart, D. (1998). Randomised controlled trials of individualised homeopathy: a state-of-the-art review. Journal of Alternative and Complementary Medicine 4: 371-388.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Linde K, Jobst K (2000) Homeopathy for asthma. The Cochrane Library (2). CD000353	Y -Category 1 (McCarney 2008 version)		
Long, L. & Ernst, E. (2001). Homeopathic remedies for the treatment of osteoarthritis: a systematic review. British Homeopathic Journal, 90: 37-43.	Y -Category 1		
Lüdtke R, Rutten ALB (2008) The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. Journal of Clinical Epidemiology 61: 1197-1204			Y
Mathie, R. (2003). The research base of homeopathy: a fresh assessment of the literature. Homeopathy, 92: 84-91.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
McCarney RW, Warner J, Fisher P, van Haselen R. (2003). Homeopathy for dementia. Cochrane Database of Systematic Reviews, Issue 1..	Y -Category 1 (2009 version)		
Maxion-Bergemann, S., M. Wolf, et al. (2006). "Complementary and alternative medicine costs - a systematic literature review." Forsch Komplementmed **13 Suppl 2**: 42-45.		Y -focus on cost of CAM not efficacy of homeopathy	
O'Meara, S., P. Wilson, et al. (2002). "Homoeopathy." Qual Saf Health Care **11**(2): 189-194		Y -Umbrella review	

Riley D, Fischer M, Singh B, Haidvogl M, Heger M (2001) Homeopathy and conventional medicine: an outcomes study comparing effectiveness in a primary care setting. J Altern Complement Med 7:149–159			Y -primary study
Rutten ALB, Stolper CF (2008) The 2005 meta-analysis of homeopathy: the importance of post-publication data. Homeopathy 97: 169-177			Y
Shang, A. Huwiler-Mutener, K. Nartey, L. Juni, P. Dorig, S., Sterne, J.A. 2005. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo controlled trials of homoeopathy and allopathy. The Lancet, Vol. 366, pp. 726-732.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Smith, C.A. (2001). Homoeopathy for induction of labour (Cochrane Review). In: The Cochrane Library	Y -Category 1 (2010 version)		
Taylor, M.A., Reilly, D., Llewellyn-Jones, R.H., McSharry, C., Aitchison, T.C. (2000). Randomized controlled trial of homeopathic versus placebo in perennial allergic rhinitis with overview of four trial series. British Medical Journal 321: 471-476.			Y
Vickers, A. J. (1999), 'Independent replication of pre-clinical research in homoeopathy: A systematic review', *FORSCHENDE KOMPLEMENTARMEDIZIN*, 6 (6), 311-20.			Y- pre-clinical study
Vickers A, Smith C. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database of Systematic Reviews 2009		Y -excluded as Cochrane review update in 2009 was never finished, and Cochrane Library indicated that earlier versions were out of date	
Walach H, Jonas W, Lewith G (2005a) Are the clinical effects of homeopathy placebo effects? Lancet 366:2081; DOI:10.1016/S0140-6736(05)67877-4)			Y - letter to editor
Walach H, Haeusler W, Lowes T, Mussbach D, Schamell U, Springer W, Stritzl G, Gaus W, Haag G (1997) Classical homeopathic treatment of chronic headaches. Cephalalgia 17:11–18			Y- primary study

3. Etat des lieux de l'homeopathie en Belgique (Homeopathy: the state of affairs in Belgium) a report published by the Belgium Federal Health Care Knowledge Centre 2011.

This report was conducted at the request of the Minister of Public Health and Social Affairs, Belgium, in order to review and/or implement the 1999 laws around non-conventional medicine. As these laws were not in use some 10 years later when this report was conducted, the group were commissioned to assess the current efforts to review or implement the law.

The report aimed to respond to the following questions:

1. How effective are alternative medicines? What are their benefits and drawbacks?
2. How are these medicines defined and how are they used by the Belgian population?
3. What is the legal status of these medicines and how are they organised in Belgium?
4. How are the therapists trained?

After assessing 26 relevant systematic reviews they found in their search process, they noted:

"We did not find compelling evidence that homeopathy works for any single condition. Shang et al pooled 110 studies on homeopathy and came to the similar conclusion that the findings are compatible with the notion that the clinical effects of homeopathy are placebo effects. We did not include this study however because we consider it inappropriate to pool all treatments for all conditions, given the very diverse nature of the conditions that are treated [...] the quality of the reviews was variable but in general acceptable. A lot of the studies included in the reviews were of low quality. The well conducted large trials did not show an effect" (p 19).

In light of these findings, they conclude that

"From a purely clinical perspective, the fact remains that there is no valid empirical proof of the efficacy of homeopathy (evidence-based medicine) beyond the placebo effect. In the case of homeopathy, the placebo effect probably has some significance but it is difficult to define. Therapists base the success of their treatments on their subjective experience and on patient satisfaction. In part, we have objectified this satisfaction by the survey of the general population and interviews with satisfied patients, some of whom report impressive and rapid healing after many a long search for solutions in conventional medicine. However, it should be stressed that satisfaction is no guarantee of efficacy, in the strict sense, any more than it is of safety. Even though homeopathy does not offer any inherent clinical efficacy, it may help physicians in catering medical assistance for patients in search of an alternative medical practice. They can do so without having to resort to prescription drugs. When applied by physicians, this approach offers the advantage of maintaining a therapeutic relationship without the risk of leaving the framework of conventional medicine." (p154)

It should be noted that this document does not address either the efficacy or the clinical utilization of homeopathy; rather, it critically reviews the implementation of the 1999 laws around non-conventional medicine. As such, it does not fit into the inclusion criteria required by NHMRC. All references were listed in French; no new references were found within the translated body of the report, as such the reference list was not pearled for relevant secondary evidence which may have been missed in the other search approaches for the NHMRC overview review.

4. The research working group of the Liga Medicorum Homeopathica Internationalis (LMHI) about the clinical efficacy of homeopathy. 2011

The research reported here was conducted in response to the report produced by the Belgium Federal Health Care Knowledge Centre, as requested by the Belgian LMHI vice-president, owing to doubts regarding the scientific relevance of some parts of the Belgium Federal Health Care Knowledge Centre report.

The LIGA report concluded that

> "It is clear that the search to highest clinical level of evidence for homeopathy reported by the Belgium Federal Health Care Knowledge Centre (KCE) report is of poor quality, conclusions are clearly questionable:
> 1) reviews are included who didn't include any clinical trial on homeopathy
> 2) references are wrongly used and doesn't concern the trials included
> 3) the content of the reviews is poorly reported and contains a number of errors
> 4) references are not correctly cited
> 5) authors conclusions not correctly reported
> 6) reviews not included by KCE. We don't know if these reviews were not found or excluded for some reason.
> 7) the exclusion of reviews with search date before 2000 has led to a misrepresentation of the evidence overall" (p43)

From the LIGA independent systematic review of the evidence, citing the relevant systematic reviews provided in the supporting evidence tables (secondary evidence reported in Table 10 in this report), the LIGA report concluded:

> *"There is convincing evidence for efficacy of*
>
> - *Aconitum in post-operative agitation in children (Pilkington 2006, Altunc 2007).*
> - *Belladonna 7cH and X-ray 15cH and topical calendula for the treatment of radiodermatitis and for Traumeel S for the treatment of chemotherapy- induced stomatitis (Milazzo 2006, Kassab 2009, Bornhoft 2006).*
>
> *There is evidence for the efficacy of homeopathy for diarrhoea in childhood. This is confirmed by two meta-analyses reported in Bornhoft (2006), Jacobs (2003) and Linde (1998).*
>
> *There is strong evidence that homeopathy works for upper respiratory tract infections (URTI) (Shang 2005, Bornhoft 2006, Bellavite 2006a Rutten 2010).*
>
> *Ulman et al. (2003) reported that homeopathic medicine may play a useful role as an adjunctive and/or alternative therapy for HIV.*
>
> *Oscillococcinum can treat influenza-like symptoms (Vickers 2004).*

Some evidence exists to support the superiority of homeopathic remedies over placebo for treating osteoarthritis and rheumatoid arthritis (Weiner 2004, De Silva 2011, Long & Ernst 2001).

The evidence for the efficacy of homeopathy in fibromyalgia is based on four RCTs which all reported positive results (Langhorst 2008, Baranowsky 2009, De Silva 2010, Perry 2010).

When taking into account the evidence for upper respiratory tract infections, allergic rhinitis and allergic conditions, we conclude that there is a positive overall result in favour of homeopathy for these three conditions (Bornhoft 2006, Bellavite 2006a,b).

Isopathic nosodes were different from placebo on both subjective and objective measures for allergic conditions (Taylor 2000).

The available evidence is positive for post-operative ileus (Shang 2005, Linde 1997, Barnes 1997). Galphimia glauca is statistically significantly more effective than placebo for seasonal allergy (Wiesenauer 1996, Linde 1997).

There is possible evidence for insomnia (Cooper 2009, 2010), chronic fatigue syndrome (Centre for Reviews and Dissemination 2007), low back pain (Quinn 2006), depression (Pilkington 2005), ADHD (Altunc 2007, Coulter & Dean 2007)". p.42

As well as the 54 secondary evidence references listed in Table 10, the LIGA report also included 18 primary studies and one letter to the editor. Table 10 reports on the iCAHE decision-making regarding the cited evidence in the LIGA report, which casts some doubt on the recency and relevance of some included references in the LIGA report.

Table 10: Relevant secondary evidence references

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
Altunc U, Pittler MH, Ernst E. Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. Mayo Clin Proc. 2007 Jan;82(1):69-75.	Y- Category3		
Baranowsky J, Klose P, Musial F, Haeuser W, Dobos G, Langhorst J. Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia (Structured abstract). Rheumatology International [serial on the Internet]. 2009; (1). Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12010000503/frame.html.	Y –Category 2		
Barnes J, Resch KL, Ernst E. Homeopathy for postoperative ileus? A meta-analysis. J Clin Gastroenterol. 1997 Dec;25(4):628-33.	Y – Category 1		

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
Bellavite P, Ortolani R, Pontarollo F, Piasere V, Benato G, Conforti A. Immunology and homeopathy. 4. Clinical studies-part 1. Evid Based Complement Alternat Med. 2006 Sep;3(3):293-301.	Y, update review in 2011, therefore this review was considered redundant		
Bellavite P, Ortolani R, Pontarollo F, Piasere V, Benato G, Conforti A. Immunology and homeopathy. 4. Clinical studies-part 2. Evid Based Complement Alternat Med. 2006 Dec;3(4):397-409.		Y-part one of this series addressed homeopathy and was included.	
Bornhoft G, Wolf U, von Ammon K, Righetti M, Maxion-Bergemann S, Baumgartner S, et al. Effectiveness, safety and cost-effectiveness of homeopathy in general practice - summarized health technology assessment. Forsch Komplementmed. 2006;13 Suppl 2:19-29		Y- Government review (HTA) (see ref. 4 in this government report section).	
Cooper KL, Relton C. Homeopathy for insomnia: a systematic review of research evidence. Sleep Med Rev. 2009 Oct;14(5):329-37.	Y – Category 1		
Cooper KL, Relton C. Homeopathy for insomnia: summary of additional RCT published since systematic review. Sleep Med Rev. 2010 Dec;14(6):411.			Y – Not a SR, this was a letter to the editor.
Coulter MK, Dean ME. Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane Database Syst Rev. 2007(4):CD005648.	Y-included the updated version-Heirs & Dean 2009 Category 1		
Cucherat M, Haugh MC, Gooch M, Boissel JP. Evidence of clinical efficacy of homeopathy: a meta-analysis of clinical trials (Structured abstract). European Journal of Clinical Pharmacology [serial on the Internet]. 2000; (1): Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12000001151/frame.html.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Centre for Reviews and Dissemination. The treatment and management of chronic fatigue syndrome (CFS) / myalgic encephalomyelitis (ME) in adults and children: update of CRD Report 22. CRD Report 35. 2007;York: University of York.	Y -Category 2		
Dantas F, Rampes H. Do homeopathic medicines provoke adverse effects? A systematic review. Br Homeopath J. 2000 Jul;89 Suppl 1:S35-8.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ. Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review. Rheumatology (Oxford). 2010 Jun;49(6):1063-8	Y - Category 2		

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ. Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. Rheumatology (Oxford). 2011 May;50(5):911-20.	Y – Category 2		
Ernst E. Classical homeopathy versus conventional treatments: A systematic review. Perfussion. 1999;12:13-5	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Ernst E. Homeopathic prophylaxis of headaches and migraine? A systematic review. J Pain Symptom Manage. 1999 Nov;18(5):353-7.	Y – Category 1		
Glazener Cathryn MA, Evans Jonathan HC, Cheuk Daniel KL. Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database of Systematic Reviews [serial on the Internet]. 2005; (2): Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005230/frame.html.	Y-updated version-Huang et al. (2011) Category 1		
Grabia S, Ernst E. Homeopathic aggravations: a systematic review of randomised, placebo-controlled clinical trials. Homeopathy. 2003 Apr;92(2):92-8.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Holdcraft LC, Assefi N, Buchwald D. Complementary and alternative medicine in fibromyalgia and related syndromes (Structured abstract). Best Practice and Research in Clinical Rheumatology [serial on the Internet]. 2003; (4): Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12003001645/frame.html.	Y-Category 2		
Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D. Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. Pediatr Infect Dis J. 2003 Mar;22(3):229-34			Y –primary paper
Jonas WB, Kaptchuk TJ, Linde K. A critical overview of homeopathy. Ann Intern Med. 2003 Mar 4;138(5):393-9.			Y
Kassab S, Cummings M, Berkovitz S, van Haselen R, Fisher P. Homeopathic medicines for adverse effects of cancer treatments. Cochrane Database of Systematic Reviews [serial on the Internet]. 2009; (2): Available from: http://www.mrw.interscience.wiley.com/coch	Y- Category 1		

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
rane/clsysrev/articles/CD004845/frame.html.			
Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homoeopathy. BMJ. 1991 Feb 9;302(6772):316-23.		Y –outside of specified date range	
Langhorst J, Hauser W, Irnich D, Speeck N, Felde E, Winkelmann A, et al. [Alternative and complementary therapies in fibromyalgia syndrome]. Schmerz. 2008 Jun;22(3):324-33.		Y –Not available in English for full text	
Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: a state-of-the-art review. J Altern Complement Med. 1998 Winter;4(4):371-88	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet. 1997 Sep 20;350(9081):834-43.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
Long L, Ernst E. Homeopathic remedies for the treatment of osteoarthritis: a systematic review (Structured abstract). British Homoeopathic Journal [serial on the Internet]. 2001; (1): Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12001003447/frame.html.	Y- Category 1		
Ludtke R, Rutten AL. The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. J Clin Epidemiol. 2008 Dec;61(12):1197-204.			Y
Ludtke R, Wiesenauer M. [A meta-analysis of homeopathic treatment of pollinosis with Galphimia glauca]. Wien Med Wochenschr. 1997;147(14):323-7.		Y – article written in German	
Mathie RT. Systematic reviews of RCTs in homeopathy A focused appraisal. Focus on Alternative and Complementary Therapies.15(2):104-6.	Y, assigned as Category 4 and excluded from our clinical review as did not have a focused clinical question		
McCarney Robert W, Warner J, Fisher P, van Haselen R. Homeopathy for dementia. Cochrane Database of Systematic Reviews [serial on the Internet]. 2003; (1): Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003803/frame.html.	Y -2009 update Category 1		
McCarney Robert W, Linde K, Lasserson Toby J. Homeopathy for chronic asthma. Cochrane Database of Systematic Reviews [serial on the Internet]. 2004; (1): Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000353/frame.html.	Y -2008 update Category 1		

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
Milazzo S, Russell N, Ernst E. Efficacy of homeopathic therapy in cancer treatment. European Journal of Cancer [serial on the Internet]. 2006; (3): Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12006000867/frame.html.	Y –Category 1		
Mills E, Wu P, Ernst E. Complementary therapies for the treatment of HIV: in search of the evidence. Int J STD AIDS. 2005 Jun;16(6):395-403.	Y – Category 2		
Owen JM, Green BN. Homeopathic treatment of headaches: a systematic review of the literature. J Chiropr Med. 2004 Spring;3(2):45-52	Y – Category 1		
Passalacqua G, Bousquet PJ, Carlsen KH, Kemp J, Lockey RF, Niggemann B, et al. ARIA update: I--Systematic review of complementary and alternative medicine for rhinitis and asthma. J Allergy Clin Immunol. 2006 May;117(5):1054-62.	Y – Category 2		
Perry R, Terry R, Ernst E. A systematic review of homoeopathy for the treatment of fibromyalgia. Clin Rheumatol. 2010 May;29(5):457-64.	Y – Category 1		
Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J. Homeopathy for depression: a systematic review of the research evidence (Structured abstract). Homeopathy [serial on the Internet]. 2005; (3): Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12005004392/frame.html.	Y – Category 1		
Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J. Homeopathy for anxiety and anxiety disorders: a systematic review of the research (Provisional abstract). Homeopathy [serial on the Internet]. 2006; (3): Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12006004029/frame.html.	Y - Category 1		
Quinn F, Hughes C, Baxter GD. Complementary and alternative medicine in the treatment of low back pain: a systematic review. Physical Therapy Reviews. 2006;11:2.	Y – Category 2		
Rada G, Capurro D, Pantoja T, Corbal·n J, Moreno G, Letelier Luz M, et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database of Systematic Reviews [serial on the Internet]. 2010; (9): Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004923/frame.html.	Y -Category 2		
Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, et al. A systematic literature review of the effectiveness of nonpharmacological interventions to prevent		Y –not homeopathy	

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
wandering in dementia and evaluation of the ethical implications and acceptability of their use. Health Technol Assess. 2006 Aug;10(26):iii, ix-108.			
Rutten AL, Lewith G, Mathie RT, Fisher P. Homeopathy In Upper Respiratory Tract Infections ? The Impact Of Plausibility Bias. WebmedCentral HOMEOPATHY. 2010;1(11):WMC001126.			Y
Rutten AL, Stolper CF. The 2005 meta-analysis of homeopathy: the importance of post-publication data. Homeopathy. 2008 Oct;97(4):169-77.			Y – methodological paper
Sarris J, Byrne GJ. A systematic review of insomnia and complementary medicine. Sleep Med Rev. 2010 Apr;15(2):99-106.	Y – Category 2		
Schneider B, Klein P, Weiser M. Treatment of vertigo with a homeopathic complex remedy compared with usual treatments: a meta-analysis of clinical trials. Arzneimittelforschung. 2005;55(1):23-9.	Y – Category 1		
Shang A, Huwiler-Muntener K, Nartey L, Juni P, Dorig S, Sterne JA, et al. Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet. 2005 Aug 27-Sep 2;366(9487):726-32.	Y, assigned as Category 4 as did not have a focused clinical question		
Smith Caroline A. Homoeopathy for induction of labour. Cochrane Database of Systematic Reviews [serial on the Internet]. 2003; (4): Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003399/frame.html.	Y- Category1		
Stevinson C, Ernst E. Complementary /alternative therapies for premenstrual syndrome: a systematic review of randomized controlled trials (Structured abstract). American Journal of Obstetrics and Gynecology [serial on the Internet]. 2001; (1): Available from: http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12001001913/frame.html.	Y –Category 2		
Ullman D. Controlled clinical trials evaluating the homeopathic treatment of people with human immunodeficiency virus or acquired immune deficiency syndrome. J Altern Complement Med. 2003 Feb;9(1):133-41.			Y
Vickers AJ, Smith C. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database Syst Rev. 2004(1):CD001957		Y –Cochrane review update was not completed, Cochrane pulled older versions as these were deemed out of date by review board standards.	
Vickers AJ, Smith C. Homoeopathic		See above.	

Reference	Included by iCAHE (See Appendix 2)	Review excluded by iCAHE (See Appendix 2 & 3)	Not a systematic review
Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database Syst Rev. 006;3:CD001957.			
Weiner DK, Ernst E. Complementary and alternative approaches to the treatment of persistent musculoskeletal pain. Clin J Pain. 2004 Jul-Aug;20(4):244-55.			Y, discussion paper
Wiesenauer M, Lüdtke R. A meta-analysis of thehomeopathic treatment of pollinosis with galphimia glauca. Forsch Komplementärmed. 1996(3):230-4.		Y – outside of date range specified.	

Part 4: Critique of Public Submissions to NHMRC

Submissions from the Australian Homeopathic Association (AHA), and the Australian Medical Fellowship of Homeopathy (AMFH) were sent to NHMRC in May 2011 in response to the Draft NHMRC Public Statement on Homeopathy, which had been circulated for limited comment. This document presents a critique of these submissions.

Primary purpose of critique: As part of the comprehensive and multipronged strategy to develop a comprehensive list of clinically-focused secondary evidence for the NHMRC overview review, the reference lists in both submissions and references provided by the public, were searched by the independent contractors. The secondary evidence references found in this process were correlated with the references found in the independent contractors' search, and these are reported and cross-referenced in Appendix A2 to the Project Report. No new relevant references were identified from submission from the general public, and thus, the focus of this critique is on the submissions from the two associations.

Typographical error: Appendix 2 not Appendix A2

This paragraph is poorly expressed. The intent is to articulate that AHA and AMFH input represented only 30% of what NHMRC independent contractors found. AHA and AMFH did not offer any new evidence that these contractors had already located.

Summary of critique findings: The search conducted by the independent NHMRC contracts identified all the secondary evidence cited in the submissions' reference lists. No new reviews were identified from these reference lists, and the reference lists of the submissions reported on approximately 30% of the systematic reviews which were identified by the independent NHMRC contractors and which would have been available for inclusion at the time the submissions were written. Thus the references which were provided in support of the effectiveness of homeopathy in the submissions presented by the AHA and the AMFH, provide an incomplete view of the available evidence.

Typographical error: contractor not contract

Moreover, neither submission presented a transparent systematic approach to sourcing the cited literature. There appears to be a reliance in both submissions, on work written by international experts. The notion that homeopathy produces an effect at least as good as the placebo arm of an allopathic trial is presented eloquently in both submissions.

How does the Contractor reach this conclusion... 'presented eloquently in ....' suggest this is too subjective for such a report

Submission by the Australian Homeopathic Association: The AHA provided two responses to the NHMRC.

a. In May 2011, as an attachment to a letter of complaint to NHMRC regarding the tight timelines for a considered response, and as evidence of the effectiveness of homeopathy, the AHA provided a document entitled 'An overview of positive homeopathy research and surveys' produced by the European Network of Homeopathy Researchers (August 2009). This document provided no search strategy by which it identified relevant trials or secondary evidence, although it provided the range of evidence sources from which studies had been identified (p. 20 of this report, provided in Appendix 1 at the end of this report). These sources comprised some library databases, and a number of internet-sources of homeopathic information.

   From references which were identified from these sources (using a non-specified search strategy), the European Network of Homeopathy Researchers report described positive primary research for the effectiveness of homeopathy for a number of conditions (childhood diarrhoea, respiratory tract complaints, musculoskeletal problems, hay fever, asthma and perennial rhinitis, pre-menstrual syndrome, menopausal complaints, homeopathy after oestrogen withdrawal, hot flashes after breast cancer therapy, infertility, sperm quality, pregnancy-related problems, ADHD, chronic fatigue syndrome, surgery, Dengue haemorrhagic fever).

   The literature supporting these claims reflected some secondary research (systematic reviews and meta-analyses, all of which had been sourced independently in the NHMRC literature search), and a number of primary (experimental) studies. It is of note for the purpose of this critique, that all the cited reviews provided positive evidence for effectiveness (whilst no review which reported no effect or equivocal/ inconclusive findings was cited). Moreover the cited primary studies were not the only ones available for the conditions cited, as in the comprehensive data extraction approach taken by the NHMRC independent contractors, details on all experimental studies cited in all included systematic reviews were extracted, and a comprehensive primary evidence evidence-base was provided for a number of conditions. Similarly to the situation with cited secondary evidence, the primary references cited in the European Network article were the ones with positive findings. The ones with negative findings were not included.

b. A comprehensive submission was provided in July 2011, regarding homeopathy and the evidence available to support it was also provided. The executive summary (p. 3) noted that

   'This paper presents an introduction to homoeopathy and the controversial matter of ultra-molecular medicines used in homoeopathy. An overview of research in homoeopathy is presented. The paper identifies positive findings for homoeopathic treatment in some randomised controlled trials, details positive findings in four out of five comprehensive systematic reviews of homoeopathic research and describes the compellingly positive data derived from observational studies of homoeopathic

treatment at a population level. Homoeopathy is a complex health care intervention and the challenges of research in this field are discussed.'

This submission cited as evidence of the effectiveness of homeopathy, a number of the reviews that were classified as Category 4 in the independent NHMRC contractors' review of available secondary evidence (eg Cucherat 2000, Linde 1997, 1998, Mathie 2003, Shang 2005). The submission also noted the criticism within homeopathy research community regarding the methodology and conclusions in the Shang (2005) review. This submission highlighted the debate within the complementary and alternative therapy community regarding the effectiveness of homeopathy, and the most appropriate ways of researching and demonstrating this. In support of the effectiveness of homeopathy, this submission provided NHMRC with an overview of the work of Dr Robert Mathie, which had been published in the UK House of Commons report (summarised in Part 3 of the NHMRC overview review). An extract from the AHA submission, which summarises Mathie's findings, is provided in Appendix 2 of this critique. It is noted that a number of the supporting references for the effectiveness of homeopathy, provided by Mathie and cited in the AHA report, did not provide the best available evidence (i.e. not systematic literature reviews, not the most recent version of the review, and/or not available in full text or English language (as identified in Appendix A2 of the NHMRC overview review)).

This AHA submission noted the need for observational studies that would assist a better understanding of homeopathic service delivery issues. This is a common thread through the evidence summaries derived from the included systematic reviews presented in Part 2 of this overview review. The AHA submission cites eminent homeopathic researchers who have called for this type of research, and notes that Mathie (2003) makes these recommendations for future research in homoeopathy: *"A fresh agenda of inquiry should go beyond (but include) the placebo-controlled trial. Each study should adopt research methods and outcomes measurements linked to a question addressing the clinical significance of homoeopathy's effects"* (p.84). The NHMRC independent contractors note however, that homeopathy is not the only area of health which requires this type of research, as the need for observational research to define and better understand service delivery issues, clinician decision-making and patient-clinician relationships is relevant to all health disciplines, and the issue has been raised in peer-reviewed literature many times.

***The Australian Medical Fellowship of Homeopathy*:** This submission was provided by a group of Australian doctors who use homeopathy as part of their medical practice. This submission questioned the perceived sole reliance of the NHMRC on the UK House of Commons report on the effectiveness and safety of homeopathy (summarised in Part 3 of this overview review). The AMFH suggested that the UK House of Commons report presented a biased view of homeopathy effectiveness because it cited Shang's (2005) negative secondary evidence perspective on the effectiveness of homeopathy. The AMFH noted that there was value in the NHMRC conducting a broader review of current literature. This submission also noted that the NHMRC could assist the homeopathic research community by funding further research into homeopathy.

This submission identified two responses to the House of Commons report, which it felt NHMRC should investigate, in order to present a balanced view of homeopathic practice and effectiveness

(Memorandum submitted by the Complementary Medicine Research Group, University of York, and the British Homeopathic Association (BHA) response to the House of Common's report). The NHMRC independent contractors searched for these additional references, and found access only to the University of York memorandum. Membership of the BHA was required before their report could be accessed.

The evidence summary from the University of York memorandum is provided below, and the list of supporting references. As for the European report cited by the AHA, no search strategy was provided in this memorandum, and the cited literature does not appear to reflect the comprehensive literature source identified by the NHMRC independent contractors. All cited systematic reviews from this University of York report had been identified in the independent NHMRC contractors' search, and many of the supporting references for clinical effectiveness of homeopathy provided in this memorandum reflect only a portion of available primary experimental evidence for these clinical conditions (as synthesised in Part 2 of this overview review for NHMRC). The reference list to support this extract is provided in Appendix 3 of this section of the overview report.

> *'Since the early 1970s, there have been a total of 99 randomised controlled trials investigating homeopathy with over half of those conducted since 2000. The reports of those trials have been published in good quality peer reviewed journals, and the results show a mixed picture. In 44% (n=60) the studies report positive findings, where the homeopathy treatment showed statically significant superior effect compared to placebo, and those effects have been replicated by two or more studies in conditions of Childhood diarrhoea (individualized treatment)[1-3], Fibromyalgia [4,5], Influenza [6, 7], Osteoarthritis [8,9,10], Seasonal allergic rhinitis [11, 12-21], Sinusitis [22-25] and Vertigo.[26,27]*
>
> *There have also been positive findings in RCTs investigating: Chronic fatigue syndrome[28], Premenstrual syndrome [29], Post-partum bleeding[30], Sepsis [31], and Stomatitis[32], however, for these conditions conducted between 2001 and 2005, there has been no replication to verify the findings.*
>
> *In contrast 7% of the RCTs reported negative findings, where the homeopathy was considered to have a worse effect than the placebo, whilst nearly half (49% n=68) find inconclusive results.*
>
> *Negative or inconclusive results have been observed for: Anxiety[33-35], Childhood asthma[36,37] Insect bites[38,39] Menopausal symptoms in breast cancer [41,41], Migraine [42-44], Muscle soreness[45-49], Post-operative bruising / haematoma / pain / swelling[50, 51-57], Rheumatoid arthritis [58-60], Stroke [61,62], Upper respiratory tract infection (prevention) [63,64] and Warts [65,66].*
>
> *The most robust evidence presented is from several major systematic reviews of randomised controlled trials. The aim of the systematic review is to assess the quality and rigour of the individual trials that are included, and then compare and contrast the findings of each and comment on the consistency or inconsistency of the findings as a*

body of work. To date there are eight systematic reviews that provide evidence that the effects of homeopathy are beyond placebo when used as a treatment for childhood diarrhoea, influenza, post-operative ileus, respiratory tract infection and vertigo, and three providing consistent evidence of effectiveness for hay fever and associated pollenitis.' (p.2-3).

The AMFH submission also raised the issue of the lack of evidence for many accepted mainstream medical procedures (p.4), citing a BMJ website for the quotation below (http://clinicalevidence.bmj.com/ceweb/about/knowledge.jsp). It was not possible to identify the cited article from this website reference, thus the quote provided in the AMFH submission is provided as referenced in the submission:

'Much of general medical therapeutics in use today also lacks an evidence base according to the BMJ. Of around 2500 treatments covered, 13% are rated as beneficial, 23% likely to be beneficial, 8% as trade off between benefits and harms, 6% unlikely to be beneficial, 4% likely to be ineffective or harmful, and 46%, the largest proportion, as unknown effectiveness' .

The AHMF then argues 'Why single out Homeopathy, when it has a stronger evidence base than 50% of those treatments?' (p.4).

The AMHF submission also discussed methodological concerns of testing a complex form of treatment (such as homeopathy), which applies a sound clinician-consumer relationship, by using the elegant randomised controlled trial designs as are usual in allopathic medicine, particularly drug trials. This discussion raised the issue of faith in treatment, the placebo effect, and the intangible effects of a relationship between homeopath and patient.

References

An Overview of Positive Homeopathy Research and Surveys (2009): The European Network of Homeopathy Researchers.

British Homeopathic Association http://www.homeopathy-soh.org/whats-new/documents/STparts1-6forpdf.pdf (NB unavailable to non-members)

MacPherson H. 2009. HO 24: Memorandum submitted by the Complementary Medicine Research Group, University of York. Complementary Medicine Research Group, University of York http://www.publications.parliament.uk.ac/pa/cm200910/cmselect/cmsctech/memo/homeopathy/ucm2402.htm

Mathie R. (2003). The research base of homeopathy: a fresh assessment of the literature. *Homeopathy,* 92: 84-91.

Shang et al. 2005. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. Lancet 366: 726-732

Submission of the AUSTRALIAN HOMOEOPATHIC ASSOCIATION INC. *to the* National Health & Medical Research Council: *review of the evidence towards the development of a position statement on Homoeopathy (July 2011).*

Critique Appendix 1. Source of positive evidence for the European Network of Homeopathy Researchers (2009) provided by the AHA in its submission to NHMRC.

RESEARCH WEBSITE ADDRESSES

CAM base http://cambase.dmz.uni-wh.de/opencam/index_en.html

HomBRex Database (Carstens stiftung) http://www.carstens-stiftung.de/hombrex/index.php

Pubmed (National Library of Medicine) www.pubmed.com

British Medical Journal http://bmj.bmjjournals.com (search for 'homeopathy')

New Scientist www.newscientist.com (search for 'homeopathy')

Healthworld Online (Medline, Medical Research & Document Delivery)
www4.infotrieve.com/newmedline/summary.asp

Biomail www.biomail.org This site offers free regular updates by e-mail. Hosted by Medical Informatics Department at State University of New York, Stony Brook University Hospital and Medical Centre.

An evidence-based resource about Complementary and Alternative Medicine www.cam.org.nz
Funded by the New Zealand Ministry of Health.

Annals of Internal Medicine www.annals.org/cgi/search?fulltext=homeopathy

University of York www.york.ac.uk/inst/crd/ehc73.pdf

Biomed Central (homeopathy review) www.biomedcentral.com/1472-6882/1/12

British Homeopathic Library http://hominform.soutron.com

The Research Council for Complementary Medicine www.rccm.org.uk

Groupe International de Recherche sur l'Infinitésimal www.giriweb.com

National Centre for Homeopathy www.homeopathic.org/research.htm

Homeopathic Educational Services www.homeopathic.com/articles/research_index.php

Homeopathy (the journal) www.harcourt-international.com/journals/homp

Homeopathy Research Institute http://www.homeopathyresearchinstitute.org/index.htm

Boiron www.boiron.com/en/htm/04-politique/clinique.htm

Official Indian research centre www.ccrhindia.org

Carstens stiftung (Germany)
http://www.carstens-stiftung.de/eng/index.html (English pages)

ISI Web of Knowledge (resembles PubMed but includes more areas)
http://isi3.isiknowledge.com/portal.cgi

BMC Complementary and Alternative Medicine (free articles)
www.biomedcentral.com/1472-6882

NAFKAM, Tromsø (Norway) (research info will be included) http://uit.no/nafkam/omnafkam

Vifab (Denmark) www.vifab.dk

Townsend Letter for Doctors & Patients publishes a print alternative medicine magazine.
www.townsendletter.com

Critique Appendix 2. Summary of Mathie's review findings, extracted from AHA submission to NHMRC (p. 37). Notations are made in bold in [ ] by the NHMRC Independent contractors, against the references cited by Mathie, relevant to the NHMRC Overview review (2012). Decisions regarding the inclusion/ exclusion of articles in the NHMRC Overview review is supported by Appendix 2 in the project report.

'Five reviews concluded there was a positive effect for homoeopathy:

- *childhood diarrhoea (Jacobs, et al, 2003)* **[excluded in NHMRC overview review as was not a systematic review]**
- *post-operative ileus (Barnes, et al, 1997)* **[included in NHMRC overview review]**
- *seasonal allergic rhinitis (Wiesenauer, & Ludtke, 1996; Taylor et al, 2000)* **[respectively out of date, and not a systematic review]** *and*
- *vertigo (Schnieder, et al, 2005).* **[included but found to be an inadequate review]**

Three reviews concluded there was little or no evidence of an effect from treatment in the following three conditions: attention-deficit hyperactivity disorder (Coulter & Dean, 2007) **[included in NHMRC overview review in updated format (Heirs & Dean 2009)],** *delayed-onset muscle soreness (Ernst & Barnes, 1998)***[included]** *and headache and migraine prevention (Ernst, 1999)* **[included].**

In nine systematic reviews, a clear conclusion regarding response to treatment could not be reached. These were trials in anxiety (Pilkington, et al, 2006) **[included],** *chronic asthma (McCarney, et al, 2004)* **[included as updated Cochrane review],** *dementia (McCarney, et al, 2004)* **[included as updated 2009 Cochrane review],** *depression (Pilkington, et al, 2005)* **[included],** *headache and migraine treatment (Owen & Green, 2004)* **[included],** *HIV/AIDS (Ullman 2003)* [**excluded as not a systematic review**], *induction of labour (Smith, 2004)* **[included as updated 2010 Cochrane review**], *influenza (Vickers & Smith, 2006)* **[excluded as not a systematic review]** *and osteoarthritis (Long & Ernst, 2001)* **[included].**

Seven systematic reviews focused on particular groups of diseases. Of these, four were found to be positive:

- *allergies (Bellavite et al, 2006)***[included in updated 2011 review form]**
- *upper respiratory infections (Bornhoft, et al, 2006; Bellavite, et al, 2006)***[excluded as umbrella review, and out of date, respectively***]*
- *rheumatic diseases (Jonas, et al, 2000) [***excluded as unavailable in English***].*

Two reviews were negative: ailments of childhood and adolescence (Altunc, et al, 2007) **[included]** *and the review of trials of the homoeopathic treatment of cancer (Milazzo et al 2006);* **[included]** *one review of treatment for the side-effects of cancer (Kassab et al, 2009)* **[included]** *was non-conclusive.'*

Critique Appendix 3. References cited in the University of York submission (p.4-9) Notations are made in bold in [ ] by the NHMRC Independent contractors, against these references, relevant to the NHMRC Overview review. It is of note that no secondary evidence was cited in this submission, rather a selection of available primary experimental studies.

1 Jacobs J, Jiminez LM, Gloyds SS, et al. Homoeopathic treatment of acute childhood diarrhoea. A randomized clinical trial in Nicaragua. British Homeopathic Journal, 1993; 82: 83-86. **[primary study incl in review article]**

2 Jacobs J, Jimenez LM, Gloyds SS, et al. Treatment of acute childhood diarrhea with homeopathic medicine; a randomized clinical trial in Nicaragua. Pediatrics, 1994; 93: 719-725. **[primary study incl in review article]**

3 Jacobs J, Jimenez LM, Malthouse S, et al. Homeopathic treatment of acute childhood diarrhoea: results from a clinical trial in Nepal. Journal of Alternative and Complementary Medicine, 2000; 6: 131-139. **[primary study incl in review article]**

4 Bell I, Lewis D, Brooks A, et al. Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. Rheumatology, 2004; 43: 577-582. **[primary study incl in review article]**

5 Fisher P. An experimental double-blind clinical trial method in homoeopathy. Use of a limited range of remedies to treat fibrositis. British Homeopathic Journal, 1986; 75: 142-147. **[primary study incl in review article]**

6 Ferley JP, Zmirou D, D'Adhemar D, Balducci F. A controlled evaluation of a homoeopathic preparation in the treatment of influenza like syndromes. British Journal of Clinical Pharmacology, 1989; 27: 329-335. **[primary study incl in review article]**

7 Papp R, Schuback G, Beck E, et al. Oscillococcinum in patients with influenza-like syndromes: a placebo-controlled double-blind evaluation. British Homeopathic Journal, 1998; 87: 69-76. **[primary study incl in review article]**

8 Shealy CN, Thomlinson RP, Cox RH, Borgmeyer RN. Osteoarthritic pain: a comparison of homeopathy and acetaminophen. American Journal of Pain Management, 1998; 8: 89-91. **[primary study incl in review article]**

9 Shipley M, Berry H, Broster G, et al. Controlled trial of homoeopathic treatment of osteoarthritis. Lancet, 1983; i: 97-98. **[primary study incl in review article]**

10 van Haselen RA, Fisher PAG. A randomized controlled trial comparing topical piroxicam gel with a homeopathic gel in osteoarthritis of the knee. Rheumatology, 2000; 39: 714-719. **[primary study incl in review article]**

11 Taylor MA, Reilly D, Llewellyn-Jones RH, et al. Randomised controlled trials of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. British Medical Journal, 2000; 321: 471-476. **[primary study incl in review article]**

12 Aabel S, Laerum E, Dølvik S, Djupesland P. Is homeopathic 'immunotherapy' effective? A double-blind, placebo-controlled trial with the isopathic remedy Betula 30c for patients with birch pollen allergy. British Homeopathic Journal, 2000; 89: 161-168. **[primary study incl in review article]**

13 Aabel S. No beneficial effect of isopathic prophylactic treatment for birch pollen allergy during a low-pollen season: a double-blind, placebo-controlled clinical trial of homeopathic Betula 30c. British Homeopathic Journal, 2000; 89: 169-173. **[primary study incl in review article]**

14 Aabel S. Prophylactic and acute treatment with the homeopathic medicine Betula 30c for birch pollen allergy: a double-blind, randomized, placebo-controlled study of consistency of VAS responses. British Homeopathic Journal, 2001; 90: 73-78. **[primary study incl in review article]**

15 Kim LS, Riedlinger JE, Baldwin CM, et al. Treatment of seasonal allergic rhinitis using homeopathic preparation of common allergens in the southwest region of the US: a randomized, controlled clinical trial. Annals of Pharmacotherapy, 2005; 39: 617-624. **[primary study incl in review article]**

16 Reilly DT, Taylor MA. Potent placebo or potency? A proposed study model with initial findings using homoeopathically prepared pollens in hayfever. British Homeopathic Journal, 1985; 74: 65-75. **[primary study incl in review article]**

17 Reilly DT, Taylor MA, McSharry C, Aitchison T. Is homeopathy a placebo response? Controlled trial of homeopathic potency, with pollen in hayfever as model. Lancet, 1986; ii: 881-885.

18 Wiesenauer M, Häussler S, Gaus W. [Treatment of pollinosis with Galphimia glauca]. Fortschritte der Medizin, 1983; 101: 811-814. **[primary study incl in review article]**

19 Wiesenauer M, Gaus W. Double-blind trial comparing the effectiveness of the homoeopathic preparation

Galphimia potentization D6, Galphimia dilution 10-6 and placebo on pollinosis. Arzneimittelforschung, 1985; 35: 1745-1747. **[primary study incl in review article]**
20 Wiesenauer M, Gaus W, Häussler S. [Treatment of pollinosis with the homeopathic preparation Galphimia glauca. A double-blind trial in clinical practice]. Allergologie, 1990; 13: 359-363. **[primary study incl in review article]**
21 Weiser M, Gegenheimer LH, Klein P. A randomized equivalence trial comparing the efficacy and safety of Luffa comp.-Heel nasal spray with cromolyn sodium spray in the treatment of seasonal allergic rhinitis. Forschende Komplementärmedizin und Klassische Naturheilkunde, 1999; 6: 142-148. **[primary study incl in review article]**
22 Friese K-H, Zabalotnyi DI. [Homeopathy in acute rhinosinusitis. A double-blind, placebo controlled study shows the effectiveness and tolerability of a homeopathic combination remedy]. HNO, 2007; 55: 271-277. **[primary study incl in review article]**
23 Weiser M, Clasen B. [Randomized, placebo-controlled, double-blind study of the clinical efficacy of the homeopathic Euphorbium compositum-S nasal spray in cases of chronic sinusitis]. Forschende Komplementärmedizin, 1994; 1: 251-259. **[primary study incl in review article]**
24 Wiesenauer M, Gaus W, Bohnacker U, Häussler S. [Effectiveness trial of homeopathic drug combinations for the treatment of sinusitis. Results of a randomized double-blind study in primary care]. Arzneimittelforschung, 1989; 39: 620-625. **[primary study incl in review article]**
25 Zabolotnyi DI, Kneis KC, Richardson A, et al. Efficacy of a complex homeopathic medication (Sinfrontal) in patients with acute maxillary sinusitis: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial. Explore (NY), 2007; 3: 98-109. **[primary study incl in review article]**
26 Issing W, Klein P, Weiser M. The homeopathic preparation Vertigoheel versus Ginkgo biloba in the treatment of vertigo in an elderly population: a double-blinded, randomized, controlled clinical trial. Journal of Alternative and Complementary Medicine, 2005; 11: 155-160. **[possibly one of the articles included in Schneider 2005, but unable to be verified]**
27 Weiser M, Strösser W, Klein P. Homeopathic vs. conventional treatment of vertigo: a randomized double-blind controlled clinical study. Archives of Otolaryngology - Head and Neck Surgery, 1998; 124: 879-885. **[possibly one of the articles included in Schneider 2005, but unable to be verified]**
28 Weatherley-Jones E, Nicholl JP, Thomas KJ, et al. A randomized, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. Journal of Psychosomatic Research, 2004; 56: 189-197. **[primary study incl in review article]**
29 Yakir M, Kreitler S, Brzezinski A, et al. Effects of homeopathic treatment in women with premenstrual syndrome: a pilot study. British Homeopathic Journal, 2001; 90: 148-153. **[primary study incl in review article]**
30 Oberbaum M, Galoyan N, Lerner-Geva L, et al. The effect of the homeopathic remedies Arnica and Bellis perennis on mild postpartum bleeding - a randomized, double-blind, placebo-controlled study -preliminary results. Complementary Therapies in Medicine, 2005; 13: 87-90. **[primary study incl in review article]**
31 Frass M, Linkesch M, Banyai S, et al. Adjunctive homeopathic treatment in patients with severe sepsis: a randomized, double-blind, placebo-controlled trial in an intensive care unit. Homeopathy, 2005; 94: 75-80. **[Not included in NHMRC overview as no secondary evidence was found for this condition]**
32 Oberbaum M, Yaniv I, Ben-Gal Y, et al. A randomized, controlled clinical trial of the homeopathic medication Traumeel S in the treatment of chemotherapy-induced stomatitis in children undergoing stem cell transplantation. Cancer, 2001; 92: 684-690. **[primary study incl in review article]**
33 Baker DG, Myers SP, Howden I, Brooks L. The effects of homeopathic Argentum nitricum on test anxiety. Complementary Therapies in Medicine, 2003; 11: 65-71. **[primary study incl in review article]**
34 Bonne O, Shemer Y, Gorali Y, et al. A randomized, double-blind, placebo-controlled study of classical homeopathy in generalized anxiety disorder. Journal of Clinical Psychiatry, 2003; 64: 282-287. **[primary study incl in review article]**
35 McCutcheon LE. Treatment of anxiety with a homeopathic remedy. Journal of Applied Nutrition, 1996; 48: 2-6. **[primary study incl in review article]**
36 Freitas L, Goldenstein E, Sanna OM. [The indirect patient-doctor relationship and the homeopathic treatment of childhood asthma]. Revista de Homeopatia, 1995; 60: 26-31. **[primary study incl in review article]**
37 White A, Slade P, Hunt C, et al. Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomized placebo controlled trial. Thorax, 2003; 58: 317-321. **[primary study incl in review article]**
38 Hill N, Stam C, Tuinder S, van Haselen RA. A placebo controlled clinical trial investigating the efficacy of a homeopathic after-bite gel in reducing mosquito bite induced erythema. European Journal of Clinical

Pharmacology, 1995; 49: 103-108. **[primary study incl in review article]**
39 Hill N, Stam C, van Haselen RA. The efficacy of Prrrikweg gel in the treatment of insect bites: a double-blind, placebo-controlled clinical trial. Pharmacy World and Science, 1996; 18: 35-41. **[primary study incl in review article]**
40 Jacobs J, Herman P, Heron K, et al. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled trial. Journal of Alternative and Complementary Medicine, 2005; 11: 21-27. **[primary study incl in review article]**
41 Thompson EA, Montgomery A, Douglas D, Reilly D. A pilot, randomized, double-blinded, placebo-controlled trial of individualized homeopathy for symptoms of estrogen withdrawal in breast-cancer survivors. Journal of Alternative and Complementary Medicine, 2005; 11: 13-20. **[primary study incl in review article]**
42 Brigo B, Serpelloni G. Homoeopathic treatment of migraines: a randomized double-blind study of sixty cases (homoeopathic remedy versus placebo). Berlin Journal on Research in Homeopathy, 1991; 1: 98-106. **[primary study incl in review article]**
43 Straumsheim P, Borchgrevink C, Mowinckel P, et al. Homeopathic treatment of migraine: a double blind, placebo controlled trial of 68 patients. British Homeopathic Journal, 2000; 89: 4-7. **[primary study incl in review article]**
44 Whitmarsh TE, Coleston-Shields DM, Steiner TJ. Double-blind randomized placebo-controlled study of homoeopathic prophylaxis of migraine. Cephalalgia, 1997; 17: 600-604. **[primary study incl in review article]**
45 Jawara N, Lewith G, Mullee M, Smith C. Homoeopathic Arnica and Rhus Toxicodendron for delayed onset muscle soreness: a randomized, double-blind, placebo-controlled trial. British Homeopathic Journal, 1997; 86: 10-15. **[primary study incl in review article]**
46 Tveiten D, Bruseth S, Borchgrevink CF, Løhne K. [Effect of Arnica D30 on hard physical exertion. A double-blind randomized trial during the 1990 Oslo Marathon]. Tidsskrift for den Norske Lægeforening, 1991; 111: 3630-3631. **[primary study incl in review article]**
47 Tveiten D, Bruseth S, Borchgrevink CF, Norseth J. Effects of the homoeopathic remedy Arnica D30 on marathon runners: a randomized, double-blind study during the 1995 Oslo Marathon. Complementary Therapies in Medicine, 1998; 6: 71-74. **[primary study incl in review article]**
48 Vickers AJ, Fisher P, Smith C, et al. Homoeopathy for delayed onset muscle soreness: a randomized double blind placebo controlled trial. British Journal of Sports Medicine, 1997; 31: 304-307. **[primary study incl in review article]**
49 Vickers AJ, Fisher P, Smith C, et al. Homeopathic Arnica 30X is ineffective for muscle soreness after long-distance running: a randomized, double-blind, placebo-controlled trial. Clinical Journal of Pain, 1998; 14: 227-231. **[primary study incl in review article]**
50 Hart O, Mullee MA, Lewith G, Miller J. Double-blind, placebo-controlled, randomized clinical trial of homoeopathic arnica C30 for pain and infection after total abdominal hysterectomy. Journal of the Royal Society of Medicine, 1997; 90: 73-78. **[primary study incl in review article]**
51 Kaziro GS. Metronidazole (Flagyl) and Arnica montana in the prevention of post-surgical complications, a comparative placebo controlled clinical trial. British Journal of Oral & Maxillofacial Surgery, 1984; 22: 42-49. **[primary study incl in review article]**
52 Lökken P, Straumsheim PA, Tveiten D, et al. Effect of homoeopathy on pain and other events after acute trauma; placebo controlled trial with bilateral oral surgery. British Medical Journal, 1995; 310: 1439-1442. **[primary study incl in review article]**
53 Seeley BM, Denton AB, Ahn MS, Maas CS. Effect of homeopathic Arnica montana on bruising in face-lifts: results of a randomized, double-blind, placebo-controlled clinical trial. Archives of Facial Plastic Surgery, 2006; 8: 54-59. **[Not included in review as review timeframe predated this]**
54 Stevinson C, Devaraj VS, Fountain-Barber A, et al. Homeopathic arnica for prevention of pain and bruising: randomized placebo-controlled trial in hand surgery. Journal of the Royal Society of Medicine, 2003; 96: 60-65. **[Not included in review as review timeframe predated this]**
55 Robertson A, Suryanarayanan R, Banerjee A. Homeopathic Arnica montana for post-tonsillectomy analgesia: a randomised placebo control trial. Homeopathy, 2007; 96: 17-21. **[Not included in review as review timeframe predated this]**
56 Wolf M, Tamaschke C, Mayer W, Heger M. [Efficacy of Arnica in varicose vein surgery: results of a randomized, double-blind, placebo-controlled pilot study]. Forschende Komplementär-medizin und Klassische Naturheilkunde, 2003; 10: 242-247. **[Not included in review as review timeframe predated this]**

57 Andrade L, Ferraz MB, Atra E, et al. A randomized controlled trial to evaluate the effectiveness of homoeopathy in rheumatoid arthritis. Scandinavian Journal of Rheumatology, 1991; 20: 204-208. **[primary study incl in review article]**
58 Fisher P, Scott DL. A randomized controlled trial of homeopathy in rheumatoid arthritis. Rheumatology, 2001; 40: 1052-1055. **[primary study incl in review article]**
59 Wiesenauer M, Gaus W. [A randomized double-blind trial on the efficacy of a homeopathic drug for rheumatoid arthritis]. Aktuelle Rheumatologie, 1991; 16: 1-9. **[primary study incl in review article]**
60 Savage RH, Roe PF. A double blind trial to assess the benefit of Arnica mo ntana in acute stroke illness. British Homeopathic Journal, 1977; 66: 207-220. **[primary study incl in review article]**
61 Savage RH, Roe PF. A further double blind trial to assess the benefit of Arnica montana in acute stroke illness. British Homeopathic Journal, 1978; 67: 210-222. **[primary study incl in review article]**
62 Davies AE. Clinical investigations into the actions of potencies. British Homeopathic Journal, 1971; 60: 36-41. **[not relevant to review]**
63 Steinsbekk A, Bentzen N, Fønnebø V, Lewith G. Self treatment with one of three self selected, ultramolecular homeopathic medicines for the prevention of upper respiratory tract infections in children. A double-blind randomized placebo controlled trial. British Journal of Clinical Pharmacology, 2005; 59: 447-455. **[primary study incl in review article]**
64 Steinsbekk A, Fønnebø V, Lewith G, Bentzen N. Homeopathic care for the prevention of upper respiratory tract infections in children: a pragmatic, randomized, controlled trial comparing randomized homeopathic care and waiting-list controls. Complementary Therapies in Medicine, 2005; 13: 231-238. **[primary study incl in review article]**
65 Kainz JT, Kozel G, Haidvogl M, Smolle J. Homoeopathic versus placebo therapy of children with warts on the hands: a randomized, double-blind clinical trial. Dermatology, 1996; 193: 318-320. **[primary study incl in review article]**
66 Labrecque M, Audet D, Latulippe LG, Drouin J. Homoeopathic treatment of plantar warts. Canadian Medical Association Journal, 1992; 146: 1749-1753**[primary study incl in review article]**
67 Linde K, Scholz M, Ramirez G, et al. Impact of study quality on outcome in placebo controlled trials of homeopathy. Journal of Clinical Epidemiology, 1999; 52: 631-636.) **[not relevant to review]**
68 Dean ME, Coulter MK, Fisher P, Jobst K, Walach H. Reporting data on homeopathic treatments (RedHot): a supplement to CONSORT. HOMP 2007; 96(1): 42-45. **[not relevant to review]**

Appendices to Report

Appendix 1A. NHMRC FORM Matrix

http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/evidence_statement_form.pdf

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population*	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Appendix 1B. CEBM Critical Appraisal Tool for Systematic Reviews

http://www.cebm.net/index.aspx?o=1157

SYSTEMATIC REVIEW: Are the results of the review valid?

What question (PICO) did the systematic review address?	
What is best?	Where do I find the information?
The main question being addressed should be clearly stated. The exposure, such as a therapy or diagnostic test, and the outcome(s) of interest will often be expressed in terms of a simple relationship.	The ***Title, Abstract*** *or final paragraph of the* ***Introduction*** should clearly state the question. If you still cannot ascertain what the focused question is after reading these sections, search for another paper!
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
F - Is it unlikely that important, relevant studies were missed?	
What is best?	Where do I find the information?
The starting point for comprehensive search for all relevant studies is the major bibliographic databases (e.g., Medline, Cochrane, EMBASE, etc) but should also include a search of reference lists from relevant studies, and contact with experts, particularly to inquire about unpublished studies. The search should not be limited to English language only. The search strategy should include both MESH terms and text words.	The ***Methods*** section should describe the search strategy, including the terms used, in some detail. The ***Results*** section will outline the number of titles and abstracts reviewed, the number of full-text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
A - Were the criteria used to select articles for inclusion appropriate?	
What is best?	Where do I find the information?
The inclusion or exclusion of studies in a systematic review should be clearly defined a priori. The eligibility criteria used should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.	The ***Methods*** section should describe in detail the inclusion and exclusion criteria. Normally, this will include the study design.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
A - Were the included studies sufficiently valid for the type of question asked?	
What is best?	Where do I find the information?
The article should describe how the quality of each study was assessed using predetermined quality criteria appropriate to the type of clinical question (e.g., randomization, blinding and completeness of follow-up)	The ***Methods*** section should describe the assessment of quality and the criteria used. The ***Results*** section should provide information on the quality of the individual studies.
This paper: Yes ☐ No ☐ Unclear ☐ Comment:	
T - Were the results similar from study to study?	
What is best?	Where do I find the information?
Ideally, the results of the different studies should	The ***Results*** section should state whether the results

be similar or homogeneous. If heterogeneity exists the authors may estimate whether the differences are significant (chi-square test). Possible reasons for the heterogeneity should be explored.	are heterogeneous and discuss possible reasons. The forest plot should show the results of the chi-square test for heterogeneity and if discuss reasons for heterogeneity, if present.

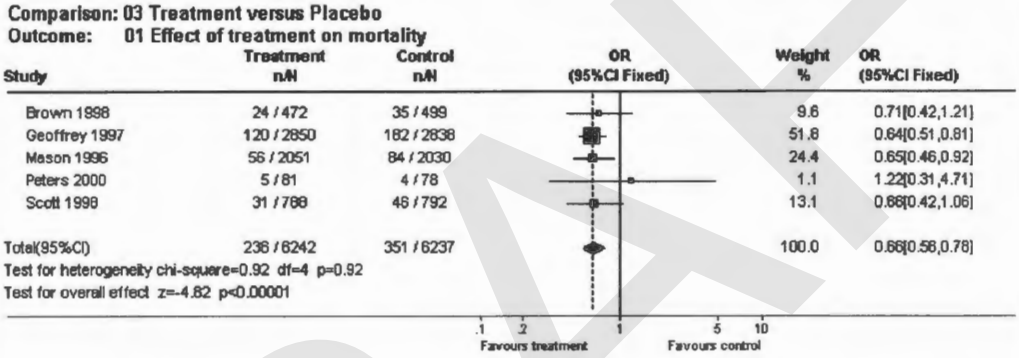
This paper: Yes ☐ No ☐ Unclear ☐

Comment:

What were the results?

How are the results presented?

A systematic review provides a summary of the data from the results of a number of individual studies. If the results of the individual studies are similar, a statistical method (called meta-analysis) is used to combine the results from the individual studies and an overall summary estimate is calculated. The meta-analysis gives weighted values to each of the individual studies according to their size. The individual results of the studies need to be expressed in a standard way, such as relative risk, odds ratio or mean difference between the groups. Results are traditionally displayed in a figure, like the one below, called a **forest plot.**



The forest plot depicted above represents a meta-analysis of 5 trials that assessed the effects of a hypothetical treatment on mortality. Individual studies are represented by a black square and a horizontal line, which corresponds to the point estimate and 95% confidence interval of the odds ratio. The size of the black square reflects the weight of the study in the meta-analysis. The solid vertical line corresponds to 'no effect' of treatment - an odds ratio of 1.0. When the confidence interval includes 1 it indicates that the result is not significant at conventional levels (P>0.05).

The diamond at the bottom represents the combined or pooled odds ratio of all 5 trials with its 95% confidence interval. In this case, it shows that the treatment reduces mortality by 34% (OR 0.66 95% CI 0.56 to 0.78). Notice that the diamond does not overlap the 'no effect' line (the confidence interval doesn't include 1) so we can be assured that the pooled OR is statistically significant. The test for overall effect also indicates statistical significance (p<0.0001).

Exploring heterogeneity

Heterogeneity can be assessed using the "eyeball" test or more formally with statistical tests, such as the Cochran Q test. With the "eyeball" test one looks for overlap of the confidence intervals of the trials with the summary estimate. In the example above note that the dotted line running vertically through the combined odds ratio crosses the horizontal lines of all the individual studies indicating that the studies are homogenous. Heterogeneity can also be assessed using the Cochran chi-square (Cochran Q). If Cochran Q is statistically significant there is definite heterogeneity. If Cochran Q is not statistically significant but the ratio of Cochran Q and the degrees of freedom (Q/df) is > 1 there is possible heterogeneity. If Cochran Q is not statistically significant and Q/df is < 1 then heterogeneity is very unlikely. In the example above Q/df is <1 (0.92/4= 0.23) and the p-value is not significant (0.92) indicating no heterogeneity.

Note: The level of significance for Cochran Q is often set at 0.1 due to the low power of the test to detect heterogeneity.

Appendix 2. Articles identified from various sources, and the decision regarding their relevance to the search (The excluded articles can be cross-referenced with Appendix 3)

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
1.	Adler, U. C. (2005). "The influence of childhood infections and vaccination on the development of atopy: a systematic review of the direct epidemiological evidence." *Homeopathy* **94**(3): 182-195.				✓ X excluded		
2.	Albrecht, H. Klinische Forschung zur Homoopathie - eine kritische Bewertung.				✓ X excluded		
3.	Alraek, T., M. S. Lee, et al. (2011). "Complementary and alternative medicine for patients with chronic fatigue syndrome: A systematic review." BMC Complementary and Alternative Medicine **11**(1): 87-87.				✓		
4.	Altunç, U., M. H. Pittler, et al. (2006). "Homoeopathy for childhood and adolescence ailments: systematic review of randomised clinical trials... 13th Annual Symposium on Complementary Health Care, 12th-14th December, 2006, University of Exeter, UK." Focus on Alternative & Complementary Therapies **11**: 37-37.				X Excluded (conf abstract only, see below)		
5.	Altunç, U, Pittler, MH, Ernst, E. (2007). Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic Proceedings*, 82: 69-75.	✓			✓	✓ Ernst 2010	✓ House of Commons ✓ LMHI
6.	Anonymous (2011). "Complementary Medicine; Recent Studies from Faculty of Medicine Add New Data to Complementary Medicine." Obesity, Fitness & Wellness Week: 909.				✓ X excluded		
7.	Baranowsky, J., P. Klose, et al. (2009). "Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia." Rheumatology International **30**(1): 1-21.					✓ Terry 2012	✓ LMHI

No#	Reference:	Reference was cited in:			Found in ICAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
8.	Barnes, J. (1997). "Effects of homoeopathy are more than placebo." FACT **2**(4): 161-162.				✓ X excluded		✓ House of Commons
9.	Barnes, J., Resch, K.L., & Ernst, E. (1997). Homoeopathy for postoperative ileus? A meta-analysis. *Journal of Clinical Gastroenterology*, 25: 628-633.	✓				✓ O'Meara 2002 ✓ Linde 2001	✓ LMHI ✓ Bornhoft & Matthiessen 2011
10.	Barrett, B. B., D. D. Kiefer, et al. (1999). "Assessing the risks and benefits of herbal medicine: an overview of scientific evidence." Alternative therapies in health and medicine **5**(4): 40-49.				✓ X excluded		
11.	Becker-Witt C, Lüdtke R, Weisshuhn TER, Willich SN (2004) Diagnoses and treatment in homeopathic medical practice. Forschende Komplementärmedizin und Klassische Naturheilkunde 11:98-103				✓ X excluded		✓ Bornhoft & Matthiessen 2011
12.	Bellavite., P., R. Ortolani., et al. (2006a). "Immunology and Homeopathy. 4. Clinical Studies—Part 1." eCAM **3**(3): 293-301.				✓		
13.	Bellavite P, Ortolani R, Pontarollo F. (2006b). Immunology and homeopathy. 4. Clinical studies—Part 2. *Evidence-based Complementary and Alternative Medicine: eCAM*, 3: 397-409.	✓		✓	✓		✓ LMHI
14.	Bellavite, P., S. Chirumbolo, et al. (2008). "Effectiveness of homeopathy in immunology and inflammation disorders: a literature overview of clinical studies." *Homoeopathic Heritage International* **33**(3): 35-57.				✓		
15.	Bellavite., P., M. Marzotto., et al. (2011). "Advances in homeopathy and immunology: a review of clinical research." Frontiers in Bioscience **S3**: 1363-1389.				✓		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
16.	Benveniste, J. (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 367.				✓ X excluded		
17.	Bielory, L. and J. Heimall (2003). "Review of complementary and alternative medicine in treatment of ocular allergies." Curr Opin Allergy Clin Immunol **3**(5): 395-399.				✓ X excluded		
18.	Birnesser, H. and P. Stolt (2007). "The homeopathic antiarthitic preparation zeel comp. N: A review of molecular and clinical data." *Explore-the Journal of Science and Healing* **3**(1): 16-22.				✓ X exclude		
19.	Bloom, B. S., A. Retbi, et al. Evaluation of randomized controlled trials on complementary and alternative medicine.				✓ X excluded		
20.	Bobak, M. and A. Donald (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 368.				✓ X excluded		
21.	Boiron, C. (2011). "Homeopathy, a tremendous opportunity for medicine!" *Eur J Intern Med* 22(1): 117-118; author reply 118-119.				✓ X Excluded		
22.	Bol, A. (1991) Clinical trials of homeopathy.				✓ X Excluded		
23.	Bornhöft, G., Wolf, U., Ammon, K., et al 2006. Effectiveness, safety and cost-effectiveness of homeopathy in general practice—summarized health technology assessment. *Forschende Komplementärmedizin, 13 (Suppl 2): 19-29*	✓			✓ Govt. review (component articles will be assessed) X Excluded		
24.	Brinkaus, B. (2006). Homeopathic Arnica therapy in patients receiving knee surgery: results of three randomised double-blind trials. *Comp Ther Med* 14: 237-246.	✓			✓ X excluded		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
25.	Calabrese, E. J., Blain, R. (2005). The occurrence of hormetic dose responses in the toxicological literature, the hormesis database: An overview. *Toxicol. Appl. Pharmacol.* 202, 289-301.	✓			✓ X excluded		
26.	Castro, M. (1999). "Homeopathy - A theoretical framework and clinical application." *Journal of Nurse-Midwifery* 44(3): 280-290.				✓ X excluded		
27.	Caulfield, T. and S. DeBow (2005). "A systematic review of how homeopathy is represented in conventional and CAM peer reviewed journals." BMC Complementary and Alternative Medicine **5**.				✓ X excluded		
28.	Cooper, K. L. and C. Relton (2010). "Homeopathy for insomnia: A systematic review of research evidence." Sleep Medicine Reviews **14**(5): 329-337.				✓		
29.	Cooper, K. L. and C. Relton (2010). "Homeopathy for insomnia: summary of additional RCT published since systematic review." Sleep Med Rev **14**(6): 411.				✓ X excluded		
30.	Coulter, M. K., M. E. Dean, et al. (2006). "A systematic review of homoeopathy for attention-deficit hyperactivity disorder/hyper-kinetic disorder... 13th Annual Symposium on Complementary Health Care, 12th-14th December, 2006, University of Exeter, UK." Focus on Alternative & Complementary Therapies **11**: 15-15.				✓ X Excluded (conf abstract only, see below)		
31.	Coulter, M.K., Dean, M.E. (2007). Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder (Cochrane Review). In. The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD005648. **UPDATED TO:** • Heirs M, Dean ME. Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane	✓ 2007		✓ 2007	✓ 2009	✓ Ernst 2010 (2007 edn)	

No#	Reference:	Reference was cited in: AHA	AMFH	Public response	Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
	Database of Systematic Reviews 2009, Issue 4. Art. No.: CD005648. DOI: 10.1002/14651858.CD005648.pub2 NB: different dates and lead author						
32.	Cucherat, M. & Linde, K. (2000). Evidence of clinical effectiveness of homeopathy: a meta-analysis of clinical trials. Eur J Clin Pharmacol 56: 27-33.	✓				✓ Bornhoft 2006 ✓ Ernst 2002 ✓ O'Meara 2002 ✓ Linde 2001	✓ House of Commons ✓ LMHI ✓ Bornhoft & Matthiessen 2011
33.	Daniele, C., G. Mazzanti, et al. (2006). "Adverse-Event Profile of Crataegus Spp.: A Systematic Review." Drug Safety **29**(6): 523-535.				✓ X excluded		
34.	Dantas, F. & Fisher, P. (1998). A systematic review of homoeopathic pathogenetic trials ('provings') published in the United Kingdom from 1945-1995. In: E. Ernst & E.G. Kahn (Eds.) Homoeopathy: a critical appraisal, pp. 69-97. London: Butterworth Heinemann.	✓			✓		
35.	Dantas, F. & Rampes, H. (2000). Do Homeopathic Medicines Provoke Adverse Effects? A Systematic Review. British Homeopathic Journal; 89: 70-74.	✓				✓ Bornhoft 2006	✓ LMHI ✓ Bornhoft & Matthiessen 2011
36.	Dantas, F. (2003). "Homeopathy in childhood asthma." Thorax 58(9): 826; author reply 828.				✓ X excluded		
37.	Dantas, F., P. Fisher, et al. (2007). "A systematic review of the quality of				✓ X exclude		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
	homeopathic pathogenetic trials published from 1945 to 1995." Homeopathy **96**(1): 4-16.				d		
38.	Davidson, J. R. T., C. Crawford, et al. (2011). "Homeopathic treatments in psychiatry: A systematic review of randomized placebo-controlled studies." Journal of Clinical Psychiatry **72**(6): 795-805.				✓		
39.	Dean, M. E., M. K. Coulter, et al. (2007). "Reporting data on homeopathic treatments (RedHot): a supplement to CONSORT." Homeopathy **96**(1): 42-45.				✓ X excluded		
40.	De Silva, V., A. El-Metwally, et al. (2010). "Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review." Rheumatology (Oxford) **49**(6): 1063-1068.				✓		✓ LMHI
41.	De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ. Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. Rheumatology (Oxford). 2011 May;50(5):911-20.				✓		✓ LMHI
42.	Eames, S. and P. Darby (2011). "Homeopathy and its ethical use in dentistry." Br Dent J **210**(7): 299-301.				✓ X excluded		
43.	ENHR: European Network of Homeopathy Researchers. (2006). An overview of positive homeopathy research and surveys. Available on the website of the European Central Council of Homeopaths - www.homeopathy-ecch.org	✓			✓ X excluded (2007 update)		
44.	Erlewyn-Lajeunesse, M. (2012). "Homeopathic medicines for children." Archives of Disease in Childhood **97**(2): 135-				✓ X excluded		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
	138.						
45.	Ernst, E. & Barnes, A. (1998). Are homeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo controlled trials. Perfusion, 11: 4-8.	✓				✓ Bornhoft 2006 ✓ O'Meara 2002 ✓ Ernst 2002 ✓ Linde 2001	✓ House of Commons ✓ Bornhoft & Matthiessen 2011
46.	Ernst, E. and Pittler, M. H. (1998), 'Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials', Archives of surgery (Chicago, Ill. : 1960), 133 (11), 1187-90.	✓				✓ Bornhoft 2006 ✓ Ernst 2002 ✓ O'Meara 2002 ✓ Linde 2001	✓ House of Commons ✓ Bornhoft & Matthiessen 2011
47.	Ernst, E. (1999a). "Homeopathic prophylaxis of headaches and migraine? A systematic review." Journal of Pain & Symptom Management **18**(5): 353-357.				✓	✓ Bornhoft 2006 ✓ Ernst 2002 ✓ Linde 2001 ✓ O'Meara 2002	✓ House of Commons ✓ LMHI
48.	Ernst, E. (1999b), 'Classical homoeopathy versus conventional treatments: a systematic review (Structured abstract)', *PERFUSION*, (1), 13-15. <http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-				✓	✓ Bornhoft 2006 ✓ Ernst 2002 ✓	✓ House of Commons ✓

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
	11999000356/frame.html>.					O'Meara 2002 ✓ Linde 2001	LMHI ✓ Bornhoft & Matthiessen 2011
49.	Ernst, E. and A. Huntley (2000). "Tea tree oil: A systematic review of randomized clinical trials." FORSCHENDE KOMPLEMENTARMEDIZIN UND KLASSISCHE NATURHEILKUNDE 7(1): 17-20.				✓ X excluded		
50.	Ernst, E. (2000). "The usage of complementary therapies by dermatological patients: a systematic review." British Journal of Dermatology **142**(5): 857-861.				✓ X excluded		✓ Bornhoft & Matthiessen 2011
51.	Ernst E (2000) Prevalence of use of complementary/alternative medicine: a systematic review. Bull World Health Organ 78:252–257				✓ X Excluded		✓ Bornhoft & Matthiessen 2011
52.	Ernst, E. (2002), 'A systematic review of systematic reviews of homeopathy', *British Journal of Clinical Pharmacology, 54 (6), 577-82.*				✓ umbrella review (component articles will be assessed) X Excluded	✓ Bornhoft 2006 ✓ Ulbricht 2011	✓ House of commons report ✓ Bornhoft & Matthiessen 2011
53.	Ernst, E. and K. Schmidt (2004). "Homotoxicology--a review of randomised clinical trials." European Journal of Clinical Pharmacology **60**(5): 299-306.				✓		
54.	Ernst, E. (2010). "Homeopathy: what does the "best" evidence tell us?" *Med J Aust 192(8): 458-460.*				✓ umbrella review		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
					(component articles will be assessed) X Excluded		
55.	Ernst, E. (2011a). "Homeopathic Galphimia glauca for hay fever: a systematic review of randomised clinical trials and a critique of a published meta-analysis." Focus on Alternative & Complementary Therapies **16**(3): 200-203.				✓		
56.	Ernst, E. (2011b). "Homeopathy for insomnia and sleep-related disorders: a systematic review of randomised controlled trials." Focus on Alternative & Complementary Therapies **16**(3): 195-199.				✓		
57.	Fisher, P., B. Berman, et al. (2005). "Are the clinical effects of homoeopathy placebo effects?" Lancet **366**(9503): 2082-2083; author reply 2083-2086.				✓ X excluded		✓ Bornhoft & Matthiessen 2011
58.	Franklin, P. (1999). "Review, critique, and guidelines for the use of herbs and homeopathy." J Child Fam Nurs **2**(6): 418-419.				✓ X excluded		
59.	Friese, K.H. Kruse, S. Ludtke, R. Moeller, H. (1997). Homeopathic treatment of otits media in children: comparisons with conventional therapy. Int J Clin Pharmacol Ther; 35: 296-301.	✓			✓ X excluded		✓ Bornhoft & Matthiessen 2011
60.	Frei H, Everts R, von Ammon K, Kaufmann F, Walter D, Hsu Schmitz SF, Collenberg M, Fuhrer K, Hassink R, Steinlin M, Thurneysen A (2005) Homeopathic treatment of children with attention deficit hyperactivity disorder. Eur J Pediatr 164:758–767				✓ X Excluded		✓ Bornhoft & Matthiessen 2011

No#	Reference:	Reference was cited in: AHA	AMFH	Public response	Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
61.	Frye, J. (1997). "Homeopathy in office practice." Primary Care **24**(4): 845-+.				✓ X excluded		
62.	Gagnier, J. J., M. W. van Tulder, et al. (2007). "Herbal medicine for low back pain: a Cochrane review." Spine (Phila Pa 1976) **32**(1): 82-92.				✓ X excluded		
63.	Glisson, J., R. Crawford, et al. (1999). "Review, critique, and guidelines for the use of herbs and homeopathy." The Nurse practitioner **24**(4): 44-60.				✓ X excluded		
64.	Grabia, S. and E. Ernst (2003). "Homeopathic aggravations: a systematic review of randomised, placebo-controlled clinical trials." Homeopathy **92**(2): 92-98.				✓	✓ Bornhoft 2006	✓ LMHI ✓ Bornhoft & Matthiessen 2011
65.	Heirs, M. and M. E. Dean (2009). "Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder." Cochrane Database of Systematic Reviews(4).	SEE COULTER & DEAN 2007 ABOVE					
66.	Heger M, Riley DS, Haidvogl M (2000) International integrative primary care outcomes study (IIPCOS-2): an international research project of homeopathy in primary care. Br Homeopathic J 89 [Suppl 1]:S10–13				✓ X Excluded		✓ Bornhoft & Matthiessen 2011
67.	Holdcraft, L. C., N. Assefi, et al. (2003). "Complementary and alternative medicine in fibromyalgia and related syndromes." Best Pract Res Clin Rheumatol **17**(4): 667-683.				✓		✓ LMHI
68.	Huang, T., X. Shu, et al. (2011). "Complementary and miscellaneous interventions for nocturnal enuresis in children." Cochrane Database of Systematic Reviews(12).				✓ 2011	✓ Ernst 2010 (2005 edn.)	✓ LMHI (2005 edn.)

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
	NB: Different dates						
69.	Hunt, K. and E. Ernst (2011). "The evidence-base for complementary medicine in children: a critical overview of systematic reviews." Arch Dis Child **96**(8): 769-776.				✓ umbrella review (component articles will be assessed) X excluded		
70.	Jacobs, J. Jonas, W.B. Jimenez-Perez, M. Crothers, D. (2003). Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. Pediatric Infectious Disease Journal, 22: 229-234.	✓			✓ X excluded		✓ House of Commons ✓ LMHI ✓ Bornhoft & Matthiessen 2011
71.	Johnson, M. A. (1998). "Homeopathy: Another tool in the bag." JAMA **279**(9): 707-707.				✓ X excluded		
	Jonas, W.B. (1997). Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo controlled trials. Lancet, 350: 834-843. *This is actually Linde 1997- it has been incorrectly referenced in the submission files.*	✓			See Linde 1997		
72.	Jonas, W. B., R. L. Anderson, et al. (2000). "A systematic review of the quality of homeopathic clinical trials." BMC Complementary and Alternative Medicine **1**: 12.				✓ X excluded		✓ Bornhoft & Matthiessen 2011

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
73.	Jonas, W.B. (2003). A critical overview of homoeopathy. Ann Int Med 138: 393-399.	✓			✓ X Excluded		✓ LMHI ✓ Bornhoft & Matthiessen 2011
74.	Jorm, A. F., H. Christensen, et al. (2004). "Effectiveness of complementary and self-help treatments for anxiety disorders." Medical Journal of Australia **181**(7): S29-46.				✓		
75.	Karkos, P. D., S. C. Leong, et al. (2007). "'Complementary ENT': a systematic review of commonly used supplements." The Journal of Laryngology and Otology **121**(8): 779-782.				✓ X Excluded		
76.	Kassab, S. Cummings, M. Berkovitz, S. et al (2011). Homeopathic medicines for adverse effects of cancer treatments (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD 004845.	✓ 2009		✓ 2009	✓ 2011	✓ Ernst 2010 (2009)	✓ LMHI (2009)
77.	Kienle GS, Kiene H, Albonico HU (2006) Anthroposophische Medizin: Health Technology Assessment Bericht – Kurzfassung. Forschende Komplementärmedizin 13 [Suppl 2]:7–18				✓ X Excluded		✓ Bornhoft & Matthiessen 2011
78.	Kirkby, R. and P. Herscu (2010). "Homeopathic trial design in influenza treatment." Homeopathy **99**(1): 69-75.				✓ X Excluded		
79.	Kleijnen, J., P. Knipschild, et al. (1991). "CLINICAL-TRIALS OF HOMEOPATHY." BRITISH MEDICAL JOURNAL **302**(6772): 316-323.				✓ X Excluded		✓ LMHI

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
80.	Langhorst J, Häuser W, Irnich D, Speeck N, Felde E, Winkelmann A, Lucius H, Michalsen A, Musial F. 2008. [Alternative and complementary therapies in fibromyalgia syndrome]. Schmerz 22(3), 324-33.				✓ X Excluded		✓ LMHI
81.	Linde, K., Clausius, N., Ramirez, G., Melchart, D., Eitel, F., Hedges, L.V. & & Jonas, W.B. (1997). Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo controlled trials. Lancet, 350: 834-843.	✓			✓	✓ Bornhoft 2006 ✓ Ernst 2002 ✓ O'Meara 2002 ✓ Linde 2001 ✓ Terry 2012	✓ House of Commons ✓ LMHI ✓ Bornhoft & Matthiessen 2011
82.	Linde, K. & Melchart, D. (1998). Randomised controlled trials of individualised homeopathy: a state-of-the-art review. Journal of Alternative and Complementary Medicine 4: 371-388.	✓			✓	✓ Ernst 2002 ✓ O'Meara 2002 ✓ Linde 2001	✓ House of Commons ✓ LMHI ✓ Bornhoft & Matthiessen 2011
83.	Linde, K., M. Hondras, et al. (2001). Systematic reviews of complementary therapies - an annotated bibliography. Part 3: Homeopathy.				✓ umbrella review (component articles will be assessed) X Excluded	✓ Ulbricht 2011	✓ Bornhoft & Matthiessen 2011

No#	Reference:	Reference was cited in: AHA	AMFH	Public response	Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
84.	Linde, K., G. ter Riet, et al. (2003). "Characteristics and quality of systematic reviews of acupuncture, herbal medicines, and homeopathy." Forsch Komplementarmed Klass Naturheilkd **10**(2): 88-94.				✓ X Excluded		
85.	Linde K, Jonas W (2005) Are the clinical effects of homeopathy placebo effects? Lancet 366:2081–2082; DOI:10.1016/S0140-6736(05)67878-6				✓ X Excluded		✓ Bornhoft & Matthiessen 2011
86.	Long, L. & Ernst, E. (2001). Homeopathic remedies for the treatment of osteoarthritis: a systematic review. British Homeopathic Journal, 90: 37-43.	✓			✓	✓ Bornhoft 2006 ✓ Ernst 2002 ✓ O'Meara 2002	✓ LMHI ✓ Bornhoft & Matthiessen 2011
87.	Ludtke R, Wiesenauer M. (1997) A meta-analysis of homeopathic treatment of pollinosis with Galphimia glauca. Wien Med Wochenschr 1997;147: 323–7.				✓ X Excluded		✓ LMHI
88.	Ludtke, R. & Wilkins, R. (1999). Clinical trials of Arnica in homoeopathic preparations. In: Albrecht, H. Fruhwald, M. (eds) Jahrbuch. Carl & Veronica Carstens-Stiftung. KVC Verlag: Essen pp. 97-112.	✓			✓ X Excluded		✓ House of Commons
89.	Ludtke, R. & Stolper, C.F. (2008). The 2005 meta-analysis of homeopathy: the importance of post-publication data. Homoeopathy, Vol. 97:169-77. *This is actually Rutten 2008- it has been incorrectly referenced in the submission files.*	✓			See Rutten 2008		
90.	Lüdtke R, Rutten ALB (2008) The conclusions on the effectiveness of homeopathy highly	✓	✓	✓	✓ X		✓ House

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
	depend on the set of analyzed trials. Journal of Clinical Epidemiology 61: 1197-1204				Excluded		of Commons ✓ LMHI ✓ Bornhoft & Matthiessen 2011
91.	Martin, K. W. and E. Ernst (2003). "Herbal medicines for treatment of bacterial infections: a review of controlled clinical trials." The Journal of antimicrobial chemotherapy **51**(2): 241-246.				✓ X Excluded		
92.	Mathie, R. (2003). The research base of homeopathy: a fresh assessment of the literature. Homeopathy, 92: 84-91.	✓			✓	✓ Bornhoft 2006	✓ House of Commons ✓ LMHI ✓ Bornhoft & Matthiessen 2011
93.	Maxion-Bergemann, S., M. Wolf, et al. (2006). "Complementary and alternative medicine costs - a systematic literature review." Forsch Komplementmed **13 Suppl 2**: 42-45.				✓ X Excluded		✓ Bornhoft & Matthiessen 2011
94.	McCarney, R. W., T. J. Lasserson, et al. (2004). An overview of two Cochrane systematic reviews of complementary treatments for chronic asthma: acupuncture and homeopathy. *Respiratory Medicine 98(8): 687-696.*				✓ umbrella review (component articles will be assessed) X exclude		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
					d		
95.	McCarney RW, Linde K, Lasserson TJ (2008). Homeopathy for chronic asthma (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD000353.	✓ 2004		✓ 2004	✓ 2008	✓ Bornhoft 2006 (2000 edn.) ✓ McCarney 2004 (2004 edn.) ✓ Ernst 2002 (1998 edn.) ✓ Ernst 2010 (2004 edn.) ✓ O'Meara 2002 (2001 edn.) ✓ Linde 2001 (1998 edn.)	✓ LMHI (2004 edn.) ✓ Bornhoft & Matthiessen 2011 (2000 edn.)
96.	McCarney RW, Warner J, Fisher P, van Haselen R. (2009). Homeopathy for dementia. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD003803. DOI: 10.1002/14651858.CD003803 NB: different dates			✓ 2003	✓ 2009 update	✓ Ernst 2010 (2003 edn.)	✓ LMHI (2003 edn.) ✓ Bornhoft & Matthiessen 2011 (2003 edn.)
97.	Merrell, W. C. and E. Shalts (2002). "Homeopathy." Medical Clinics of North				✓ X exclude		

No#	Reference:	Reference was cited in: AHA	AMFH	Public response	Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
	America **86**(1): 47-+				d		
98.	Milazzo S, et al. (2006). Efficacy of homeopathic therapy in cancer treatment. European Journal of Cancer, 42: 282-289.	✓			✓		✓ LMHI
99.	Milgrom, L. R. (2008). "Homeopathy and the new fundamentalism: A critique of the critics." Journal of Alternative and Complementary Medicine **14**(5): 589-594.				✓ X excluded		
100	Mills, E., P. Wu, et al. (2005). "Complementary therapies for the treatment of HIV: in search of the evidence." International Journal of STD & AIDS **16**(6): 395-403.				✓		✓ LMHI
101	Nowak, A. L. V. and H. M. Hale (2012). "Prevalence of Complementary and Alternative Medicine Use Among U.S. College Students: A Systematic Review." American Journal of Health Education **43**(2): 116-126.				✓ X excluded		
102	Nuhn, T., R. Lüdtke, et al. (2010). "Placebo effect sizes in homeopathic compared to conventional drugs - a systematic review of randomised controlled trials." Homeopathy **99**(1): 76-82.				✓ X excluded		
103	O'Meara, S., P. Wilson, et al. (2002). "Homoeopathy." Qual Saf Health Care **11**(2): 189-194.				✓ umbrella review (component articles will be assessed) X excluded		✓ Bornhoft & Matthiessen 2011
104	Owen, J.M. Green, B.N. (2004). Homeopathic treatment of headaches: A systematic review of the literature. Journal of Chiropractic Medicine, 3: 45-52.	✓			✓		✓ LMHI
105	Passalacqua, G., P. J. Bousquet, et al. (2006).				✓		✓ LMHI

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
	"ARIA update: I--Systematic review of complementary and alternative medicine for rhinitis and asthma." J Allergy Clin Immunol **117**(5): 1054-1062.						
106	Paterson, C. (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 365-366				✓ X excluded		
107	Peckham Emily, J., E. A. Nelson, et al. (2012) "Homeopathy for treatment of irritable bowel syndrome." Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD009710.				✓ X excluded		
108	Perry, R., R. Terry, et al. (2010) A systematic review of homoeopathy for the treatment of fibromyalgia (Provisional abstract). Clinical Rheumatology 457-464				✓	Terry 2012	✓ LMHI
109	Pilkington, K., G. Kirkwood, et al. (2005). "Homeopathy for depression: a systematic review of the research evidence." Homeopathy **94**(3): 153-163.				✓		✓ LMHI
110	Pilkington, K, Kirkwood, G, Rampes H, et al (2006). Homeopathy for anxiety and anxiety disorders: A systematic review of the research. Homeopathy, 95: 151-162.	✓			✓		✓ LMHI
111	Pilkington, K. (2007). "Searching for CAM evidence: An evaluation of therapy-specific search strategies." Journal of Alternative and Complementary Medicine **13**(4): 451-459.				✓ X excluded		
112	Pittler, M. H. and E. Ernst (2005). "Complementary therapies for reducing body weight: a systematic review." Int J Obes (Lond) **29**(9): 1030-1038.				✓		
113	Porter, N. S., L. A. Jason, et al. (2010). "Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia." Journal of Alternative & Complementary Medicine **16**(3): 235-249.				✓		
114	Practice and Policy Guidelines Panel (1997).				✓ X		✓ Bornho

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
	"Clinical practice guidelines in complementary and alternative medicine. An analysis of opportunities and obstacles. National Institutes of Health Office of Alternative Medicine." Arch Fam Med 6(2): 149-154.				excluded		ft & Matthiessen 2011
115	Quinn F, Hughes C, Baxter GD. Complementary and alternative medicine in the treatment of low back pain: a systematic review. Physical Therapy Reviews. 2006;11:2.				✓		✓ LMHI
116	Rada G, Capurro D, Pantoja T, Corbal·n J, Moreno G, Letelier Luz M, et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database of Systematic Reviews				✓		✓ LMHI
117	Reilly, D. (2001). "The puzzle of homeopathy." Journal of Alternative and Complementary Medicine 7: S103-S109.				✓ X excluded		
118	Resnick, E. S., B. P. Bielory, et al. (2008). "Complementary therapy in allergic rhinitis." Curr Allergy Asthma Rep 8(2): 118-125.				✓ X excluded		
119	Riley D, Fischer M, Singh B, Haidvogl M, Heger M (2001) Homeopathy and conventional medicine: an outcomes study comparing effectiveness in a primary care setting. J Altern Complement Med 7:149–159				✓ X Excluded		✓ Bornhoft & Matthiessen 2011
120	Roberts, M., W. Brodribb, et al. (2012). "Reducing the Pain: A Systematic Review of Postdischarge Analgesia Following Elective Orthopedic Surgery." Pain Medicine.				✓		
121	Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, et al. A systematic literature review of the effectiveness of nonpharmacological interventions to				✓ X excluded		✓ LMHI

No#	Reference:	Reference was cited in: AHA	AMFH	Public response	Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
	prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use. Health Technol Assess. 2006 Aug;10(26):iii, ix-108						
122	Rutten, L. and E. Stolper (2006). "'Proof' against homeopathy in fact supports Homeopathy." Homeopathy **95**(1): 57-61.				✓ X Excluded		
123	Rutten ALB, Stolper CF (2008) The 2005 meta-analysis of homeopathy: the importance of post-publication data. Homeopathy 97: 169-177	✓		✓	✓ X Excluded	✓ Ernst 2010	✓ LMHI ✓ Bornhoft & Matthiessen 2011
124	Sarris, J. and G. J. Byrne (2011). "A systematic review of insomnia and complementary medicine." Sleep Medicine Reviews **15**(2): 99-106.				✓		✓ LMHI
125	Schneider, B., Klein, P., Weiser, M. (2005). Treatment of vertigo with a homeopathic complex remedy compared with usual treatments: a meta-analysis of clinical trials. Arzneimittelforschung, 55: 23-29.	✓		✓	✓		✓ House of Commons ✓ LMHI
126	Seed, P. (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 365				✓ X Excluded		
127	Seidl, M. M. and D. E. Stewart (1998). "Alternative treatments for menopausal symptoms. Systematic review of scientific and lay literature." Can Fam Physician **44**: 1299-1308.				✓		
128	Selekman, J., E. Thomas, et al. (1998). "The school nurse's role in homeopathic interventions." Journal of School Health **68**(8): 342-345.				✓ X excluded		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
129	Shang, A. Huwiler-Mutener, K. Nartey, L. Juni, P. Dorig, S., Sterne, J.A. 2005. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo controlled trials of homoeopathy and allopathy. The Lancet, Vol. 366, pp. 726-732.	✓				✓ Ernst 2010	✓ House of Commons ✓ LMHI ✓ Bornhoft & Matthiessen 2011
130	Shaw, D. (2010). "Unethical aspects of homeopathic dentistry." Br Dent J **209**(10): 493-496.				✓ X excluded		
131	Sherr, J. and T. Quirk (2007). "Systematic review of homeopathic pathogenetic trials: an excess of rigour?" Homeopathy 96(4): 273-275; discussion 275-276, 278.				✓ X Excluded		
132	Signorini, A. (2007). "Finally, some light on the 'Pillar of Homeopathy'." Homeopathy **96**(1): 1-2.				✓ X excluded		
133	Sim, J. and N. Adams (2002). "Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia." The Clinical journal of pain **18**(5): 324-336.				✓ X excluded	✓ Terry 2012	
134	Sismondo S (2008) Pharmaceutical company funding and its consequences: A qualitative systematic review. Contemporary Clinical Trials 29: 109-113			✓	✓ X excluded		
135	Simonart, T., C. Kabagabo, et al. (2011). "Homoeopathic remedies in dermatology: a systematic review of controlled clinical trials." British Journal of Dermatology **165**(4): 897-905.				✓		
136	Smith, C.A. (2010). Homoeopathy for induction of labour (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD003399. NB: Different dates	✓ 2004		✓ 2003	✓ 2010 update	✓ Bornhoft 2006 (2001 edn.)	✓ LMHI ✓ Bornhoft &

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response		✓ Ernst 2010 (2006 edn.) ✓ O'Meara 2002 (2001 edn.)	Matthiessen 2011
137	Steinberg, D. and M. W. Beal (2003). "Homeopathy and women's health care." Jognn-Journal of Obstetric Gynecologic and Neonatal Nursing 32(2): 207-214.				✓ X excluded		
138	Stevinson, C. and E. Ernst (2001). "Complementary/alternative therapies for premenstrual syndrome: a systematic review of randomized controlled trials." Am J Obstet Gynecol **185**(1): 227-235.				✓		✓ LMHI
139	Stock-Schroer, B., H. Albrecht, et al. (2009). "Reporting experiments in homeopathic basic research (REHBaR)--a detailed guideline for authors." Homeopathy **98**(4): 287-298.				✓ X excluded		
140	Su C, Lichtenstein GR, Krok K, Brensinger CM, Lewis JD. A metaanalysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. Gastroenterology 2004; 126(5): 1257–1269.				✓ X excluded		
141	Szeto, A. L., F. Rollwagen, et al. (2004). "Rapid induction of protective tolerance to potential terrorist agents: a systematic review of low- and ultra-low dose research." Homeopathy **93**(4): 173-178.				✓ X excluded		
142	Tan, G., M. H. Craine, et al. (2007). "Efficacy of selected complementary and alternative medicine interventions for chronic pain." Journal of Rehabilitation Research & Development **44**(2): 195-222.				✓ X excluded		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
143	Taylor, M.A., Reilly, D., Llewellyn-Jones, R.H., McSharry, C., Aitchison, T.C. (2000). Randomized controlled trial of homeopathic versus placebo in perennial allergic rhinitis with overview of four trial series. British Medical Journal 321: 471-476.	✓		✓	✓ X excluded		✓ House of Commons ✓ Bornhoft & Matthiessen 2011
144	Teixeira, M. Z., C. H. F. Guedes, et al. (2010). "The placebo effect and homeopathy." Homeopathy **99**(2): 119-129.				✓ X excluded		
145	Terry, R., R. Perry, et al. (2012). "An overview of systematic reviews of complementary and alternative medicine for fibromyalgia." Clinical Rheumatology **31**(1): 55-66.				✓ umbrella review (component articles will be assessed) X Excluded		
146	Tiran, D. (2008). "Homeopathy in pregnancy: issues for midwives." Pract Midwife **11**(5): 14-16, 18-20.				✓ X excluded		
147	Tough, E. A., A. R. White, et al. (2009). "Acupuncture and dry needling in the management of myofascial trigger point pain: A systematic review and meta-analysis of randomised controlled trials." European Journal of Pain **13**(1): 3-10.				✓ X excluded		
148	Ulbricht, C., W. Chao, et al. (2011). "Oscillococcinum: An Evidence-Based Systematic Review by the Natural Standard Research Collaboration." Alternative & Complementary Therapies **17**(1): 41-49.				✓ umbrella review (component articles will be assessed) X		

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
					excluded		
149	Ullman D. (2003). Controlled clinical trials evaluating the homeopathic treatment of people with human immunodeficiency virus or acquired immune deficiency syndrome. Journal of Alternative and Complementary Medicine, 9: 133-141.	✓			✓ X excluded		✓ LMHI
150	Ullman, D. and M. Frass (2010). "A review of homeopathic research in the treatment of respiratory allergies." Alternative Medicine Review 15(1): 48-58.				✓ X excluded		
151	Vallance, A. K. and K. A. Jobst (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 366;				✓ X excluded		
152	van der Wouden, J. C., R. van der Sande, et al. (2009). "Interventions for cutaneous molluscum contagiosum." Cochrane database of systematic reviews (Online)(4): CD004767.					✓ Ernst 2010	
153	Vernon, H., C. S. McDermaid, et al. (1999). "Systematic review of randomized clinical trials of complementary/alternative therapies in the treatment of tension-type and cervicogenic headache." Complement Ther Med **7**(3): 142-155.				✓		
154	Vickers, A. J. (1999), 'Independent replication of pre-clinical research in homoeopathy: A systematic review', *FORSCHENDE KOMPLEMENTARMEDIZIN,* 6 (6), 311-20.				✓ X excluded	✓ Bornhoft 2006 ✓ Ernst 2002	✓ Bornhoft & Matthiessen 2011
155	Vickers A, Smith C. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database of Systematic Reviews	✓ 2006	✓ 2009		✓ X excluded	✓ Bornhoft 2006 (2000	✓ House of comm

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			
	2009, Issue 3. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub4. NB: date is different				2009 update	edn.) ✓ Ernst 2002 (2001 edn.) ✓ Ernst 2010 (2006 edn.) ✓ O'Meara 2002 (2001 edn.) ✓ Linde 2001 (2000 edn) ✓ Ulbricht 2011 (2009 edn)	ons ✓ LMHI (2004, 2006 edn.) ✓ Bornhoft & Matthiessen 2011 (2000)
156	Walach, H. (1998). Methodology beyond controlled clinical trials. In: E. Ernst, E.G. Hahn, (Eds.) Homoeopathy: a critical appraisal, pp. 48-59. London: Butterworth Heinemann.	✓			✓ X excluded		
157	Walach, H., W. B. Jonas, et al. (2005). "Research on homeopathy: state of the art." J Altern Complement Med **11**(5): 813-829.				✓ X excluded		
158	Walach H, Haeusler W, Lowes T, Mussbach D, Schamell U, Springer W, Stritzl G, Gaus W, Haag G (1997) Classical homeopathic treatment of chronic headaches. Cephalalgia 17:11–18				✓ X Excluded		✓ Bornhoft & Matthiessen 2011
159	Walach H, Jonas W, Lewith G (2005a) Are the clinical effects of homeopathy placebo effects? Lancet 366:2081; DOI:10.1016/S0140-6736(05)67877-4)				✓ X Excluded		✓ Bornhoft & Matthiessen

No#	Reference:	Reference was cited in:			Found in iCAHE 2012 (≥ 1997)	SRs gleaned from umbrella reviews	SRs gleaned from government reports
		AHA	AMFH	Public response			2011
160	Weatherley-Jones, E. (2005). "Homeopathy: a complementary view." Trends Pharmacol Sci **26**(11): 545-546.				✓ X excluded		
161	Weiner, D. K. and E. Ernst (2004). "Complementary and alternative approaches to the treatment of persistent musculoskeletal pain." Clin J Pain **20**(4): 244-255.				✓ X excluded		✓ LMHI
162	Witt CM, Bluth M, Albrecht H, Weißhuhn TER, Baumgartner S, Willich SN (2007) The in vitro evidence for an effect of high homeopathic potencies - A systematic review of the literature. Complementary Therapies in Medicine 15: 128-138	✓	✓	✓	✓ X excluded	✓ Ernst 2010	
163	Wiesenauer M, Lüdtke R (1996) A meta-analysis of the homeopathic treatment of pollinosis with Galphimia glauca. Forschende Komplementärmedizin 3:230–234				X Excluded		✓ Bornhoft & Matthiessen 2011

Appendix 3. reference and abstract of excluded articles and reason they were excluded.

1. Adler, U. C. (2005). "The influence of childhood infections and vaccination on the development of atopy: a systematic review of the direct epidemiological evidence." Homeopathy **94**(3): 182-195.
BACKGROUND: The 'hygiene hypothesis' has been used to justify a belief common among homeopaths, that the suppression of childhood infections and immunisation may lead to the development of chronic atopic diseases. OBJECTIVES: To analyse the influence of childhood infections and immunisation on the development of atopy. METHODS: Qualitative systematic review of direct epidemiological evidence (Medline 1993-2004) concerning the influence of childhood infections and immunisation on the development of atopy and discussion based on homeopathy. CONCLUSIONS: (1) Childhood infections do not protect against atopy; on the contrary, they increase the risk of allergic diseases, in agreement to Hahnemann's observations, which included epidemic diseases among the factors capable of stimulating the development of chronic diseases. (2) Vaccination is not a risk factor for atopy, notwithstanding the allergenic effect of some vaccines.

Excluded on feedback from NH&MRC

2. Albrecht, H. Klinische Forschung zur Homoopathie - eine kritische Bewertung.
The problem of clinical research on homoeopathy is discussed including the meta-analysis of all randomized trials on homoeopathy until 1995, the meta-analyses of trials on certain conditions and the randomized trials published until the end of 1998. The results are critically analyzed. The suitability of the randomized double blind study for the proof of effectiveness of homoeopathy is discussed as well as the significance of observational and outcomes studies.

The full text is in German –Exclude

3. Altunç, U., M. H. Pittler, et al. (2006). "Homoeopathy for childhood and adolescence ailments: systematic review of randomised clinical trials... 13th Annual Symposium on Complementary Health Care, 12th-14th December, 2006, University of Exeter, UK." Focus on Alternative & Complementary Therapies **11**: 37-37.

Confrence abstract –exclude

4. Anonymous (2011). "Complementary Medicine; Recent Studies from Faculty of Medicine Add New Data to Complementary Medicine." Obesity, Fitness & Wellness Week: 909.
We sought to address this via a rigorous systematic review of hypnotic CAM interventions, including herbal and nutritional medicine, acupuncture, acupressure, yoga, tai chi, massage, aromatherapy and homoeopathy. The electronic databases MEDLINE (PubMed), CINAHL, PsycINFO, and The Cochrane Library were accessed during late 2009 for CAM randomized controlled trials (RCTs) in the treatment of chronic insomnia. Sixty-four RCTs were identified, of which 20 studies involving eight CAM interventions met final inclusion criteria. Effect size calculations (where possible) and a quality control analysis using a modified Jadad scale were undertaken. Many RCTs lacked methodological rigor, and were commonly excluded due to small sample size or an inadequate control condition.

Article on paper by Sarris 2011 – exclude

5. Barnes, J. (1997). "Effects of homoeopathy are more than placebo." FACT **2**(4): 161-162.
Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges L et al. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 1997;350:834-43.
Data extraction: Data were extracted by 2 independent reviewers using a pretested form. Studies were categorised into 4 main types of homoeopathy and into 3 levels of dilution. All trials were evaluated with 2 quality scores for internal validity. Main results: 186 trials were identified of which 89 met all inclusion and exclusion criteria. The overall odds ratio (OR) was 2.45 in favour of homoepathy (95% confidence interval [CI] 2.05 to 2.93; random-effects model). The OR for the 26 high-quality studies was 1.66 (95% CI 1.33 to 2.08). Two tests for reproducibility were done: 4 homogenous studies of Galphimia glauca for seasonal allergies gave a pooled OR for ocular symptoms of 2.03 (95% CI 1.51 to 2.74; fixed-effects model); 5 studies of different combinations of homoeopathic remedies for postoperative ileus gave a pooled mean effect size difference of -0.22 (95% CI -0.36 to -0.09; $p < 0.05$) for time to first flatus. Comment - The authors of this meta-analysis of placebo-controlled trials of homoeopathy are to be commended for conducting such a methodologically rigourous piece of research on such an important question. The significance of the

paper is reflected by the fact that when publised in the Lancet it was accompanied by not one but two (somewhat critical) editorials (a rare occurrence indeed).

Exclude- editorial on Linde paper.

6. Barrett, B. B., D. D. Kiefer, et al. (1999). "Assessing the risks and benefits of herbal medicine: an overview of scientific evidence." Alternative therapies in health and medicine **5**(4): 40-49.
The use of herbal medicine is widespread and growing, with as many as 3 in 10 Americans using botanical remedies in a given year. Because many herbal medicines have significant pharmacological activity, and thus potential adverse effects and drug interactions, healthcare professionals must be familiar with this therapeutic modality. This article summarizes the history and current use of plant-based medicine and highlights the evidence of the risks and benefits associated with 6 plants: echinacea, garlic, ginger, ginkgo, St John's wort, and valerian. Therapies outside the medical mainstream tend to suffer from a dearth of research and critical evaluation. Critics and supporters alike note the conceptual and practical difficulties in studying many complementary and alternative therapies such as acupuncture, homeopathy, and meditation. Herbal medicine, however, lends itself well to standard evaluation methods. This article summarizes and evaluates evidence from randomized controlled trials and meta-analyses. We present the results of meta-analyses and subsequent randomized controlled trials for garlic and St John's wort; a comprehensive critical review and subsequent randomized controlled trials for ginkgo; and summaries of all identified randomized controlled trials for echinacea, ginger, and valerian.

Exclude- review of herbal medicines

7. Becker-Witt C, Weisshuhn TER, Lüdtke R, Willich SN (2003) Quality assessment of physical research in homeopathy. J Altern Complement Med 9:113–132
BACKGROUND: Despite increasing interest in complementary medicine worldwide, there has been no systematic large-scale documentation of medical homeopathic care. OBJECTIVE: We therefore conducted a prospective cohort study aimed at characterizing patients seeking homeopathic care and their treatment. PATIENTS AND METHODS: From September 1997 to June 1999, patients of all age groups who were visiting a homeopathic care center for the first time were included consecutively in the study and followed up for 24 months. Diagnostic procedures and prescriptions were documented using specific case report forms. MAIN OUTCOME MEASURES: Diagnoses (ICD-9), medical history, consultations, and prescriptions. RESULTS: A total of 3,981 patients were included in the study, 2,851 adults (29% men, mean age 42.5 +/- 13.1 years; 71% women, 39.9 +/- 12.4 years) and 1,130 children (52% boys, 6.5 +/- 3.9 years; 48% girls, 7.0 +/- 4.3 years). Almost all patients suffered from chronic conditions for 10.3 +/- 9.8 (adults) and 4.3 +/- 3.7 years (children). The most frequent diagnoses were allergic rhinitis in adult males, headache in adult females, and atopic dermatitis in children (both genders). The typical homeopathic initial consultations took 117 +/- 43 minutes for adults and 86 +/- 36 minutes for children, not varying much between primary diagnoses. In the observed 2 years the patients had on average 8.6 +/- 9.3 (adults) and 8.9 +/- 9.6 (children) consultations, approximately 50% each by telephone and face-to-face. Physicians most often prescribed the classical 'great' remedies (like sepia, sulfur, natrium mur., lycopodium), but in total, nearly 600 different homeopathic remedies were used.
CONCLUSIONS: Our study provides a wealth of data on the medical practice of classical homeopathy. In terms of treatment, polychrests are used frequently, although it should be noted that a large proportion of patients received 'small remedies' instead. Most patients are treated for chronic diseases. The present results will, in concert with follow-up outcome analysis, aid in determining the effectiveness of medical homeopathic practice.

Exclude- primary study

8. Benveniste, J. (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 367.

Exclude, this is a letter, not the meta-analysis.

9. Bielory, L. and J. Heimall (2003). "Review of complementary and alternative medicine in treatment of ocular allergies." Curr Opin Allergy Clin Immunol **3**(5): 395-399.

PURPOSE OF REVIEW: Ocular allergy is a common complaint of allergy sufferers, many of whom may choose to use complementary and alternative medicine in the treatment of these symptoms. In this review major complementary and alternative medicine modalities including herbal therapies, acupuncture, homeopathy, alternative immunotherapy and behavior modification are assessed for evidence of their effectiveness in the treatment of ocular allergy symptoms. RECENT FINDINGS: Certain herbs including Euphrasia officinalis, Petasites hybridus and Argemone mexicana have been evaluated in control studies in the treatment of ocular allergy. Honey is no more effective than placebo in the treatment of ocular allergy. Acupuncture used regularly has demonstrated some positive trends in ocular allergy sufferers. Homeopathy has shown conflicting results in the treatment of ocular allergy, while alternative forms of immunotherapy have been shown to develop immunologic tolerogenic effects in the control of the condition. SUMMARY: Several forms of complementary and alternative medicine have been studied for their effectiveness in treatment of ocular allergy symptoms. Further research is needed to assess mechanisms of action and to establish practice guidelines for the use of these modalities

Exclide- not a SR

10. Birnesser, H. and P. Stolt (2007). "The homeopathic antiarthitic preparation zeel comp. N: A review of molecular and clinical data." Explore-the Journal of Science and Healing **3**(1): 16-22.
Zeel comp. N (Zeel) is a homeopathic medication that has been widely used for many years for the treatment of arthritic disorders in a large number of countries worldwide. In recent years, a growing body of clinical and molecular evidence has been accumulating that shed light on the possible antiarthritic effects of this preparation. A number of studies report anti-inflammatory effects from Zeel. In vitro studies have indicated Zeel-mediated inhibition of the pathways involving the enzymes cyclooxygenase-1 and -2, and also the 5-lipoxygenase pathways, affecting levels of both eicosanoids and leukotrienes. Thus, Zeel may reduce the main two classes of molecules responsible for arthritic pain and inflammation. This review describes recent research on Zeel and discusses the need for further studies to clarify the role of the compound in the antiarthritic armamentarium of complementary medicine.

Exclude – Not a SR

11. Bloom, B. S., A. Retbi, et al. (2000). "Evaluation of randomized controlled trials on complementary and alternative medicine." Intl Jof Technology Assessment in Health Care **16**(1): 13-21. Objectives: Use of complementary and alternative medicine (CAM) is growing in all Western countries. The goal of this study was to evaluate randomised controlled trials. (RCTs) of CAM interventions for specific diagnosis to inform clinical decision making. *Ordered 1/5 #* 43484 received 3/5

Exclude- methodological paper

12. Bobak, M. and A. Donald (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 368.
Sir, The commentaries accompanying Klaus Linde and colleagues' meta-analysis list reasons why the results are not to be believed. This approach seems paradoxical. Scientists set rules to evaluate treatments in medicine, with the randomised controlled trial as the gold standard. However, the two commentators seem to say we should follow those rules only if the results conform with our beliefs. We are aware that common sense should not be replaced by rules, but we find this logic disturbing. When Stanely Prusiner suggested 20 years ago that prions might multiply without having any DNA, his sanity was doubted. Neither of us are enthusiasts of homoeopathy but an aftertaste remains: are not double standards being used here?

Exclude-letter re: Linde 1997 meta-analysis.

13. Boiron, C. (2011). "Homeopathy, a tremendous opportunity for medicine!" Eur J Intern Med **22**(1): 117-118; author reply 118-119.

This is a letter to the editor- Exclude

14. Bol, A. Clinical trials of homeopathy.
The meta-analysis by Kleijnen et al. published in the BMJ 1991;302:316-323 is reviewed.

Exclude- 1991 is outside of the date range.

15. Bornhoeft, G., U. Wolf, et al. (2006). "Effectiveness, Safety and Cost-Effectiveness of Homeopathy in General Practice - Summarized Health Technology Assessment." FORSCHENDE KOMPLEMENTARMEDIZIN **13**: 19-29.
Introduction: The Health Technology Assessment report on effectiveness, cost-effectiveness and appropriateness of homeopathy was compiled on behalf of the Swiss Federal Office for Public Health (BAG) within the framework of the 'Program of Evaluation of Complementary Medicine (PEK)'. Materials and Methods: Databases accessible by Internet were systematically searched, complemented by manual search and contacts with experts, and evaluated according to internal and external validity criteria. Results: Many high-quality investigations of pre-clinical basic research proved homeopathic high-potencies inducing regulative and specific changes in cells or living organisms. 20 of 22 systematic reviews detected at least a trend in favor of homeopathy. In our estimation 5 studies yielded results indicating clear evidence for homeopathic therapy. The evaluation of 29 studies in the domain 'Upper Respiratory Tract Infections/Allergic Reactions' showed a positive overall result in favor of homeopathy. 6 out of 7 controlled studies were at least equivalent to conventional medical interventions. 8 out of 16 placebo-controlled studies were significant in favor of homeopathy. Swiss regulations grant a high degree of safety due to product and training requirements for homeopathic physicians. Applied properly, classical homeopathy has few side-effects and the use of high-potencies is free of toxic effects. A general health-economic statement about homeopathy cannot be made from the available data. Conclusion: Taking internal and external validity criteria into account, effectiveness of homeopathy can be supported by clinical evidence and professional and adequate application be regarded as safe. Reliable statements of cost-effectiveness are not available at the moment. External and model validity will have to be taken more strongly into consideration in future studies.

Exclude – umbrella review- pearl reference list for new SR's

16. Brinkhaus, B., J. M. Wilkens, et al. (2006). "Homeopathic arnica therapy in patients receiving knee surgery: results of three randomised double-blind trials." Complementary therapies in medicine **14**(4): 237-246.
We investigated the effectiveness of homeopathic Arnica montana on postoperative swelling and pain after arthroscopy (ART), artificial knee joint implantation (AKJ), and cruciate ligament reconstruction (CLR). Three randomised, placebo-controlled, double-blind, sequential clinical trials. Single primary care unit specialised in arthroscopic knee surgery. Patients suffering from a knee disease that necessitated arthroscopic surgery. Prior to surgery, patients were given 1 x 5 globules of the homeopathic dilution 30x (a homeopathic dilution of 1:10(30)) of arnica or placebo. Following surgery, 3 x 5 globules were administered daily. The primary outcome parameter was difference in knee circumference, defined as the ratio of circumference on day 1 (ART) or day 2 (CLR and AKJ) after surgery to baseline circumference. A total of 227 patients were enrolled in the ART (33% female, mean age 43.2 years;), 35 in the AKJ (71% female, 67.0 years), and 57 in the CLR trial (26% female; 33.4 years). The percentage of change in knee circumference was similar between the treatment groups for ART (group difference Delta=-0.25%, 95% CI: -0.85 to 0.41, p=0.204) and AKJ (Delta=-1.68%, -4.24 to 0.77, p=0.184) and showed homeopathic arnica to have a beneficial effect compared to placebo in CLR (Delta=-1.80%, -3.30 to -0.30, p=0.019). In all three trials, patients receiving homeopathic arnica showed a trend towards less postoperative swelling compared to patients receiving placebo. However, a significant difference in favour of homeopathic arnica was only found in the CLR trial.

Not an SR- Exclude

17. Calabrese, E. J. and R. Blain (2005). "The occurrence of hormetic dose responses in the toxicological literature, the hormesis database: an overview." Toxicology and Applied Pharmacology **202**(3): 289-301.
A relational retrieval database has been developed compiling toxicological studies assessing the occurrence of hormetic dose responses and their quantitative characteristics. This database permits an evaluation of these studies over numerous parameters, including study design and dose-response features and physical/chemical properties of the agents. The database contains approximately 5600 dose-response relationships satisfying evaluative criteria for hormesis across over approximately 900 agents from a broadly diversified spectrum of chemical classes and physical agents. The assessment

reveals that hormetic dose-response relationships occur in males and females of numerous animal models in all principal age groups as well as across species displaying a broad range of differential susceptibilities to toxic agents. The biological models are extensive, including plants, viruses, bacteria, fungi, insects, fish, birds, rodents, and primates, including humans. The spectrum of endpoints displaying hormetic dose responses is also broad being inclusive of growth, longevity, numerous metabolic parameters, disease incidences (including cancer), various performance endpoints such as cognitive functions, immune responses among others. Quantitative features of the hormetic dose response reveal that the vast majority of cases display a maximum stimulatory response less than two-fold greater than the control while the width of the stimulatory response is typically less than 100-fold in dose range immediately contiguous with the toxicological NO(A)EL. The database also contains a quantitative evaluation component that differentiates among the various dose responses concerning the strength of the evidence supporting a hormetic conclusion based on study design features, magnitude of the stimulatory response, statistical significance, and reproducibility of findings.

Not an SR- Exclude

18. Castro, M. (1999). "Homeopathy - A theoretical framework and clinical application." Journal of Nurse-Midwifery **44**(3): 280-290.
The use of homeopathic remedies for the treatment of mastitis is described. The basic principles of homeopathy are discussed, including the simillimum, the minimum dose, the single remedy, the whole person, the vital force, susceptibility, and constitutional treatment. Homeopathic research trials and papers are examined and discussed. The author explains how homeopathy can be incorporated into midwifery practice and applies this to the treatment of mastitis. Specific indications in the application of 19 homeopathic remedies for mastitis, breast abscess, and lactation difficulties (including problems with supply and painful nipples) are cited. Keynote symptoms are presented in an easy access repertory. General guidelines for potency and dosage protocol are given. (

Exclude- not a SR

19. Caulfield, T. and S. DeBow (2005). "A systematic review of how homeopathy is represented in conventional and CAM peer reviewed journals." BMC Complementary and Alternative Medicine **5**.
Background: Growing popularity of complementary and alternative medicine (CAM) in the public sector is reflected in the scientific community by an increased number of research articles assessing its therapeutic effects. Some suggest that publication biases occur in mainstream medicine, and may also occur in CAM. Homeopathy is one of the most widespread and most controversial forms of CAM. The purpose of this study was to compare the representation of homeopathic clinical trials published in traditional science and CAM journals. Methods: Literature searches were performed using Medline (PubMed), AMED and Embase computer databases. Search terms included "homeo-pathy, -path, and -pathic" and "clinical" and "trial". All articles published in English over the past 10 years were included. Our search yielded 251 articles overall, of which 46 systematically examined the efficacy of homeopathic treatment. We categorized the overall results of each paper as having either "positive" or "negative" outcomes depending upon the reported effects of homeopathy. We also examined and compared 15 meta-analyses and review articles on homeopathy to ensure our collection of clinical trials was reasonably comprehensive. These articles were found by inserting the term "review" instead of "clinical" and "trial". Results: Forty-six peer-reviewed articles published in a total of 23 different journals were compared (26 in CAM journals and 20 in conventional journals). Of those in conventional journals, 69% reported negative findings compared to only 30% in CAM journals. Very few articles were found to be presented in a "negative" tone, and most were presented using "neutral" or unbiased language. Conclusion: A considerable difference exists between the number of clinical trials showing positive results published in CAM journals compared with traditional journals. We found only 30% of those articles published in CAM journals presented negative findings, whereas over twice that amount were published in traditional journals. These results suggest a publication bias against homeopathy exists in mainstream journals. Conversely, the same type of publication bias does not appear to exist between review and meta-analysis articles published in the two types of journals.

Exclude- comparison of Cam journals and mainstream journals in representations of homeopathy trials and papers, not clinical.

20. Cooper, K. L. and C. Relton (2010). "Homeopathy for insomnia: summary of additional RCT published since systematic review." Sleep Med Rev **14**(6): 411.

Exclude- letter to the editor.

21. Coulter, M. K., M. E. Dean, et al. (2006). "A systematic review of homoeopathy for attention-deficit hyperactivity disorder/hyper-kinetic disorder... 13th Annual Symposium on Complementary Health Care, 12th-14th December, 2006, University of Exeter, UK." Focus on Alternative & Complementary Therapies **11**: 15-15.

Objective To evaluate the evidence for the efficacy and safety of homoeopathy for treating attention-deficit hyperactivity disorder (ADHD) or hyperkinetic disorder (HKD). ADHD and HKD are some of the most common paediatric psychiatric diagnoses. A proportion of patients are unable to take medication or seek alternative treatments including homoeopathy. Materials and methods Twenty-three electronic databases were searched using homoeopathy specific terms with no language restrictions. Experts in the area were also contacted for further information. Results A total of 905 titles and abstracts were scanned. Four studies met inclusion criteria for efficacy and three for adverse effects and safety. Efficacy: only one randomised study reported sufficient information to allow extraction of data for analysis. No pooling was possible. No statistically significant differences between homoeopathy and placebo were found, although the study was small (n = 43) and lacked sufficient statistical power. Safety: Of the three included papers, only one included a side-effects rating scale and none reported any increased adverse events or side-effects when compared with no control or placebo homoeopathy. Conclusion The efficacy of homoeopathy for ADHD/HKD is uncertain. Future trials should be of high quality and follow the CONSORT reporting guidelines.

Exclude conference abstract only.

22. Daniele, C., G. Mazzanti, et al. (2006). "Adverse-Event Profile of Crataegus Spp.: A Systematic Review." Drug Safety **29**(6): 523-535

Crataegus spp. (hawthorn) monopreparations are predominantly used for treating congestive heart failure. The effectiveness of hawthorn preparations (flowers with leaves; berries) is documented in a number of clinical studies, reviews and meta-analyses. The aim of this article is to assess the safety data of all available human studies on hawthorn monopreparations. Systematic searches were conducted on MEDLINE, EMBASE, AMED, The Cochrane Library, the UK National Research Register and the US ClinicalTrials.gov (up to January 2005). Data were requested from the spontaneous reporting scheme of the WHO. Hand searches were also conducted in a sample of relevant medical journals, conference proceedings, reference lists of identified articles and our own files. Eight manufacturers of hawthorn-containing preparations were contacted and asked to supply any information on adverse events or drug interactions. Data from all clinical studies and reports were assessed. Only human studies on monopreparations were included. Data from hawthorn-containing combination preparations and homeopathic preparations were excluded. All studies were read and evaluated by one reviewer and independently verified by at least one additional reviewer. Twenty-nine clinical studies were identified, of which 24 met our inclusion criteria. A total of 7311 patients were enrolled, and data from 5577 patients were available for analysis. The daily dose and duration of treatment with hawthorn monopreparations ranged from 160 to 1800mg and from 3 to 24 weeks, respectively. The extracts most used in the clinical trials were WS 1442 (extract of hawthorn standardised to 18.75% oligomeric procyanidins) and LI 132 (extract of hawthorn standardised to 2.25% flavonoids). Overall, 166 adverse events were reported. Most of these adverse events were, in general, mild to moderate; eight severe adverse events have been reported with the LI 132 extract. The most frequent adverse events were dizziness/vertigo (n = 15), gastrointestinal complaints (n = 24), headache (n = 9), migraine (n = 8) and palpitation (n = 11). The WHO spontaneous reporting scheme received 18 case reports. In the identified trials, the most frequent adverse events were dizziness (n = 6), nausea (n = 5), fall (n = 2), gastrointestinal haemorrhage (n = 2), circulation failure (n = 2) and erythematous rash (n = 2). There were no reports of drug interactions. In conclusion, all data reviewed in this article seem to indicate that hawthorn is well tolerated even if some severe adverse events were reported; this suggests that further studies are needed to better assess the safety of hawthorn-containing preparations. Moreover, the unsupervised use of this drug can be associated with problems, especially if given with concomitant medications.

Exclude- not homeopathy

23. Dantas, F. (2003). "Homeopathy in childhood asthma." Thorax **58**(9): 826; author reply 828.
This is a letter to the editor in reply to an article. Exclude.

24. Dantas, F., P. Fisher, et al. (2007). "A systematic review of the quality of homeopathic pathogenetic trials published from 1945 to 1995." Homeopathy **96**(1): 4-16.
BACKGROUND: The quality of information gathered from homeopathic pathogenetic trials (HPTs), also known as 'provings', is fundamental to homeopathy. We systematically reviewed HPTs published in six languages (English, German, Spanish, French, Portuguese and Dutch) from 1945 to 1995, to assess their quality in terms of the validity of the information they provide. METHODS: The literature was comprehensively searched, only published reports of HPTs were included. Information was extracted by two reviewers per trial using a form with 87 items. Information on: medicines, volunteers, ethical aspects, blinding, randomization, use of placebo, adverse effects, assessments, presentation of data and number of claimed findings were recorded. Methodological quality was assessed by an index including indicators of internal and external validity, personal judgement and comments of reviewers for each study. RESULTS: 156 HPTs on 143 medicines, involving 2815 volunteers, produced 20,538 pathogenetic effects (median 6.5 per volunteer). There was wide variation in methods and results. Sample size (median 15, range 1-103) and trial duration (mean 34 days) were very variable. Most studies had design flaws, particularly absence of proper randomization, blinding, placebo control and criteria for analysis of outcomes. Mean methodological score was 5.6 (range 4-16). More symptoms were reported from HPTs of poor quality than from better ones. In 56% of trials volunteers took placebo. Pathogenetic effects were claimed in 98% of publications. On average about 84% of volunteers receiving active treatment developed symptoms. The quality of reports was in general poor, and much important information was not available. CONCLUSIONS: The HPTs were generally of low methodological quality. There is a high incidence of pathogenetic effects in publications and volunteers but this could be attributable to design flaws. Homeopathic medicines, tested in HPTs, appear safe. The central question of whether homeopathic medicines in high dilutions can provoke effects in healthy volunteers has not yet been definitively answered, because of methodological weaknesses of the reports. Improvement of the method and reporting of results of HPTs are required. REFERENCES: References to all included RCTs are available on-line at.
Exclude- assesment of quality of studies.

25. Dean, M. E., M. K. Coulter, et al. (2007). "Reporting data on homeopathic treatments (RedHot): a supplement to CONSORT." Homeopathy **96**(1): 42-45.
When homeopathy is tested in clinical trials, understanding and appraisal is likely to be improved if published reports contain details of prescribing strategies and treatments. An international Delphi panel was convened to develop consensus guidelines for reporting homeopathic methods and treatments. The panel agreed 28 treatment- and provider-specific items that supplement the Consolidated Standards of Reporting Trials (CONSORT) Statement items 2, 3, 4 and 19. The authors recommend these for adoption by authors and journals when reporting trials of homeopathy.
Exclude- not a SR

26. Eames, S. and P. Darby (2011). "Homeopathy and its ethical use in dentistry." Br Dent J **210**(7): 299-301.
Media coverage of homeopathy over the past few years has tended to concentrate on the very negative position taken by sceptics, while the possible benefits of homeopathy are ignored. This has resulted in coverage that has been rather one-sided, inaccurate and at times hysterical. A perfect example is Dr David Shaw's opinion piece 'Unethical aspects of homeopathic dentistry' (Br Dent J 2010; 209: 493-496) which falls far short of providing a basis for balanced intellectual discussion. The authors are therefore grateful to the BDJ for the opportunity to outline the case for integrating homeopathy in dental practice.
Exclude – not a SR

27. ENHR: European Network of Homeopathy Researchers. (2006). An overview of positive homeopathy research and surveys. Available on the website of the European Central Council of Homeopaths - www.homeopathy-ecch.org *We have the 2007 updated version*

Exclude- umbrella review, Pearl reference list.

28. Erlewyn-Lajeunesse, M. (2012). "Homeopathic medicines for children." Archives of Disease in Childhood **97**(2): 135-138.
This article describes the homeopathic tradition and considers the safety, manufacture, effectiveness and regulation of homeopathic medicines. These medicines are commonly purchased without prescription for children, so an understanding of the basis of therapy is important to ensure appropriate and safe usage. The role of integrated medicine in the National Health Service is also reviewed with identification of research priorities. *Ordered 27/4, request #* 43402 received

Exclude- discussion paper

29. Ernst, E. and Huntley, A. (2000), 'Tea tree oil: A systematic review of randomized clinical trials', *FORSCHENDE KOMPLEMENTARMEDIZIN UND KLASSISCHE NATURHEILKUNDE,* 7 (1), 17-20.

Excluded on feedback from NHMRC

30. Ernst E (2000) Prevalence of use of complementary/alternative medicine: a systematic review. Bull World Health Organ 78:252–257
Reported are the results of a systematic review of the prevalence of use of complementary/alternative medicine. Computerized literature searches were carried out in four databases. Twelve surveys thus found were selected because they dealt with the utilization of complementary/alternative medicine in random or representative samples of the general population. Data were extracted in a predefined, standardized way. Prevalence of use of complementary/alternative medicine ranged from 9% to 65%. Even for a given form of treatment such as chiropractic, as used in the USA, considerable discrepancies emerged. The data suggest that complementary/alternative therapies are used frequently and increasingly. Prevalence of use seemed to depend critically on factors that were poorly controlled in surveys of complementary/alternative medicine. The true prevalence of use of complementary/alternative medicine in the general population remains uncertain

Exclude- SR of CAM usage

31. Ernst, E. (2000). "The usage of complementary therapies by dermatological patients: a systematic review." British Journal of Dermatology **142**(5): 857-861.
Complementary medicine (CM) is more popular than ever before. Dermatology has not remained unaffected by this trend. The aim of this systematic review was to summarize all surveys of dermatological patients regarding the usage of CM. Three independent literature searches were carried out. Data were extracted in a predefined, standardized way and evaluated descriptively. Seven surveys met the inclusion/exclusion criteria. Collectively they show a high but variable prevalence of CM. Lifetime prevalence ranged from 35 to 69%. The most frequently used treatment modalities comprise homoeopathy, herbalism and food supplements. With this high level of prevalence, research into the potential risks and benefits of CM is urgently needed. Dermatologists should consider discussing CM openly with their patients.

Exclude- SR of surveys of CAM usage

32. Ernst E (2000) Prevalence of use of complementary/alternative medicine: a systematic review. Bull World Health Organ 78:252–257

Exclude- CAM focus

33. Ernst, E. (2002). "A systematic review of systematic reviews of homeopathy." Br J Clin Pharmacol **54**(6): 577-582.
Homeopathy remains one of the most controversial subjects in therapeutics. This article is an attempt to clarify its effectiveness based on recent systematic reviews. Electronic databases were searched for

systematic reviews/meta-analysis on the subject. Seventeen articles fulfilled the inclusion/exclusion criteria. Six of them related to re-analyses of one landmark meta-analysis. Collectively they implied that the overall positive result of this meta-analysis is not supported by a critical analysis of the data. Eleven independent systematic reviews were located. Collectively they failed to provide strong evidence in favour of homeopathy. In particular, there was no condition which responds convincingly better to homeopathic treatment than to placebo or other control interventions. Similarly, there was no homeopathic remedy that was demonstrated to yield clinical effects that are convincingly different from placebo. It is concluded that the best clinical evidence for homeopathy available to date does not warrant positive recommendations for its use in clinical practice.

Excluded- umbrella review.

34. Ernst, E. (2010). "Homeopathy: what does the "best" evidence tell us?" Med J Aust **192**(8): 458-460. OBJECTIVE: To evaluate the evidence for and against the effectiveness of homeopathy. DATA SOURCES: The Cochrane Database of Systematic Reviews (generally considered to be the most reliable source of evidence) was searched in January 2010. STUDY SELECTION: Cochrane reviews with the term "homeopathy" in the title, abstract or keywords were considered. Protocols of reviews were excluded. Six articles met the inclusion criteria. DATA EXTRACTION: Each of the six reviews was examined for specific subject matter; number of clinical trials reviewed; total number of patients involved; and authors' conclusions. The reviews covered the following conditions: cancer, attention-deficit hyperactivity disorder, asthma, dementia, influenza and induction of labour. DATA SYNTHESIS: The findings of the reviews were discussed narratively (the reviews' clinical and statistical heterogeneity precluded meta-analysis). CONCLUSIONS: The findings of currently available Cochrane reviews of studies of homeopathy do not show that homeopathic medicines have effects beyond placebo.

Excluded- umbrella review.

35. Fisher, P., B. Berman, et al. (2005). "Are the clinical effects of homoeopathy placebo effects?" Lancet **366**(9503): 2082-2083; author reply 2083-2086.

Exclude, not a SR- letter to editor.

36. Franklin, P. (1999). "Review, critique, and guidelines for the use of herbs and homeopathy." J Child Fam Nurs **2**(6): 418-419.

Exclude, not a SR

37. Frei H, Everts R, von Ammon K, Kaufmann F, Walter D, Hsu Schmitz SF, Collenberg M, Fuhrer K, Hassink R, Steinlin M, Thurneysen A (2005) Homeopathic treatment of children with attention deficit hyperactivity disorder. Eur J Pediatr 164:758–767.
An increasing number of parents turn to homeopathy for treatment of their hyperactive child. Two publications, a randomised, partially blinded trial and a clinical observation study, conclude that homeopathy has positive effects in patients with attention deficit hyperactivity disorder (ADHD). The aim of this study was to obtain scientific evidence of the effectiveness of homeopathy in ADHD. A total of 83 children aged 6-16 years, with ADHD diagnosed using the Diagnostic and Statistical Manual of Mental Disorders-IV criteria, were recruited. Prior to the randomised, double blind, placebo controlled crossover study, they were treated with individually prescribed homeopathic medications. 62 patients, who achieved an improvement of 50% in the Conners' Global Index (CGI), participated in the trial. Thirteen patients did not fulfill this eligibility criterion (CGI). The responders were split into two groups and received either verum for 6 weeks followed by placebo for 6 weeks (arm A), or vice-versa (arm B). At the beginning of the trial and after each crossover period, parents reported the CGI and patients underwent neuropsychological testing. The CGI rating was evaluated again at the end of each crossover period and twice in long-term follow-up. At entry to the crossover trial, cognitive performance such as visual global perception, impulsivity and divided attention, had improved significantly under open label treatment (P<0.0001). During the crossover trial, CGI parent-ratings were significantly lower under verum (average 1.67 points) than under placebo (P =0.0479). Long-term CGI improvement reached 12 points (63%, P <0.0001). CONCLUSION: The trial suggests scientific evidence of the effectiveness of homeopathy in the treatment of attention deficit hyperactivity disorder, particularly in the areas of behavioural and cognitive functions.

Exclude, not a SR

38. Friese, K. H., S. Kruse, et al. (1997). "The homoeopathic treatment of otitis media in children - Comparisons with conventional therapy." International Journal of Clinical Pharmacology and Therapeutics **35**(7): 296-301.
In a prospective observational study carried out by 1 homoeopathic and 4 conventional ENT practitioners, the 2 methods of treating acute pediatric otitis media were compared. Group A received treatment with homoeopathic single remedies (Aconitum napellus, Apis mellifica, Belladonna, Capsicum, Chamomilla, Kalium bichromicum, Lachesis, Lycopodium, Mercurius solubilis, Okoubaka, Pulsatilla, Silicea), whereas group B received nasal drops, antibiotics, secretolytics and/or antipyretics. The main outcome measures were duration of pain, duration of fever, and the number of recurrences after 1 year, whereby alpha < 0.05 was taken as significance level. The secondary measures were improvement after 3 hours, results of audiometry and tympanometry, and necessity for additional therapy. These parameters were only considered descriptively. The study involved 103 children in group A and 28 children in group B, aged between 6 months and 11 years in both groups. For duration of pain, the median was 2 days in group A and 3 days in group B. For duration of therapy, the median was 4 days in group A and 10 days in group B: this is due to the fact that antibiotics are usually administered over a period of 8 - 10 days, whereas homoeopathics can be discontinued at an earlier stage once healing has started. Of the children treated, 70.7% were free of recurrence within a year in group A and 29.3% were found to have a maximum of 3 recurrences. In group B, 56.5% were free of recurrence, and 43.5% had a maximum of 6 recurrences. Out of the 103 children in group A, 5 subsequently received antibiotics, though homoeopathic treatment was carried through to the healing stage in the remaining 98. No permanent sequels were observed in either group.

Exclude- not SR

39. Frye, J. (1997). "Homeopathy in office practice." Primary Care **24**(4): 845-+.
Homeopathy is widely used around the world and is regaining popularity in the United States where it enjoyed popular and therapeutic success in the 1800s. Relying on systematic principles of health and disease first set forth by Samuel Hahnemann in 1810, it offers a powerful and inexpensive means of promoting self-care and of augmenting therapeutic options for the family physician. History, theory and practical considerations are reviewed.

Exclude- not SR

40. Gagnier, J. J., M. W. van Tulder, et al. (2007). "Herbal medicine for low back pain: a Cochrane review." Spine (Phila Pa 1976) **32**(1): 82-92.
STUDY DESIGN: A systematic review of randomized controlled trials. OBJECTIVES: To determine the effectiveness of herbal medicine compared with placebo, no intervention, or "standard/accepted/conventional treatments" for nonspecific low back pain. SUMMARY OF BACKGROUND DATA: Low back pain is a common condition and a substantial economic burden in industrialized societies. A large proportion of patients with chronic low back pain use complementary and alternative medicine (CAM) and/or visit CAM practitioners. Several herbal medicines have been purported for use in low back pain. METHODS: The following databases were searched: Medline (1966 to April 2003), Embase (1980 to April 2003), Cochrane Controlled Trials Register (Issue 1, 2003), and Cochrane Complementary Medicine (CM) field Trials Register. Additionally, reference lists in review articles, guidelines, and in the retrieved trials were checked. Randomized controlled trials (RCTs), using adults (>18 years of age) suffering from acute, subacute, or chronic nonspecific low back pain. Types of interventions included herbal medicines defined as a plant that is used for medicinal purposes in any form. Primary outcome measures were pain and function. Two reviewers (J.J.G. and M.W.T.) conducted electronic searches in all databases. One reviewer (J.J.G.) contacted content experts and acquired relevant citations. Authors, title, subject headings, publication type, and abstract of the isolated studies were downloaded or a hard copy was retrieved. Methodologic quality and clinical relevance were assessed separately by two individuals (J.J.G. and M.W.T.). Disagreements were resolved by consensus. RESULTS: Ten trials were included in this review. Two high-quality trials utilizing Harpagophytum procumbens (Devil's claw) found strong evidence for short-term improvements in pain and rescue medication for daily doses standardized to 50 mg or 100 mg

harpagoside with another high-quality trial demonstrating relative equivalence to 12.5 mg per day of rofecoxib. Two moderate-quality trials utilizing Salix alba (White willow bark) found moderate evidence for short-term improvements in pain and rescue medication for daily doses standardized to 120 mg or 240 mg salicin with an additional trial demonstrating relative equivalence to 12.5 mg per day of rofecoxib. Three low-quality trials using Capsicum frutescens (Cayenne) using various topical preparations found moderate evidence for favorable results against placebo and one trial found equivalence to a homeopathic ointment. CONCLUSIONS: Harpagophytum procumbens, Salix alba, and Capsicum frutescens seem to reduce pain more than placebo. Additional trials testing these herbal medicines against standard treatments will clarify their equivalence in terms of efficacy. The quality of reporting in these trials was generally poor; thus, trialists should refer to the CONSORT statement in reporting clinical trials of herbal medicines.

to do with herbal medicines, exclude

41. Glisson, J., R. Crawford, et al. (1999). "Review, critique, and guidelines for the use of herbs and homeopathy." The Nurse practitioner **24**(4): 44-60.
The number of Americans that use alternative therapies, including herbal products, is increasing by overwhelming proportions. Hundreds of herbal products and homeopathic remedies are available to the consumer, but most of these have not been proved safe or effective. Consumers are now turning to their health care provider for guidance concerning the quality, proper use, adverse effects, and precautions associated with these products. Health care providers must develop a thorough understanding of the available literature concerning herbal products and homeopathy to provide patients with truthful, unbiased information regarding the potential risks and benefits of each herbal product. This article addresses the distinct difference between herbalism and homeopathy, the importance of standardization, and general use precautions concerning herbal products.

Exclude- not SR

42. Heger M, Riley DS, Haidvogl M (2000) International integrative primary care outcomes study (IIPCOS-2): an international research project of homeopathy in primary care. Br Homeopathic J 89 [Suppl 1]:S10–13
OBJECTIVE: The primary objective is to evaluate the effectiveness of homeopathic treatment compared to conventional treatment for respiratory and ear complaints commonly seen in the primary care setting: runny nose, sore throat, ear pain, sinus pain, and cough. METHOD: This study is an international, multi-center, prospective, outcomes study on the effectiveness of homeopathic treatment compared to conventional treatment. The participating investigators will be divided into three groups: * Homeopathic treatment; * Homeopathic or conventional treatment according to the patient's preference, either randomized or non-randomized; * Conventional treatment. A total of 2400 patients will be recruited. Consecutive patients, age one month or older, presenting with one of the five chief complaints, and onset of symptoms less than seven days will be included into the study. Prior to enrolment into the trial each patient must provide written informed consent. Patient outcome will be measured using the Integrative Medicine Outcomes Scale (IMOS) at 7-, 14- and 28-d telephone follow-up. In addition, covariate data related to the following will be collected: patient demographics and medical history, patient preference for treatment and willingness to be randomized, health-related quality of life, primary treatment and adjunctive therapies prescribed, adverse events, type and length of consultation, follow-up recommendation, patient compliance, patient satisfaction with treatment, and patient willingness to choose therapy and health care provider again. The main outcome criterion will be the response rate according to the IMOS after 14 days of treatment. RESULTS: Preliminary interim results will be presented. CONCLUSIONS: Lessons learned from the study will be discussed.

Exclude- primary research

43. Hunt, K. and E. Ernst (2011). "The evidence-base for complementary medicine in children: a critical overview of systematic reviews." Arch Dis Child **96**(8): 769-776.
BACKGROUND: The use of complementary and alternative medicine (CAM) in paediatric populations is common yet, to date, there has been no synthesis of the evidence of its effectiveness in that population. This overview of systematic review evaluates the evidence for or against the effectiveness

of CAM for any childhood condition. METHODS: Medline, AMED and Cochrane were searched from inception until September 2009. Reference lists of retrieved articles were hand-searched. Experts in the field of CAM were contacted. No language restrictions were applied. RESULTS: 17 systematic reviews were included in this overview, covering acupuncture, chiropractic, herbal medicine, homeopathy, hypnotherapy, massage and yoga. Results were unconvincing for most conditions although there is some evidence to suggest that acupuncture may be effective for postoperative nausea and vomiting, and that hypnotherapy may be effective in reducing procedure-related pain. Most of the reviews failed to mention the incidence of adverse effects of CAMs. CONCLUSIONS: Although there is some encouraging evidence for hypnosis, herbal medicine and acupuncture, there is insufficient evidence to suggest that other CAMs are effective for the treatment of childhood conditions. Many of the systematic reviews included in this overview were of low quality, as were the randomised clinical trials within those reviews, further reducing the weight of that evidence. Future research in CAM for children should conform to the reporting standards outlined in the CONSORT and PRISMA guidelines. Ordered 2/5/12 # 43514 received 7/5/12

Exclude – umbrella review- pearl reference list

44. Jacobs, J., W. B. Jonas, et al. (2003). "Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials." The Pediatric infectious disease journal **22**(3): 229-234.
Previous studies have shown a positive treatment effect of individualized homeopathic treatment for acute childhood diarrhea, but sample sizes were small and results were just at or near the level of statistical significance. Because all three studies followed the same basic study design, the combined data from these three studies were analyzed to obtain greater statistical power. Three double blind clinical trials of diarrhea in 242 children ages 6 months to 5 years were analyzed as 1 group. Children were randomized to receive either an individualized homeopathic medicine or placebo to be taken as a single dose after each unformed stool for 5 days. Parents recorded daily stools on diary cards, and health workers made home visits daily to monitor children. The duration of diarrhea was defined as the time until there were less than 3 unformed stools per day for 2 consecutive days. A metaanalysis of the effect-size difference of the three studies was also conducted. Combined analysis shows a duration of diarrhea of 3.3 days in the homeopathy group compared with 4.1 in the placebo group (P = 0.008). The metaanalysis shows a consistent effect-size difference of approximately 0.66 day (P = 0.008). The results from these studies confirm that individualized homeopathic treatment decreases the duration of acute childhood diarrhea and suggest that larger sample sizes be used in future homeopathic research to ensure adequate statistical power. Homeopathy should be considered for use as an adjunct to oral rehydration for this illness.

Exclude- not SR

45. Johnson, M. A. (1998). "Homeopathy: Another tool in the bag." JAMA **279**(9): 707-707.
Homeopathy could complement modern medicine, but the lack of legal and medical guidelines hinders homeopathy's widespread use. The lack of insurance coverage is one barrier facing alternative practices.

Exclude- not SR

46. Jonas, W. B., R. L. Anderson, et al. (2001). "A systematic review of the quality of homeopathic clinical trials." BMC Complementary and Alternative Medicine **1**: 12.
While a number of reviews of homeopathic clinical trials have been done, all have used methods dependent on allopathic diagnostic classifications foreign to homeopathic practice. In addition, no review has used established and validated quality criteria allowing direct comparison of the allopathic and homeopathic literature. In a systematic review, we compared the quality of clinical-trial research in homeopathy to a sample of research on conventional therapies using a validated and system-neutral approach. All clinical trials on homeopathic treatments with parallel treatment groups published between 1945-1995 in English were selected. All were evaluated with an established set of 33 validity criteria previously validated on a broad range of health interventions across differing medical systems. Criteria covered statistical conclusion, internal, construct and external validity. Reliability of criteria application is greater than 0.95. 59 studies met the inclusion criteria. Of these, 79% were from peer-reviewed journals, 29% used a placebo control, 51% used random assignment,

and 86% failed to consider potentially confounding variables. The main validity problems were in measurement where 96% did not report the proportion of subjects screened, and 64% did not report attrition rate. 17% of subjects dropped out in studies where this was reported. There was practically no replication of or overlap in the conditions studied and most studies were relatively small and done at a single-site. Compared to research on conventional therapies the overall quality of studies in homeopathy was worse and only slightly improved in more recent years. Clinical homeopathic research is clearly in its infancy with most studies using poor sampling and measurement techniques, few subjects, single sites and no replication. Many of these problems are correctable even within a "holistic" paradigm given sufficient research expertise, support and methods.

Exclude- this is a methodological paper.

47. Jonas, Wayne B., Kaptchuk, Ted J., and Linde, Klaus (2003), 'A critical overview of homeopathy', *Annals of internal medicine,* 138 (5), 393-99.

Homeopathy is a 200-year-old therapeutic system that uses small doses of various substances to stimulate autoregulatory and self-healing processes. Homeopathy selects substances by matching a patient's symptoms with symptoms produced by these substances in healthy individuals. Medicines are prepared by serial dilution and shaking, which proponents claim imprints information into water. Although many conventional physicians find such notions implausible, homeopathy had a prominent place in 19th-century health care and has recently undergone a worldwide revival. In the United States, patients who seek homeopathic care are more affluent and younger and more often seek treatment for subjective symptoms than those who seek conventional care. Homeopathic remedies were allowed by the 1939 Pure Food and Drug Act and are available over the counter. Some data--both from randomized, controlled trials and laboratory research--show effects from homeopathic remedies that contradict the contemporary rational basis of medicine. Three independent systematic reviews of placebo-controlled trials on homeopathy reported that its effects seem to be more than placebo, and one review found its effects consistent with placebo. There is also evidence from randomized, controlled trials that homeopathy may be effective for the treatment of influenza, allergies, postoperative ileus, and childhood diarrhea. Evidence suggests that homeopathy is ineffective for migraine, delayed-onset muscle soreness, and influenza prevention. There is a lack of conclusive evidence on the effectiveness of homeopathy for most conditions. Homeopathy deserves an open-minded opportunity to demonstrate its value by using evidence-based principles, but it should not be substituted for proven therapies.

Exclude- not SR

48. Karkos, P. D., S. C. Leong, et al. (2007). "'Complementary ENT': a systematic review of commonly used supplements." The Journal of Laryngology and Otology **121**(8): 779-782.

Abstract Objective: To assess the evidence surrounding the use of certain complementary supplements in otolaryngology. We specifically focussed on four commonly used supplements: spirulina, Ginkgo biloba, Vertigoheel® and nutritional supplements (cod liver oil, multivitamins and pineapple enzyme). Materials and methods: A systematic review of the English and foreign language literature. Inclusion criteria: in vivo human studies. Exclusion criteria: animal trials, in vitro studies and case reports. We also excluded other forms of 'alternative medicine' such as reflexology, acupuncture and other homeopathic remedies. Results: Lack of common outcome measures prevented a formal meta-analysis. Three studies on the effects of spirulina in allergy, rhinitis and immunomodulation were found. One was a double-blind, placebo, randomised, controlled trial (RCT) of patients with allergic rhinitis, demonstrating positive effects in patients fed spirulina for 12 weeks. The other two studies, although non-randomised, also reported a positive role for spirulina in mucosal immunity. Regarding the use of Ginkgo biloba in tinnitus, a Cochrane review published in 2004 showed no evidence for this. The one double-blind, placebo-controlled trial that followed confirmed this finding. Regarding the use of Vertigoheel in vertigo, two double-blind RCTs and a meta-analysis were identified. The first RCT suggested that Vertigoheel was equally effective in reducing the severity, duration and frequency of vertigo compared with betahistine. The second RCT suggested that Vertigoheel was a suitable alternative to G biloba in the treatment of atherosclerosis-related vertigo. A meta-analysis of only four clinical trials confirms that Vertigoheel was equally effective compared with betahistine, G biloba and dimenhydrinate. Regarding multivitamins and sinusitis, two small paediatric pilot studies reported a positive response for chronic sinusitis and otitis media following a

course of multivitamins and cod liver oil. Regarding bromelain (pineapple enzyme) and sinusitis, one randomised, multicentre trial including 116 children compared bromelain monotherapy to bromelain with standard therapy and standard therapy alone, for the treatment of acute sinusitis. The bromelain monotherapy group showed a faster recovery compared with the other groups. Conclusion: The positive effects of spirulina in allergic rhinitis and of Vertigoheel in vertigo are based on good levels of evidence, but larger trials are required. There is overwhelming evidence that G biloba may play no role in tinnitus. There is limited evidence for the use of multivitamins in sinus symptoms, and larger randomised trials are required.

Exclude- not a true SR- supplies none of the imnformation needed to extract data. (no PICO, critical appraisa, literature selection processs, methodology etc.)

49. Kirkby, R. and P. Herscu (2010). "Homeopathic trial design in influenza treatment." Homeopathy **99**(1): 69-75.
This review presents a critical evaluation of methodological quality in controlled trials on homeopathic treatment of influenza. First, a short summary on the prevalence, quality, and most commonly cited shortcomings of homeopathic controlled trials in general is presented to support the more specific points within influenza trials alone. To this end, three areas of the homeopathic literature are examined; large meta-analyses looking at study quality and results across research areas, reviews on research within specific diagnostic categories, and the available reviews and primary studies on influenza treatment trials. The specific methodological designs of homeopathic influenza treatment trials are then compared, on a point by point basis, to pharmaceutical trials on influenza antiviral drugs. The goal of the evaluation is to highlight frequently cited problems in homeopathic trial design, suggest possible improvement for future studies, and make specific recommendations for homeopathic influenza trials based on a comparison to standard antiviral trials.

Exclude- this is a methodological paper.

50. Kienle GS, Kiene H, Albonico HU (2006b)Anthroposophic medicine. Effectiveness, utility, costs, safety. Schattauer, Stuttgart New York.
This Health Technology Assessment (HTA) report (http://www.bag.admin.ch www.ifaemm.de) was commissioned by the Swiss Federal Social Insurance Office and produced as part of the national Complementary Medicine Evaluation Programme (PEK). The presented review is an update of this HTA-report, providing an overview of the available scientific literature on the effectiveness, utility, costs and safety of anthroposophic medicine.

Exclude- this is not homeopathy.

51. Kleijnen, J., P. Knipschild, et al. (1991). "CLINICAL-TRIALS OF HOMEOPATHY." BRITISH MEDICAL JOURNAL **302**(6772): 316-323.
Objective-To establish whether there is evidence of the efficacy of homoeopathy from controlled trials in humans. Design-Criteria based meta-analysis. Assessment of the methodological quality of 107 controlled trials in 96 published reports found after an extensive search. Trials were scored using a list of predefined criteria of good methodology, and the outcome of the trials was interpreted in relation to their quality. Setting-Controlled trials published world wide. Main outcome measures-Results of the trials with the best methodological quality. Trials of classical homoeopathy and several modern varieties were considered separately. Results-In 14 trials some form of classical homoeopathy was tested and in 58 trials the same single homoeopathic treatment was given to patients with comparable conventional diagnoses. Combinations of several homoeopathic treatments were tested in 26 trials; isopathy was tested in nine trials. Most trials seemed to be of very low quality, but there were many exceptions. The results showed a positive trend regardless of the quality of the trial or the variety of homoeopathy used. Overall, of the 105 trials with interpretable results, 81 trials indicated positive results whereas in 24 trials no positive effects of homoeopathy were found. The results of the review may be complicated by publication bias, especially in such a controversial subject as homoeopathy. Conclusions-At the moment the evidence of clinical trials is positive but not sufficient to draw definitive conclusions because most trials are of low methodological quality and because of the unknown role of publication bias. This indicates that there is a legitimate case for further evaluation of homoeopathy, but only by means of well performed trials.

Not in date-Exclude

52. Langhorst J, Häuser W, Irnich D, Speeck N, Felde E, Winkelmann A, Lucius H, Michalsen A, Musial F. 2008. [Alternative and complementary therapies in fibromyalgia syndrome]. *Schmerz* 22(3), 324-33.

INTRODUCTION: Interdisciplinary S3 level guidelines were devised in cooperation with 8 medical, 2 psychological and 2 patient support groups. Results were elaborated in a multilevel group process. METHODS: On the bases of the "Cochrane Library" (1993-2006), "Medline" (1980-2006), "PsychInfo" (2006) and "Scopus" (2006) controlled studies and meta-analyses of controlled studies were analyzed. RESULTS: Only few controlled studies were found supporting in part the effectiveness of CAM therapies in the treatment of fibromyalgia syndrome. Due to the lack of information on long term efficacy and cost-effectiveness, only limited recommendations for CAM therapies can be given. CONCLUSION: Within a multicomponent therapy setting, selective CAM therapies (acupuncture, vegetarian diet, homeopathy, Tai Chi, Qi Gong, music-oriented and body-oriented therapies) can be recommended for a limited period of time.

Exclude-not in English

53. Linde, K., M. Hondras, et al. (2001). Systematic reviews of complementary therapies - an annotated bibliography. Part 3: Homeopathy.

BACKGROUND: Complementary therapies are widespread but controversial. We aim to provide a comprehensive collection and a summary of systematic reviews of clinical trials in three major complementary therapies (acupuncture, herbal medicine, homeopathy). This article is dealing with homeopathy. Potentially relevant reviews were searched through the register of the Cochrane Complementary Medicine Field, the Cochrane Library, Medline, and bibliographies of articles and books. To be included articles had to review prospective clinical trials of homeopathy; had to describe review methods explicitly; had to be published; and had to focus on treatment effects. Information on conditions, interventions, methods, results and conclusions was extracted using a pretested form and summarized descriptively. RESULTS: Eighteen out of 22 potentially relevant reviews preselected in the screening process met the inclusion criteria. Six reviews addressed the question whether homeopathy is effective across conditions and interventions. The majority of available trials seem to report positive results but the evidence is not convincing. For isopathic nosodes for allergic conditions, oscillococcinum for influenza-like syndromes and galphimia for pollinosis the evidence is promising while in other areas reviewed the results are equivocal.

Exclude- umbrella review- pearl reference list

54. Linde, K., G. ter Riet, et al. (2003). "Characteristics and quality of systematic reviews of acupuncture, herbal medicines, and homeopathy." Forsch Komplementarmed Klass Naturheilkd **10**(2): 88-94.

BACKGROUND: We aimed to describe the approaches and characteristics of systematic reviews on three major complementary therapies and to assess their methodological quality. METHODS: Systematic reviews of clinical trials of acupuncture, herbal medicines, and homeopathy were identified from a database developed for the Cochrane Collaboration Complementary Medicine Field. Information on conditions, interventions, methods, results, and conclusions was extracted using a pre-tested form; methodological quality was assessed using the Oxman scale. RESULTS: 115 reviews were included (39 on acupuncture, 58 on herbal medicine, 18 on homeopathy). Research questions were most specific in herbal medicine, and tended to be very general in homeopathy. The main comparison in most reviews was with placebo. The methodological quality of reviews was highly variable. Deficiencies were most frequent for the description of the selection process and the summary of the results of primary studies. CONCLUSION: Systematic reviews tend to approach different complementary therapies in different manner. Compared to a set of reviews on analgesic interventions methodological quality was slightly better on the average, but there is ample room for improvement in future complementary medicine reviews.

Will need to order this one. Ordered 27/4 request # 43398 received.

Exclude- a methodological paper that provides no clinical data.

55. Linde K, Jonas W (2005) Are the clinical effects of homeopathy placebo effects? Lancet 366:2081–2082; DOI:10.1016/S0140-6736(05)67878-6

Exclude- letter to the editor.

56. Ludtke R, Wiesenauer M. A meta-analysis of homeopathic treatment of pollinosis with Galphimia glauca. Wien Med Wochenschr 1997;147: 323–7.

Exclude - This article is in German

57. Ludtke, R. & Wilkins, R. (1999). Clinical trials of Arnica in homoeopathic preparations. In: Albrecht, H. Fruhwald, M. (eds) Jahrbuch. Carl & Veronica Carstens-Stiftung. KVC Verlag: Essen pp. 97-112.

Exclude - This is in German

58. Lüdtke, R. and A. L. B. Rutten (2008). "The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials." Journal of clinical epidemiology **61**(12): 1197-1204.
Shang's recently published meta-analysis on homeopathic remedies (Lancet) based its main conclusion on a subset of eight larger trials out of 21 high quality trials (out of 110 included trials). We performed a sensitivity analysis on various other meaningful trial subsets of all high quality trials. Subsets were defined according to sample size, type of homeopathy, type of publication, and treated disease/condition. For each subset, we estimated the overall odds ratios (ORs) from random effect meta-analyses. All trials were highly heterogeneous (I2=62.2%). Homeopathy had a significant effect beyond placebo (OR=0.76; 95% CI: 0.59-0.99; p=0.039). When the set of analyzed trials was successively restricted to larger patient numbers, the ORs varied moderately (median: 0.82, range: 0.71-1.02) and the P-values increased steadily (median: 0.16, range: 0.03-0.93), including Shang's results for the eight largest trials (OR=0.88, CI: 0.66-1.18; P=0.41). Shang's negative results were mainly influenced by one single trial on preventing muscle soreness in 400 long-distance runners. The meta-analysis results change sensitively to the chosen threshold defining large sample sizes. Because of the high heterogeneity between the trials, Shang's results and conclusions are less definite than had been presented.

Exclude, not an SR

59. Martin, K. W. and E. Ernst (2003). "Herbal medicines for treatment of bacterial infections: a review of controlled clinical trials." The Journal of antimicrobial chemotherapy **51**(2): 241-246.
Many hundreds of plant extracts have been tested for in vitro antibacterial activity. This review is a critical evaluation of controlled clinical trials of herbal medicines with antibacterial activity. Four electronic databases were searched for controlled clinical trials of antibacterial herbal medicines. Data were extracted and validated in a standardized fashion, according to predefined criteria, by two independent reviewers. Seven clinical trials met our inclusion criteria. Four of these studies were randomized. Three trials of garlic and cinnamon treatments for Helicobacter pylori infections reported no significant effect. Bacterial infections of skin were treated in four trials. Positive results were reported for an ointment containing tea leaf extract in impetigo contagiosa infections. Two trials of tea tree oil preparations used for acne and methicillin-resistant Staphylococcus aureus, and one trial of Ocimum gratissimum oil for acne, reported results equivalent to conventional treatments. Few controlled clinical trials have been published and most are methodologically weak. The clinical efficacy of none of the herbal medicines has so far been demonstrated beyond doubt. This area seems to merit further study through rigorous clinical trials.

Exclude- not homeopathy

60. Maxion-Bergemann, S., M. Wolf, et al. (2006). "Complementary and alternative medicine costs - a systematic literature review." Forsch Komplementmed **13 Suppl 2**: 42-45.
OBJECTIVE: The aim of this literature review, performed within the framework of the Swiss governmental Program of Evaluation of Complementary Medicine (PEK), was to investigate costs of complementary and alternative medicine (CAM). MATERIALS AND METHODS: A systematic literature search was conducted in 11 electronic databases. All retrieved titles and reference lists were also hand-searched. RESULTS: 38 publications were found: 23 on CAM of various definitions (medical and non-medical practitioners, over-the-counter products), 13 on homeopathy, 2 on phytotherapy. Studies investigated different kinds of costs (direct or indirect) and used different methods (prospective or retrospective questionnaires, data analyses, cost-effectiveness models). Most studies report 'out of pocket' costs, because CAM is usually not covered by health insurance. Costs per CAM-

treatment / patient / month were AUD 7-66, CAD 250 and GBP 13.62 +/- 1.61. Costs per treatment were EUR 205 (range: 15-1,278), USD 414 +/- 269 and USD 1,127. In two analyses phytotherapy proved to be cost-effective. One study revealed a reduction of 1.5 days of absenteeism from work in the CAM group compared to conventionally treated patients. Another study, performed by a health insurance company reported a slight increase in direct costs for CAM. Costs for CAM covered by insurance companies amounted to approximately 0.2-0.5% of the total healthcare budget (Switzerland, 2003). Publications had several limitations, e.g. efficacy of therapies was rarely reported. As compared to conventional patients, CAM patients tend to cause lower costs. CONCLUSION: Results suggest lower costs for CAM than for conventional patients, but the limited methodological quality lowers the significance of the available data. Further well-designed studies and models are required.

Exclude- paper on cost of CAM, not effectiveness.

61. McCarney, R. W., T. J. Lasserson, et al. (2004). "An overview of two Cochrane systematic reviews of complementary treatments for chronic asthma: acupuncture and homeopathy." Respir Med **98**(8): 687-696.
BACKGROUND: Acupuncture and homeopathy are commonly used complementary treatments for chronic asthma. This review summarizes two recently updated Cochrane systematic reviews that assess the safety and efficacy of homeopathy or acupuncture in individuals with chronic stable asthma. INCLUSION CRITERIA: Only randomized-controlled trials were considered for inclusion. Statistical aggregation of the data was undertaken where possible. SEARCH STRATEGY: Searches for both reviews were done with the assistance of the Cochrane Airways Group, and through electronic alerts. RESULTS: ACUPUNCTURE: 11 studies with 324 participants met the inclusion criteria. Trial reporting was poor, and the trial quality was deemed inadequate to generalize the findings. There was variation in the type of active and sham acupunctures, the outcomes assessed and the time points measured. The points used in the sham arm of some studies are used for the treatment of asthma according to traditional Chinese medicine. Two studies used individualized treatment strategies, and one study used a combination strategy of formula acupuncture with the addition of individualized points. No statistically significant or clinically relevant effects were found for acupuncture compared with sham acupuncture. When data from two small studies were pooled, no difference in lung function was observed (post-treatment FEV1): standardized mean difference 0.12, 95% confidence interval 0.31 to 0.55). CONCLUSION: ACUPUNCTURE: There is not enough evidence to recommend the use of acupuncture in the treatment of asthma. Further research needs to be undertaken, and this should take into account the different types of acupuncture practiced. RESULTS: HOMEOPATHY: Six trials with a total of 556 people were included in the review. These trials were all placebo-controlled and double-blind, but were of variable quality. Standardized treatments in these trials are unlikely to represent common homeopathic practice where treatment tends to be individualized. The results of the studies are conflicting in terms of effects on lung function. There has been only a limited attempt to measure a "package of care" effect (i.e. the effect of the medication as well as the consultation, which is considered a vital part of individualized homeopathic practice). CONCLUSION: HOMEOPATHY: There is not enough evidence to reliably assess the possible role of homeopathy in the treatment of asthma. Further studies could assess whether individuals respond to a "package of care" rather than the homeopathic intervention alone.

Exclude- umbrella review- pearl reference list

62. Merrell, W. C. and E. Shalts (2002). "Homeopathy." Medical Clinics of North America **86**(1): 47-+.
Complementary and alternative medicine is increasingly being merged into mainstream medicine. Mind-body therapies (hypnosis and imagery), acupuncture and some nutritional supplements (nutraceuticals and botanicals) are now nearing inclusion in the conventional medical armamentarium. One prescriptive approach that is still thought to be untenable to most western bioscientists is homeopathy. This article will look at the historical development, philosophic and scientific tenets, practice, and evidence basis of homeopathy.

Exclude, not a SR

63. Milgrom, L. R. (2008). "Homeopathy and the new fundamentalism: a critique of the critics." J Altern Complement Med **14**(5): 589-594.

Though in use for over 200 years, and still benefiting millions of people worldwide today, homeopathy is currently under continuous attacks for being "unscientific." The reasons for this can be understood in terms of what might be called a "New Fundamentalism," emanating particularly but not exclusively from within biomedicine, and supported in some sections of the media. Possible reasons for this are discussed. New Fundamentalism's hallmarks include the denial of evidence for the efficacy of any therapeutic modality that cannot be consistently "proven" using double-blind, randomized controlled trials. It excludes explanations of homeopathy's efficacy; ignores, excoriates, or considers current research data supporting those explanations incomprehensible, particularly from outside biomedicine: it is also not averse to using experimental bias, hearsay, and innuendo in order to discredit homeopathy. Thus, New Fundamentalism is itself unscientific. This may have consequences in the future for how practitioners, researchers, and patients of homeopathy/complementary and alternative medicine engage and negotiate with primary health care systems.

Exclude, not a SR

64. Nowak, A. L. V. and H. M. Hale (2012). "Prevalence of Complementary and Alternative Medicine Use Among U.S. College Students: A Systematic Review." American Journal of Health Education **43**(2): 116-126.
Research shows that Americans are using increasing amounts of complementary and alternative medicine (CAM) and that education is a significant predictor of CAM use. The purpose of this systematic review is to summarize key research findings on CAM use rates among U.S. college students and recommend future actions for researchers and health educators. A systematic search sought out peer-reviewed studies that provide empirical data on rates of CAM use among the general college population in the U.S. Findings in 10 studies were reported and compared to 2007 NHIS data. Use of acupuncture, homeopathy, NVNM, massage therapy, healing therapy/Reiki and yoga is significantly higher among U.S. college samples than the general U.S. adult sample with NVNM and massage therapy showing small effect sizes (d>.20, r>. 10). Future research must address the limitations of previous studies. Health education efforts are needed to prepare college students for making informed decisions regarding CAM use. Health educators can incorporate CAM topics into curricula, distribute CAM literature, organize campus-wide presentations, and include CAM providers in health fairs. Health educators should be prepared to discuss CAM safety and efficacy with students and provide referrals to reputable CAM providers. [PUBLICATION ABSTRACT]

Exclude- Survey of CAM use

65. Nuhn, T., R. Lüdtke, et al. (2010). "Placebo effect sizes in homeopathic compared to conventional drugs - a systematic review of randomised controlled trials." Homeopathy **99**(1): 76-82.
BACKGROUND: It has been hypothesised that randomised, placebo-controlled clinical trials (RCTs) of classical (individualised) homeopathy often fail because placebo effects are substantially higher than in conventional medicine. OBJECTIVES: To compare placebo effects in clinical trials on homeopathy to placebo effects on trials of conventional medicines. METHODS: We performed a systematic literature analysis on placebo-controlled double-blind RCTs on classical homeopathy. Each trial was matched to three placebo-controlled double-blind RCTs from conventional medicine (mainly pharmacological interventions) involving the same diagnosis. Matching criteria included severity of complaints, choice of outcome parameter, and treatment duration. Outcome was measured as the percentage change of symptom scores from baseline to end of treatment in the placebo group. 35 RCTs on classical homeopathy were identified. 10 were excluded because no relevant data could be extracted, or less than three matching conventional trials could be located. RESULTS: In 13 matched sets the placebo effect in the homeopathic trials was larger than the average placebo effect of the conventional trials, in 12 matched sets it was lower (P=0.39). Additionally, no subgroup analysis yielded any significant difference. CONCLUSIONS: Placebo effects in RCTs on classical homeopathy did not appear to be larger than placebo effects in conventional medicine.

Exclude- this is a methodological review not a true SR- there is insufficient information in the PICO

66. O'Meara, S., P. Wilson, et al. (2002). "Homoeopathy." Qual Saf Health Care **11**(2): 189-194.

The research evidence on the effectiveness of homoeopathy presented in a recent issue of *Effective Health Care* is reviewed. This paper is based mainly on an overview of existing systematic reviews of RCTs. Some reviews are general overviews, some focus on individualised (classical) homoeopathy, while the remainder have a more specific focus. Individual RCTs published subsequent to the included reviews of individualised homoeopathy and those with a specific scope are also included (more detail on the included RCTs is available at www.york.ac.uk/inst/crd/ehcb.htm). Details of the review methods are available elsewhere.

Exclude- umbrella review- pearl reference list

67. Paterson, C. (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 365-366;

Exclude – letter- author reply 367-368.

68. Peckham Emily, J., E. A. Nelson, et al. (2012) Homeopathy for treatment of irritable bowel syndrome. Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD009710
This is the protocol for a review and there is no abstract. The objectives are as follows:The objective of this systematic review is to assess the efficacy and safety of homeopathic treatment for IBS.

Exclude this is protocol for a review, not the review itself.

69. Pilkington, K. (2007). "Searching for CAM evidence: An evaluation of therapy-specific search strategies." Journal of Alternative and Complementary Medicine **13**(4): 451-459.
Objectives: The aim of this investigation was to explore the effectiveness of search strategies developed to identify trials of specific complementary therapies in a range of clinical conditions. Design: All primary studies included in a series of systematic reviews were identified. An analysis of the original source of the study and search term(s) by means of which the study had originally been retrieved was carried out. Each study was then searched for in each of 6 databases (AMED, Cochrane CENTRAL, MEDLINE®/PubMed, EMBASE, CINAHL, PsycINFO). The proportion of studies located on each database was assessed and the indexing terms identified for each therapy were compared against the original search strategies. Results: A total of 127 primary studies were identified from 35 systematic reviews. The number of studies on each therapy varied, but Cochrane CENTRAL listed the highest proportion for all therapies. No database listed all studies, and at least one unique study was listed on all databases except MEDLINE, whereas several studies were not found on any of the databases. Index terms were effective in locating studies on acupuncture, individual herbs, hypnosis, massage, and yoga. For the remaining therapies, use of text word search terms was important and particularly so for homeopathy, meditation, and reflexology. Variation in terminology for most of the therapies was encountered. Conclusions: The small numbers of studies preclude firm recommendations, but several potential challenges in searching for complementary and alternative medicine (CAM) trials are highlighted. The findings suggest that a range of different sources is required for identifying relevant studies, particularly for certain therapies. The development of an optimum generic search strategy for each therapy is hampered by the variation in indexing of CAM studies. Possible optimum strategies are presented as a basis for discussion, and further testing of the effectiveness of these strategies is now a priority. © Mary Ann Liebert, Inc.

Exclude- not an SR on homeopathy- paper looks at the diffiuclties involved in searching for CAM papers.

70. Practice and Policy Guidelines Panel (1997). "Clinical practice guidelines in complementary and alternative medicine. An analysis of opportunities and obstacles. National Institutes of Health Office of Alternative Medicine." Arch Fam Med **6**(2): 149-154.
An estimated 1 of 3 Americans uses some form of complementary and alternative medicine (CAM), such as acupuncture, homeopathy, or herbal medicine. In 1995, the National Institutes of Health Office of Alternative Medicine convened an expert panel to examine the role of clinical practice guidelines in CAM. The panel concluded that CAM practices currently are unsuitable for the development of evidence-based practice guidelines, in part because of the lack of relevant outcomes data from well-designed clinical trials. Moreover, the notions of standardization and appropriateness, inherent in guideline development, face challenging methodologic problems when applied to CAM, which considers many different treatment practices appropriate and encourages highly individualized care. Due to different belief systems and divergent theories about the nature of health and illness, CAM disciplines have fundamental differences in how they define target conditions, causes of disease,

interventions, and outcome measures of effectiveness. These differences are even more striking when compared with those used by Western medicine. The panel made a series of recommendations on strategies to strengthen the evidence base for future guideline development in CAM and to meet better the current information needs of clinicians, patients, and guideline developers who seek information about CAM treatments.

Exclude – CAM, not homeopathy

71. Reilly, D. (2001). "The puzzle of homeopathy." Journal of Alternative and Complementary Medicine **7**: S103-S109.
Homeopathy is a branch of Western medicine that has mostly been rejected by Western orthodoxy for the last 200 years because of conceptual and scientific clashes. Homeopathy uses microdoses of potential toxins to provoke defense and self-regulatory responses, rather than the more orthodox approach of blocking body reactions. This approach hints at its clinical scope: it can help, at times resolve, conditions that are intrinsically reversible rather than mechanical problems, deficiencies, or irreversible breakdowns in body functions where it is only palliative. In recent years, there has been a renaissance of interest. Public demand has soared, and with it professional interest. Approximately 20% of Scotland's general practitioners have completed basic training. This is partly occasioned by public interest in complementary medicine and a sympathy with the more mind-body approach of homeopathy, and partly by recent scientific evidence. Some homeopathic dilutions are so extreme they are dismissed by critics as only placebo. Yet trials and meta-analyses of controlled trials are pointing toward real effects, mechanism of action unknown. Clinical outcome studies suggest useful clinical impact and excellent safety. There seems to be a potential to enhance patient care by integrating the two systems.

Exclude, not a SR

72. Resnick, E. S., B. P. Bielory, et al. (2008). "Complementary therapy in allergic rhinitis." Curr Allergy Asthma Rep **8**(2): 118-125.
The term complementary/alternative medicine (CAM) refers to those therapeutic and diagnostic approaches different from conventional allopathic medicine. CAM may encompass homeopathy, acupuncture, phytotherapy, antioxidant therapy, and numerous holistic or behavioral techniques. Allergists and physicians of all disciplines are confronted with patients using CAM treatments, making it imperative that they become familiar with the scientific literature surrounding them. Given the high prevalence of allergic diseases and associated costs of CAM treatments, proof of CAM therapies is needed to establish appropriate guidelines for their use. Efficacy of CAM modalities should be established with randomized, double-blind, placebo-controlled trials, including adverse-effects monitoring. Of all the CAM therapies examined to treat allergic rhinitis, some herbal therapies and antioxidants demonstrate a trend toward some clinical efficacy. Researchers have yet to determine how to integrate these CAM modalities into the general treatment paradigm of allergic rhinitis.

Exclude, not a SR

73. Riley D, Fischer M, Singh B, Haidvogl M, Heger M (2001) Homeopathy and conventional medicine: an outcomes study comparing effectiveness in a primary care setting. J Altern Complement Med 7:149–159
BACKGROUND: Recent meta-analyses of randomized controlled trials in homeopathy have suggested that homeopathy is more than a placebo response. OBJECTIVE: Comparison of the effectiveness of homeopathy in primary care with conventional medicine in primary care for three commonly encountered clinical conditions. DESIGN: An international multicenter, prospective, observational study in a real world medical setting comparing the effectiveness of homeopathy with conventional medicine. PARTICIPANTS: Thirty (30) investigators with conventional medical licenses at six clinical sites in four countries enrolled 500 consecutive patients with at least one of the following three complaints: (1) upper respiratory tract complaints including allergies; (2) lower respiratory tract complaints including allergies; or (3) ear complaints. MAIN OUTCOME MEASURES: The primary outcomes criterion was the response to treatment, defined as cured or major improvement after 14 days of treatment. Secondary outcomes criteria were: (1) rate of recovery; (2) occurrence of adverse events; (3) patient satisfaction; and (4) length of consultation. RESULTS: Four hundred and fifty-six

(456) patient visits were compared: 281 received homeopathy, 175 received conventional medicine. The response to treatment as measured by the primary outcomes criterion for patients receiving homeopathy was 82.6%, for conventional medicine it was 68%. Improvement in less than 1 day and in 1 to 3 days was noted in 67.3% of the group receiving homeopathy and in 56.6% of those receiving conventional medicine. The adverse events for those treated with conventional medicine was 22.3% versus 7.8% for those treated with homeopathy. Seventy-nine percent (79.0%) of patients treated with homeopathy were very satisfied and 65.1% of patients treated with conventional, medicine were very satisfied. In both treatment groups 60% of cases had consultations lasting between 5 and 15 minutes. CONCLUSIONS: Homeopathy appeared to be at least as effective as conventional medical care in the treatment of patients with the three conditions studied.

Exclude- primary study

74. Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, et al. A systematic literature review of the effectiveness of nonpharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use. Health Technol Assess. 2006 Aug;10(26):iii, ix-108.
OBJECTIVES: To determine the effectiveness and cost-effectiveness of non-pharmacological interventions (excluding subjective barriers) in the prevention of wandering in people with dementia, in comparison with usual care, and to evaluate through the review and a qualitative study the acceptability to stakeholders of such interventions and identify ethical issues associated with their use. DATA SOURCES: Major electronic databases were searched up until 31 March 2005. Specialists in the field. REVIEW METHODS: Selected studies were assessed and analysed. The results of two of the efficacy studies that used similar interventions, designs and outcome measures were pooled in a meta-analysis; results for other studies which reported standard deviations were presented in a forest plot. Owing to a lack of cost-effectiveness data, a modelling exercise could not be performed. Four focus groups were carried out with relevant stakeholders (n = 19) including people with dementia and formal and lay carers to explore ethical and acceptability issues in greater depth. Transcripts were coded independently by two reviewers to develop a coding frame. Analysis was via a thematic framework approach. RESULTS: Ten studies met the inclusion criteria (multi-sensory environment, three; music therapy, one; exercise, one; special care units, two; aromatherapy, two; behavioural intervention, one). There was no robust evidence to recommend any non-pharmacological intervention to reduce wandering in dementia. There was some evidence, albeit of poor quality, for the effectiveness of exercise and multi-sensory environment. There were no relevant studies to determine the cost-effectiveness of the interventions. Findings from the narrative review and focus groups on acceptability and ethical issues were comparable. Exercise and distraction therapies were the most acceptable interventions and raised no ethical concerns. All other interventions were considered acceptable except for physical restraints, which were considered unacceptable. Considerable ethical concerns exist with the use of electronic tagging and tracking devices and physical barriers. Existing literature ignores the perspectives of people with dementia. The small number of participants with dementia expressed caution regarding the use of unfamiliar technology. Balancing risk and risk assessment was an important theme for all carers in the management of wandering. CONCLUSIONS: There is no robust evidence so far to recommend the use of any non-pharmacological intervention to reduce or prevent wandering in people with dementia. High-quality studies, preferably randomised controlled trials, are needed to determine the clinical and cost-effectiveness of non-pharmacological interventions that allow safe wandering and are considered practically and ethically acceptable by carers and people with dementia. Large-scale, long-term cohort studies are needed to evaluate the morbidity and mortality associated with wandering in dementia for people both in the community and in residential care. Such data would inform future long-term cost-effectiveness studies.

Exclude, not Homeopathy

75. Rutten, L. and E. Stolper (2006). "'Proof' against homeopathy in fact supports Homeopathy." Homeopathy **95**(1): 57-61.

Exclude, not a SR

76. Rutten, A. L. B. and C. F. Stolper (2008). "The 2005 meta-analysis of homeopathy: the importance of post-publication data." Homeopathy **97**(4): 169-177.
Background: There is a discrepancy between the outcome of a meta-analysis published in 1997 of 89 trials of homeopathy by Linde et al and an analysis of 110 trials by Shang et al published in 2005, these reached opposite conclusions. Important data were not mentioned in Shang et al's paper, but only provided subsequently.Questions: What was the outcome of Shang et al's predefined hypotheses? Were the homeopathic and conventional trials comparable? Was subgroup selection justified? The possible role of ineffective treatments. Was the conclusion about effect justified? Were essential data missing in the original article?Methods: Analysis of post-publication data. Re-extraction and analysis of 21 higher quality trials selected by Shang et al with sensitivity analysis for the influence of single indications. Analysis of comparability. Sensitivity analysis of influence of subjective choices, like quality of single indications and of cut-off values for 'larger samples'.Results: The quality of trials of homeopathy was better than of conventional trials. Regarding smaller trials, homeopathy accounted for 14 out of 83 and conventional medicine 2 out of 78 good quality trials with n < 100. There was selective inclusion of unpublished trials only for homeopathy. Quality was assessed differently from previous analyses. Selecting subgroups on sample size and quality caused incomplete matching of homeopathy and conventional trials. Cut-off values for larger trials differed between homeopathy and conventional medicine without plausible reason. Sensitivity analyses for the influence of heterogeneity and the cut-off value for 'larger higher quality studies' were missing. Homeopathy is not effective for muscle soreness after long distance running, OR = 1.30 (95% CI 0.96DS1.76). The subset of homeopathy trials on which the conclusion was based was heterogeneous, comprising 8 trials on 8 different indications, and was not matched on indication with those of conventional medicine. Essential data were missing in the original paper.Conclusion: Re-analysis of Shang's post-publication data did not support the conclusion that homeopathy is a placebo effect. The conclusion that homeopathy is and that conventional is not a placebo effect was not based on comparative analysis and not justified because of heterogeneity and lack of sensitivity analysis. If we confine ourselves to the predefined hypotheses and the part of the analysis that is indeed comparative, the conclusion should be that quality of homeopathic trials is better than of conventional trials, for all trials (p = 0.03) as well as for smaller trials (p = 0.003).

Exclude- this is a methodological paper, not a SR.

77. Seed, P. (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 365; author reply 367-368.

Exclude, not a SR

78. Selekman, J., E. Thomas, et al. (1998). "The school nurse's role in homeopathic interventions." Journal of School Health **68**(8): 342-345.
Selekman et al discuss the role of the school nurse in homeopathic interventions. Nine guidelines for school nurses are offered.

Not an SR – Exclude

79. Shaw, D. (2010). "Unethical aspects of homeopathic dentistry." Br Dent J **209**(10): 493-496.
In the last year there has been a great deal of public debate about homeopathy, the system of alternative medicine whose main principles are that like cures like and that potency increases relative to dilution. The House of Commons Select Committee on Science and Technology concluded in November 2009 that there is no evidence base for homeopathy, and agreed with some academic commentators that homeopathy should not be funded by the NHS. While homeopathic doctors and hospitals are quite commonplace, some might be surprised to learn that there are also many homeopathic dentists practising in the UK. This paper examines the statements made by several organisations on behalf of homeopathic dentistry and suggests that they are not entirely ethical and may be in breach of various professional guidelines.

Discussion paper- exclude.

80. Sherr, J. and T. Quirk (2007). "Systematic review of homeopathic pathogenetic trials: an excess of rigour?" Homeopathy **96**(4): 273-275; discussion 275-276, 278.

Discussion paper- exclude.

81. Signorini, A. (2007). "Finally, some light on the 'Pillar of Homeopathy'." Homeopathy **96**(1): 1-2.
Exclude, not a SR

82. Sim, J. and N. Adams (2002). "Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia." The Clinical journal of pain **18**(5): 324-336.
Little is known of the effectiveness of nonpharmacological interventions for fibromyalgia syndrome (FMS). The authors therefore carried out a systematic review from 1980 to May 2000 of randomized controlled trials (RCTs) of nonpharmacological interventions for FMS. A search of computerized databases was supplemented by hand searching of bibliographies of key publications. The methodological quality of studies included in the review was evaluated independently by two researchers according to a set of formal criteria. Discrepancies in scoring were resolved through discussion. The review yielded 25 RCTs, and the main categories of interventions tested in the studies were exercise therapy, educational intervention, relaxation therapy, cognitive-behavioral therapy, acupuncture, and forms of hydrotherapy. Methodological quality of studies was fairly low (mean score = 49.5/100). Most studies had small samples (median for individual treatment groups after randomization = 20), and the mean power of the studies to detect a medium effect (> or = 0.5) was 0.36. Sixteen studies had blinded outcome assessment, but patients were blinded in only 6 studies. The median longest follow-up was 16 weeks. Statistically significant between-group differences on at least one outcome variable were reported in 17 of the 24 studies. The varying combinations of interventions studied in the RCTs and the wide range of outcome measures used make it hard to form conclusions across studies. Strong evidence did not emerge in respect to any single intervention, though preliminary support of moderate strength existed for aerobic exercise. There is a need for larger, more methodologically rigorous RCTs in this area.
Exclude- not homeopathy

83. Sismondo, S. (2008). "Pharmaceutical company funding and its consequences: A qualitative systematic review." Contemporary Clinical Trials **29**(2): 109-113.
This article systematically reviews published studies of the association of pharmaceutical industry funding and clinical trial results, as well a few closely related studies. It reviews two earlier results, and surveys the recent literature. Results are clear: Pharmaceutical company sponsorship is strongly associated with results that favor the sponsors' interests. *This article reviews the effects of funding on the published results of clinical trials, finding that pharmaceutical company funding is strongly associated with results that favour those companies' interests.*
Exclude- not about homeopathy and does not answer a clinical question.

84. Steinberg, D. and M. W. Beal (2003). "Homeopathy and women's health care." Jognn-Journal of Obstetric Gynecologic and Neonatal Nursing **32**(2): 207-214.
A 1997 survey revealed that 40% of Americans use some type of complementary therapy or medicine and that many use such therapies in conjunction with treatments prescribed to them by conventional medical practitioners. One alternative modality that is growing in popularity is homeopathy. Although use of this modality is growing, many health care providers know very little about it. This article provides an introduction to homeopathy, including its historical origins and theoretical principles. Also included is a review of two meta-analyses that examined the efficacy of homeopathy in clinical trials. The homeopathic approach to prolonged pregnancy is presented as an example of a potential application to women's health. Information on education and certification in homeopathy is provided, along with resources on homeopathy available to women's health care providers. Implications for nursing practice are discussed.
Not an SR - Exclude

85. Stock-Schroer, B., H. Albrecht, et al. (2009). "Reporting experiments in homeopathic basic research (REHBaR)--a detailed guideline for authors." Homeopathy **98**(4): 287-298.
BACKGROUND: Reporting experiments in basic research in homeopathy is an important issue as comprehensive description of what exactly was done is required. So far, there is no guideline for authors available, unlike criteria catalogues common in clinical research. METHODS: A Delphi Process

was conducted, including a total of five rounds, three rounds of adjusting and phrasing plus two consensus conferences. European researchers who published experimental work within the last five years were involved. RESULTS: A checklist of 23 items was obtained and supplemented with detailed examples emphasizing what each item implies. Background, objectives and possible hypotheses should be given in the part 'introduction'. Special emphasis is put on the 'materials and methods' section, where a detailed description of chosen controls, object of investigation, experimental setup, replication, parameters, intervention, allocation, blinding, and statistical methods is required. The section 'results' should present sufficient details on analysed data, descriptive as well as inferential. Authors should discuss their results and give an interpretation in the context of current evidence. CONCLUSION: A guideline for Reporting Experiments in Homeopathic Basic Research (REHBaR) was compiled to be applied by authors when preparing their manuscripts, and to be used by scientific journals in the reviewing process. Furthermore the guideline is a commitment to a certain minimum quality level needed in basic research, e.g. blinding and randomisation. Feedback is encouraged on applicability, strength and limitations of the list to enable future revisions.

Exclude, not a SR

86. Su C, Lichtenstein GR, Krok K, Brensinger CM, Lewis JD. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. Gastroenterology 2004; 126(5): 1257–1269.

Abstract: Placebo-controlled, randomized clinical trials (PC-RCTs) are commonly used to assess therapies for Crohn's disease (CD). Knowledge of the placebo rates of remission and response and understanding of design factors that influence these rates is important for designing future clinical trials evaluating pharmacotherapy of CD. The aims of this study were to estimate rates of remission and response in patients with active CD receiving placebo and to identify factors influencing these rates. We performed a systematic review and meta-analysis of PC-RCTs evaluating therapies for active CD identified from MEDLINE from 1966 to 2001. The pooled estimates of the placebo rates of remission and response were 18% (95% confidence interval, 14%–24%; range, 0%–50%) and 19% (95% confidence interval, 13%–28%; range, 0%–46%), respectively, both with significant heterogeneity among studies ($P < 0.01$ for remission, $P < 0.03$ for response). In multivariate models, study duration, number of study visits, and entry Crohn's Disease Activity Index score were important predictors of the placebo remission rate, with study duration the most important. However, no single factor could account for all of the heterogeneity. Factors that influence the placebo response rates were similar to those affecting the placebo remission rates. The absolute benefit of active treatment beyond placebo was generally larger when outcome was measured by response than remission. Placebo remission and response rates in PC-RCTs for active CD are variable. Study duration, number of study visits, and disease severity at entry have a large influence on placebo remission rates.

ORDERED 2/5/12 #**43501 received 2/5**

Exclude- not homeopathy

87. Szeto, A. L., F. Rollwagen, et al. (2004). "Rapid induction of protective tolerance to potential terrorist agents: a systematic review of low- and ultra-low dose research." Homeopathy **93**(4): 173-178.

OBJECTIVE: To systematically review the literature on the ability of low-dose (LD) and ultra-low-dose (ULD) toxin exposure to prevent and treat biological and chemical threats. METHODS: Laboratory research articles on protection or treatment from LD or ULD exposure for the 13 high-risk chemical and biological warfare threats were collected and systematically evaluated for quantity and scientific quality using pre-defined methodological criteria. RESULTS: Over 2600 articles were screened. Only five studies met the inclusion criteria examining stimulation and protective effects of LD- or ULD-exposures to the 13 pre-identified biological and chemical agents. The quality evaluation (QE) of these studies was above average with a mean QE score of 70.6% of maximum. Two articles of fair to good quality reported both protective and treatment efficacy from exposure of animals or humans to LD- and ULD-exposures to toxins of risk in biochemical warfare. CONCLUSION: There is little research on agents of biological and chemical warfare investigating the possible use of LD- and ULD-toxins for protection and treatment. The existing literature is generally of good quality and indicates that rapid induction of protective tolerance is a feasible but under-investigated approach to bioterrorist or biowarfare defense. In our opinion, further research into the role of induced protection with LD- and ULD-toxic agents is needed.

Exclude, not Homeopathy

88. Tan, G., M. H. Craine, et al. (2007). "Efficacy of selected complementary and alternative medicine interventions for chronic pain." Journal of Rehabilitation Research & Development **44**(2): 195-222.
Complementary and alternative medicine (CAM) is a group of diverse medical and healthcare systems, therapies, and products that are not presently considered part of conventional medicine. This article provides an up-to-date review of the efficacy of selected CAM modalities in the management of chronic pain. Findings are presented according to the classification system developed by the National Institutes of Health National Center for Complementary and Alternative Medicine (formerly Office of Alternative Medicine) and are grouped into four domains: biologically based medicine, energy medicine, manipulative and body-based medicine, and mind-body medicine. Homeopathy and acupuncture are discussed separately as "whole or professionalized CAM practices." Based on the guidelines of the Clinical Psychology Division of the American Psychological Association, findings indicate that some CAM modalities have a solid track record of efficacy, whereas others are promising but require additional research. The article concludes with recommendations to pain practitioners.

Exclude, not a SR

89. Taylor, M. A., et al. (2000), 'Randomised controlled trial of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series: 1', *BMJ [Clinical Research Ed.] [NLM - MEDLINE]*, 321 (7259), 471-76.
OBJECTIVE: To test the hypothesis that homoeopathy is a placebo by examining its effect in patients with allergic rhinitis and so contest the evidence from three previous trials in this series. Design: Randomised, double blind, placebo controlled, parallel group, multicentre study. SETTING: Four general practices and a hospital ear, nose, and throat outpatient department. PARTICIPANTS: 51 patients with perennial allergic rhinitis. Intervention: Random assignment to an oral 30c homoeopathic preparation of principal inhalant allergen or to placebo. MAIN OUTCOME MEASURES: Changes from baseline in nasal inspiratory peak flow and symptom visual analogue scale score over third and fourth weeks after randomisation. RESULTS: Fifty patients completed the study. The homoeopathy group had a significant objective improvement in nasal airflow compared with the placebo group (mean difference 19.8 l/min, 95% confidence interval 10.4 to 29.1, P=0.0001). Both groups reported improvement in symptoms, with patients taking homoeopathy reporting more improvement in all but one of the centres, which had more patients with aggravations. On average no significant difference between the groups was seen on visual analogue scale scores. Initial aggravations of rhinitis symptoms were more common with homoeopathy than placebo (7 (30%) v 2 (7%), P=0.04). Addition of these results to those of three previous trials (n=253) showed a mean symptom reduction on visual analogue scores of 28% (10.9 mm) for homoeopathy compared with 3% (1.1 mm) for placebo (95% confidence interval 4.2 to 15.4, P=0.0007). CONCLUSION: The objective results reinforce earlier evidence that homoeopathic dilutions differ from placebo.

Exclude- not a SR

90. Teixeira, M. Z., C. H. F. Guedes, et al. (2010). "The placebo effect and homeopathy." Homeopathy **99**(2): 119-129.
BACKGROUND: Like other forms of medicine, including Complementary and Alternative Medicine (CAM), homeopathy elicits expectations in patients. The physician-patient relationship, personal and comprehensive treatment and lack of adverse effects are elements in creating positive expectations. Other elements may be associated with negative expectations. METHODS: We conducted a systematic literature review on placebo and nocebo effects in acupuncture and homeopathy using Medline. RESULTS: Findings on the psychophysiological and neuromediating mechanisms of the placebo-nocebo phenomenon are reviewed. Studies of these effects reveal how expectations and unconscious conditioning can be measured by imaging and EEG methods. They result in significant, non-specific therapeutic effects, which may confuse the evaluation of the specific therapeutic effects treatment, hampering selection of the simillimum. CONCLUSIONS: Directions for future research on non-specific therapeutic effects of homeopathy to improve clinical practice and clinical research are discussed.

Exclude- methodological paper

91. Terry, R., R. Perry, et al. (2012). "An overview of systematic reviews of complementary and alternative medicine for fibromyalgia." Clinical Rheumatology **31**(1): 55-66.
Fibromyalgia (FM) is a chronic pain condition which is difficult to diagnose and to treat. Most individuals suffering from FM use a variety of complementary or alternative medicine (CAM) interventions to treat and manage their symptoms. The aim of this overview was to critically evaluate all systematic reviews of single CAM interventions for the treatment of FM. Five systematic reviews met the inclusion criteria, evaluating the effectiveness of homoeopathy, chiropractic, acupuncture, hydrotherapy and massage. The reviews found some evidence of beneficial effects arising from acupuncture, homoeopathy, hydrotherapy and massage, whilst no evidence for therapeutic effects from chiropractic interventions for the treatment of FM symptoms was found. The implications of these findings and future directions for the application of CAM in chronic pain conditions, as well as for CAM research, are discussed.[PUBLICATION ABSTRACT]

Exclude- umbrella review- pearl reference list

92. Tiran, D. (2008). "Homeopathy in pregnancy: issues for midwives." The practising midwife **11**(5): 14.
This is a discussion piece about the use of homeopathy by midwives .

Exclude, not a SR

93. Tough, E. A., A. R. White, et al. (2009). "Acupuncture and dry needling in the management of myofascial trigger point pain: A systematic review and meta-analysis of randomised controlled trials." European Journal of Pain **13**(1): 3-10.
Pain from myofascial trigger points is often treated by needling, with or without injection, although evidence is inconclusive on whether this is effective. We aimed to review the current evidence on needling without injection, by conducting a systematic literature review. We searched electronic databases to identify relevant randomised controlled trials, and included studies where at least one group were treated by needling directly into the myofascial trigger points, and where the control was either no treatment, or usual care; indirect local dry needling or some form of placebo intervention. We extracted data on pain, using VAS scores as the standard. Seven studies were included. One study concluded that direct dry needling was superior to no intervention. Two studies, comparing direct dry needling to needling elsewhere in the muscle, produced contradictory results. Four studies used a placebo control and were included in a meta-analysis. Combining these studies (n = 134), needling was not found to be significantly superior to placebo (standardised mean difference, 14.9 [95%CI, -5.81 to 33.99]), however marked statistical heterogeneity was present (I^2 = 88%). In conclusion, there is limited evidence deriving from one study that deep needling directly into myofascial trigger points has an overall treatment effect when compared with standardised care. Whilst the result of the meta-analysis of needling compared with placebo controls does not attain statistically significant, the overall direction could be compatible with a treatment effect of dry needling on myofascial trigger point pain. However, the limited sample size and poor quality of these studies highlights and supports the need for large scale, good quality placebo controlled trials in this area. (PsycINFO Database Record (c) 2012 APA, all rights reserved) (journal abstract)

Exclude, not homeopathy

94. Ulbricht, C., W. Chao, et al. (2011). "Oscillococcinum: An Evidence-Based Systematic Review by the Natural Standard Research Collaboration." Alternative & Complementary Therapies **17**(1): 41-49.
Oscillococcinum® (Anas barbariae hepatis et cordis extractum 200CK HPUS) is a patented homeopathic preparation manufactured by a French-based company (Boiron Laboratories) that is marketed and widely used for the treatment and prevention of influenza symptoms. The product is made f rom the heart and liver of wild duck and undergoes several dilutions (one part in 100; 200 times in a row [i.e., 200C]), after which there are reportedly little to no original duck-liver or heart molecules in the final product. According to secondary sources, wildfowl houses are a major reservoir of human influenza virus.

In available clinical trials,Oscillococcinum has been shown to reduce the severity and shorten the duration of influenza symptoms within a few days. 1,2 However, despite modest positive findings for the treatment of influenza, additional studies are warranted to evaluate this product's prophylactic

effectiveness. In 2009 and 2010, the U.S. Food and Drug Administration (FDA) and the U.S. Federal Trade Commission (FTC) issued warning letters stating that the manufacturer's website may contain information suggesting that Oscillococcinum may "diagnose, mitigate, prevent, treat (including to treat the symptoms of) or cure the H1N1 Flu Virus in people," which had not been approved or authorized by the FDA. More research is required to determine the efficacy and safety of Oscillococcinum, specially in young children and pregnant and lactating women

Exclude- umbrella review- pearl reference list

95. Ullman, D. (2003). "Controlled clinical trials evaluating the homeopathic treatment of people with human immunodeficiency virus or acquired immune deficiency syndrome." Journal of alternative and complementary medicine (New York, N.Y.) **9**(1): 133-141.
Homeopathic medicine developed significant popularity in the nineteenth century in the United States and Europe as a result of its successes treating the infectious disease epidemics during that era. Homeopathic medicine is a medical system that is specifically oriented to using nanopharmacologic and ultramolecular doses of medicines to strengthen a person's immune and defense system rather than directly attacking the microbial agents. To review the literature referenced in MEDLINE and in nonindexed homeopathic journals for placebo-controlled clinical trials using homeopathic medicines to treat people with AIDS or who are human immunodeficiency virus (HIV)-positive and to consider a different theoretical and methodological approach to treating people with the viral infection. A total of five controlled clinical trials were identified. A double-blinded, placebo-controlled study was conducted on 50 asymptomatic HIV-positive subjects (stage II) and 50 subjects with persistent generalized lymphadenopathy (stage III) in whom individualized single-remedy homeopathic treatment was provided. A separate body of preliminary research was conducted using homeopathic doses of growth factors. Two randomized double-blinded, placebo-controlled studies were conducted with a total of 77 people with AIDS who used only natural therapies over a 8-16-week period. Two other studies were conducted over a 2.5-year period with 27 subjects in an open-label format. The first study was conducted by the Regional Research Institute for Homeopathy in Mumbai, India, under the Central Council for Research in Homeopathy, with the approval of the Ministry of Health and Family Welfare, Government of India. The second body of studies was conducted in clinic settings in California, Oregon, Arizona, Hawaii, New York, and Washington. The first study found no statistically significant improvement in CD4 T-lymphocytes, but did find statistically significant pretest and post-test results in subjects with stage III AIDS, in CD4 ($p = 0.008$) and in CD8 ($p = 0.04$) counts. The second group of studies found specific physical, immunologic, neurologic, metabolic, and quality-of-life benefits, including improvements in lymphocyte counts and functions and reductions in HIV viral loads. As a result of the growing number of people with drug-resistant HIV infection taking structured treatment interruptions, homeopathic medicine may play a useful role as an adjunctive and/or alternative therapy.

Exclude – not a SR

96. Ullman, D. and M. Frass (2010). "A review of homeopathic research in the treatment of respiratory allergies." Alternative Medicine Review **15**(1): 48-58.
There are conceptual and historical links between homeopathic medicine and modern allergy desensitization treatment. Conventional allergy desensitization and homeopathic treatment both utilize small doses of substances that might cause symptoms in order to prevent or treat a hypersensitive state. Homeopathy has historically been associated with allergy treatment. This article reviews evidence from controlled trials for the use of homeopathy in respiratory allergies. Several clinical trials, many of which were published in "high impact" conventional medical journals, describe significant effects of homeopathic treatment in allergic patients. Most of these clinical studies have been deemed to be high quality trials, according to the three most commonly referenced meta-analyses of homeopathic research. Basic in vitro experimental studies also provide evidence that the effects of homeopathy differ from placebo.

Exclude, not a SR

97. Vallance, A. K. and K. A. Jobst (1998). "Meta-analysis of homoeopathy trials." Lancet **351**(9099): 366; author reply 367-368.

Exclude, not a SR

98. Vickers, A. J. (1999). "Independent replication of pre-clinical research in homeopathy: a systematic review." Forsch Komplementarmed **6**(6): 311-320.
OBJECTIVE: To determine whether any pre-clinical research in homoeopathy has been independently replicated. SEARCH STRATEGY: CISCOM was searched using the key words 'homeopathy' and 'basic research'. Further references were obtained from reviews, bibliographies, citation tracking and contact with experts. SELECTION CRITERIA: Studies comparing the effects of one or more homoeopathic medicines to no homoeopathic treatment on any live biological material apart from humans or animals under veterinary care. Research on intoxication and basophil degranulation was excluded. DATA COLLECTION AND ANALYSIS: Publications were grouped in experimental models. Studies were considered to comprise the same model if the outcome variable, biological material and homoeopathic treatment were the same. Publications relating to each experimental model were then arranged in chronological order. A model was considered to have been independently replicated if the first author was different and fewer than half of all authors had previously published research using that model. RESULTS: 120 papers reported 61 different experimental models. Only three models were investigated by different research teams: growth of yeast, growth of wheat coleoptiles and ultra-violet-induced erythema in albino guinea pigs. In the case of yeast, attempts to replicate findings showing increased growth after treatment with Pulsatilla were unsuccessful. For wheat, two experiments by different research teams were conducted, but no single hypothesis was tested in both papers with the same result. Different research teams conducted very similar experiments on erythema treatment by Apis, but the methodological quality of the publications was low. CONCLUSIONS: There is a lack of independent replication of any pre-clinical research in homoeopathy. In the few instances where a research team has set out to replicate the work of another, either the results were negative or the methodology was questionable.

Exclude as is Pre-clinical

99. Vickers, A. J. and C. Smith (2009). "Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes." Cochrane Database Syst Rev(1): CD001957.
BACKGROUND: Influenza is a highly infectious viral disease that is particularly common in the winter months. Oscillococcinum is a patented, commercially available homoeopathic medicine. The rationale for its use in influenza comes from the homoeopathic principle of 'let like be cured by like'. The medicine is manufactured from wild duck heart and liver, which are said to be reservoirs for influenza viruses. OBJECTIVES: To determine whether homoeopathic Oscillococcinum or similar medicines are more effective than placebo in the prevention and treatment of influenza and influenza-like syndromes. SEARCH STRATEGY: The Cochrane Central Register of Controlled Trials (CENTRAL) issue 2, 2003; MEDLINE (January 1966 to June 2003) and EMBASE (1980 to June 2003) were searched, using the term "homeopathy" with "influenza", "respiratory tract", "infection", "cough", "virus" and "fever". The manufacturers of Oscillococcinum were contacted for information. SELECTION CRITERIA: Placebo-controlled trials of Oscillococcinum or homeopathically-prepared influenza virus, influenza vaccine or avian liver in the prevention and treatment of influenza and influenza-like syndromes. DATA COLLECTION AND ANALYSIS: Two reviewers extracted data and assessed methodological quality independently. MAIN RESULTS: Seven studies were included in the review, three prevention trials (n = 2265) and four treatment trials (n = 1194). Only for two studies was there sufficient information to complete data extraction fully. There was no evidence that homoeopathic treatment can prevent influenza-like syndrome (relative risk 0.64, 95% confidence interval 0.28 to 1.43). Oscillococcinum treatment reduced length of influenza illness by 0.28 days (95% confidence interval 0.50 to 0.06). Oscillococcinum also increased the chance of a patient considering treatment effective (relative risk 1.08; 95% CI 1.17, 1). REVIEWER'S CONCLUSIONS: Though promising, the data are not strong enough to make a general recommendation to use Oscillococcinum for first-line treatment of influenza and influenza-like syndrome. Further research is warranted but required sample sizes are large. Current evidence does not support a preventative effect of Oscillococcinum-like homeopathic medicines in influenza and influenza-like syndromes.

Exclude – cochrane pulled article as the update was not able to be finished and the previous version was out of date by the cochrane review board standards.

100. Walach, H. (1998). Methodology beyond controlled clinical trials. In: E. Ernst, E.G. Hahn, (Eds.) Homoeopathy: a critical appraisal, pp. 48-59. London: Butterworth Heinemann.

Exclude- not a SR

101. Walach H, Haeusler W, Lowes T, Mussbach D, Schamell U, Springer W, Stritzl G, Gaus W, Haag G (1997) Classical homeopathic treatment of chronic headaches. Cephalalgia 17:11–18.
Abstract: We conducted a randomized, placebo-cor rolled, double-blind clinical trial in order to determine the efficacy of classical homeopathic therapy in patients with chronic headaches. After 6 weeks of baseline observation, patients received either the prescribed individualized homeopathic medication or an indistinguishable placebo for 12 weeks. Outcome parameters were headache frequency, duration, and intensity, measured daily by diary. Use of medication for acure headache was also monitored. Of the 98 patients in the sample, 37 were randomized to receive placebo, 6l received individualized homeopathic remedies. Groups were comparable at the beginning of the treatment. The median age was 48.5 years; 76% suffered from migraine, 51% from tension-type headaches, and 94% were previously treated for headache. The median headache frequency was 3 days a week. Headaches were present for 23 years (median). In both groups, patients showed an improvement of one headache day less per month. The use of medication for acute headache was reduced. The headache frequency of 11 patients was reduced by more than 40%. Thirty-nine patients either did not improve or experienced aggravations. There was no significant difference in any parameter between homeopathy and placebo.

Exclude- not a SR

102. Walach, H., W. B. Jonas, et al. (2005). "Research on homeopathy: state of the art." J Altern Complement Med **11**(5): 813-829.
In this paper, we review research on homeopathy from four perspectives, focusing on reviews and some landmark studies. These perspectives are laboratory studies, clinical trials, observational studies, and theoretical work. In laboratory models, numerous effects and anomalies have been reported. However, no single model has been sufficiently widely replicated. Instead, researchers have focused on ever-new models and experiments, leaving the picture of scattered anomalies without coherence. Basic research, trying to elucidate a purported difference between homeopathic remedies and control solutions has also produced some encouraging results, but again, series of independent replications are missing. While there are nearly 200 reports on clinical trials, few series have been conducted for single conditions. Some of these series document clinically useful effects and differences against placebo and some series do not. Observational research into uncontrolled homeopathic practice documents consistently strong therapeutic effects and sustained satisfaction in patients. We suggest that this scattered picture has to do with the fourth line of research: lack of a good theory. Some of the extant theoretical models are reviewed, including placebo, water structure, silica contamination, energy models, and entanglement models. It emerges that local models, suggesting some change in structure in the solvent, are far from convincing. The nonlocal models proposed would predict that it is impossible to nail down homeopathic effects with direct experimental testing and this places homeopathy in a scientific dilemma. We close with some suggestions for potentially fruitful research.

Exclude, not a SR

103. Walach H, Jonas W, Lewith G (2005a) Are the clinical effects of homeopathy placebo effects? Lancet 366:2081; DOI:10.1016/S0140-6736(05)67877-4)

Exclude, letter to the editor

104. Walach H, Sadaghiani C, Dehm C, Bierman DJ (2005b) The therapeutic effect of clinical trials: understanding placebo response rates in clinical trials – a secondary analysis. BMC Med Res Methodol 5:26
Background and purpose Placebo response rates in clinical trials vary considerably and are observed frequently. For new drugs it can be difficult to prove effectiveness superior to placebo. It is unclear what contributes to improvement in the placebo groups. We wanted to clarify, what elements of clinical trials determine placebo variability. Methods We analysed a representative sample of 141 published long-term trials (randomized, double-blind, placebo-controlled; duration > 12 weeks) to find out what study characteristics predict placebo response rates in various diseases. Correlational and regression analyses with study characteristics and placebo response rates were carried out.

Results We found a high and significant correlation between placebo and treatment response rate across diseases ($r = .78$; $p < .001$). A multiple regression model explained 79% of the variance in placebo variability ($F = 59.7$; $p < 0.0001$). Significant predictors are, among others, the duration of the study (beta = .31), the quality of the study (beta = .18), the fact whether a study is a prevention trial (beta = .44), whether dropouts have been documented (beta = -.20), or whether additional treatments have been documented (beta = -.17). Healing rates with placebo are lower in the following diagnoses; neoplasms (beta = -.21), nervous diseases (beta = -.10), substance abuse (beta = -.14). Without prevention trials the amount of variance explained is 42%. Conclusion Medication response rates and placebo response rates in clinical trials are highly correlated. Trial characteristics can explain some portion of the variance in placebo healing rates in RCTs. Placebo response in trials is only partially due to methodological artefacts and only partially dependent on the diagnoses treated.

Exclude, not homeopathy

105. Weatherley-Jones, E. (2005). "Homeopathy: a complementary view." Trends Pharmacol Sci **26**(11): 545-546.

Exclude, not a SR

106. Weiner, D. K. and E. Ernst (2004). "Complementary and alternative approaches to the treatment of persistent musculoskeletal pain." Clin J Pain **20**(4): 244-255.
OBJECTIVE: To review common complementary and alternative treatment modalities for the treatment of persistent musculoskeletal pain in older adults. METHODS: A critical review of the literature on acupuncture and related modalities, herbal therapies, homeopathy, and spinal manipulation was carried out. Review included 678 cases within 21 randomized trials and 2 systematic reviews of herbal therapies: 798 cases within 2 systematic reviews of homeopathy; 1,059 cases within 1 systematic review of spinal manipulation for low back pain, and 419 cases within 4 randomized controlled trials for neck pain. The review of acupuncture and related modalities was based upon a paucity of well-controlled studies combined with our clinical experience. RESULTS: Insufficient experimental evidence exists to recommend the use of traditional Chinese acupuncture over other modalities for older adults with persistent musculoskeletal pain. Promising preliminary evidence exists to support the use of percutaneous electrical nerve stimulation for persistent low back pain. While some herbals appear to have modest analgesic benefits, insufficient evidence exists to definitively recommend their use. Drug-herb interactions must also be considered. Some evidence exists to support the superiority of homeopathic remedies over placebo for treating osteoarthritis and rheumatoid arthritis. The benefits of spinal manipulation for persistent low back and neck pain have not been convincingly shown to outweigh its risks. DISCUSSION: While the use of complementary and alternative modalities for the treatment of persistent musculoskeletal pain continues to increase, rigorous clinical trials examining their efficacy are needed before definitive recommendations regarding the application of these modalities can be made.

Ordered 2/5 # 43515 received 7/5/12

Exclude- not a SR

107. World Health Organisation, Safety issues in the preparation of homeopathic medicines, 2009. This technical document was developed in 2009 by WHO, in conjunction with the Regional Government of Lombardy, in order to assure basic requirements of homeopathic medicines are met at the regional, national and international levels. According to the authors *"The document is intended as a support to national regulatory authorities – and to manufacturers of homeopathic medicines - in ensuring the safety and quality of homeopathic medicines. National authorities may want to use it as a reference when establishing appropriate regulatory requirements. The document provides definitions of commonly used technical terms in relation to the quality of homeopathic medicines." (p x)* It should be noted that this document does not cover either the efficacy or the clinical utilization of homeopathy, rather, it covers the need for safety and quality regulations in the development of homeopathic medicines, and the history, background and rational behind homeopathic therapy. As such, it does not fit into the inclusion criteria as stated by the homeopathy committee.

Exclude- focus is on whether homeopathic medicine growth, collection, and delevopment meet drug safety standards

108. Witt, C. M., M. Bluth, et al. (2007). "The in vitro evidence for an effect of high homeopathic potencies -- a systematic review of the literature." Complementary therapies in medicine **15**(2): 128-138. Objective: Systematic assessment of the in vitro research on high potency effects. Method: Publications of experiments were collected through databases, experts, previous reviews, citation tracking. Inclusion criteria: stepwise agitated dilutions <10-23; cells or molecules from human or animal. Experiments were assessed with the modified SAPEH score. Results: From 75 publications, 67 experiments (1 /3 of them replications) were evaluated. Nearly 3/4 of them found a high potency effect, and 2/3 of those 18 that scored 6 points or more and controlled contamination. Nearly 3/4 of all replications were positive. Design and experimental models of the reviewed experiments were inhomogenous, most were performed on basophiles. Conclusions: Even experiments with a high methodological standard could demonstrate an effect of high potencies. No positive result was stable enough to be reproduced by all investigators. A general adoption of succussed controls, randomization and blinding would strengthen the evidence of future experiments.

Exclude- bench science study

Appendix 4. Component systematic reviews and meta-analyses identified from the 'Umbrella' reviews

Umbrella review	Component Systematic Reviews meeting search criteria	Status of component review in search process
Bornhoft et al. 2006	Cucherat, M., et al. (2000), 'Evidence of clinical efficacy of homeopathy: A meta-analysis of clinical trials', European Journal of Clinical Pharmacology, 56 (1), 27-33.	New systematic review to iCAHE search
	Dantas, F. and H. Rampes (2000). "Do homeopathic medicines provoke adverse effects? A systematic review." British Homoeopathic Journal 89 Suppl 1: S35-38.	New systematic review to iCAHE search
	Ernst, E. (1999), 'Classical homoeopathy versus conventional treatments: a systematic review (Structured abstract)', PERFUSION, (1), 13-15. <http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11999000356/frame.html>.	New systematic review to iCAHE search
	Ernst, E. (1999), 'Homeopathic prophylaxis of headaches and migraine: a systematic review (Structured abstract)', Journal of Pain and Symptom Management, (5), 353-57. <http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11999002258/frame.html>.	Found independently in initial iCAHE search
	Ernst, E. (2002), 'A systematic review of systematic reviews of homeopathy', British Journal of Clinical Pharmacology, 54 (6), 577-82.	Found independently in initial iCAHE search
	Ernst, E. and Barnes, J. (1998), 'Are homoeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo-controlled trials', PERFUSION, 11 (1), 4-4.	New systematic review to iCAHE search
	Ernst, E. and Pittler, M. H. (1998), 'Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials', Archives of surgery (Chicago, Ill. : 1960), 133 (11), 1187-90.	New systematic review to iCAHE search
	Grabia, S. and E. Ernst (2003). "Homeopathic aggravations: a systematic review of randomised, placebo-controlled clinical trials." Homeopathy **92**(2): 92-98.	Found independently in initial iCAHE search

	Linde, K., Clausius, N., Ramirez, G., Melchart, D., Eitel, F., Hedges, L.V. & Jonas, W.B. (1997). Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo controlled trials. Lancet, 350: 834-843.	Found independently in initial iCAHE search
	Linde, K., Jobst, K.A. (2000). Homeopathy for chronic asthma. Cochrane Database of Systematic Reviews. (2)	Found in iCAHE search as: McCarney, R. W., K. Linde, et al. (2004). "Homeopathy for chronic asthma." Cochrane Database of Systematic Reviews(1).
	Long, L. and E. Ernst (2001) "Homeopathic remedies for the treatment of osteoarthritis: a systematic review (Structured abstract)." British Homoeopathic Journal, 37-43.	Found independently in initial iCAHE search
	Mathie, R. T. (2003). "The research evidence base for homeopathy: a fresh assessment of the literature." Homeopathy : the journal of the Faculty of Homeopathy 92(2): 84-91.	Found independently in initial iCAHE search
	Smith, C. A. (2001). "Homoeopathy for induction of labour." Cochrane Database of Systematic Reviews(4).	Found in iCAHE search as : Smith, C.A. (2010). Homoeopathy for induction of labour (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD003399
	Vickers, A. J. (1999), 'Independent replication of pre-clinical research in homoeopathy: A systematic review', FORSCHENDE KOMPLEMENTARMEDIZIN, 6 (6), 311-20.	New systematic review to iCAHE search
	Vickers, A. J. and C. Smith (2000). "Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes." Cochrane database of systematic reviews (Online)(3): CD001957.	Found in iCAHE search as: Vickers A, Smith C. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub4
Ernst 2002	Cucherat, M., M. C. Haugh, et al. (2000). "Evidence of clinical efficacy of homeopathy: A meta-analysis of clinical trials." European Journal of Clinical Pharmacology 56(1): 27-33.	*Found in Bornhoft 2006*
	Ernst, E. (1999) "Classical homoeopathy versus conventional treatments: a systematic review (Structured abstract)." PERFUSION, 13-15.	Found independently in initial iCAHE search
	Ernst, E. (1999) "Homeopathic prophylaxis of headaches and migraine: a systematic review (Structured abstract)." Journal of Pain and Symptom Management, 353-357.	Found independently in initial iCAHE search

	Ernst, E. and J. Barnes (1998). "Are homoeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo-controlled trials." PERFUSION 11(1): 4-4.	*Found in Bornhoft 2006*
	Ernst, E. and M. H. Pittler (1998). "Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials." Archives of surgery (Chicago, Ill. : 1960) 133(11): 1187-1190.	*Found in Bornhoft 2006*
	Linde, K., N. Clausius, et al. (1997). "Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials." Lancet 350(9081): 834-843.	Found independently in initial iCAHE search
	Linde, K. and D. Melchart (1998). "Randomized controlled trials of individualized homeopathy: A state-of-the-art review." Journal of Alternative and Complementary Medicine 4(4): 371-388.	Found independently in initial iCAHE search
	Linde, K., Jobst, K.A. (1998). Homeopathy for chronic asthma. Cochrane Database of Systematic Reviews. (1)	Found independently in initial iCAHE search
	Long, L. and E. Ernst (2001) "Homeopathic remedies for the treatment of osteoarthritis: a systematic review (Structured abstract)." British Homoeopathic Journal, 37-43.	Found independently in initial iCAHE search
	Vickers, A. J. (1999). "Independent replication of pre-clinical research in homoeopathy: A systematic review." FORSCHENDE KOMPLEMENTARMEDIZIN 6(6): 311-320.	*Found in Bornhoft 2006*
	Vickers, A. J. and C. Smith (2001). "Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes." Cochrane database of systematic reviews (Online)(3): CD001957.	Found in iCAHE search as: Vickers A, Smith C. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub4
Ernst 2010	Altunç, U., M. H. Pittler, et al. (2007). "Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials." Mayo Clinic proceedings. Mayo Clinic 82(1): 69-75.	Found independently in initial iCAHE search
	Glazener, C.M., Evans, J.H., Cheuk, D.K. (2005) Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database of Systematic Reviews (2).	Found in iCAHE search as: Huang, T., X. Shu, et al. (2011). "Complementary and miscellaneous interventions for nocturnal enuresis in children." Cochrane Database of Systematic Reviews(12).

Heirs, M. and M. E. Dean (2007). "Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder." Cochrane Database of Systematic Reviews(4).	Found independently in initial iCAHE search
Kassab, S., M. Cummings, et al. (2009). "Homeopathic medicines for adverse effects of cancer treatments." Cochrane database of systematic reviews (Online)(2): CD004845.	Found independently in initial iCAHE search
McCarney, R. W., J. Warner, et al. (2003). "Homeopathy for dementia." Cochrane Database of Systematic Reviews(1).	Found in iCAHE search as: McCarney RW, Warner J, Fisher P, van Haselen R. (2009) Homeopathy for dementia. Cochrane Database of Systematic Reviews
McCarney, R. W., K. Linde, et al. (2004). "Homeopathy for chronic asthma." Cochrane Database of Systematic Reviews(1).	Found in iCAHE search as: McCarney, R. W., K. Linde, et al. (2009). "Homeopathy for chronic asthma." Cochrane Database of Systematic Reviews(1).
Rutten, A. L. B. and C. F. Stolper (2008). "The 2005 meta-analysis of homeopathy: the importance of post-publication data." Homeopathy : the journal of the Faculty of Homeopathy 97(4): 169-177.	Found independently in initial iCAHE search
Shang, A., K. Huwiler-Müntener, et al. (2005). "Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy." Lancet 366(9487): 726-732.	Found independently in initial iCAHE search
Smith, C. A. (2006). "Homoeopathy for induction of labour." Cochrane Database of Systematic Reviews(4).	Found in iCAHE search as: Smith, C.A. (2010). Homoeopathy for induction of labour (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD003399
van der Wouden, J. C., R. van der Sande, et al. (2009). "Interventions for cutaneous molluscum contagiosum." Cochrane database of systematic reviews (Online)(4): CD004767.	van der Wouden, J. C., R. van der Sande, et al. (2009). "Interventions for cutaneous molluscum contagiosum." Cochrane database of systematic reviews (Online)(4): CD004767.
Vickers, A. J. and C. Smith (2006). "Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes." Cochrane database of systematic reviews (Online)(3): CD001957.	Found in iCAHE search as: Vickers A, Smith C. Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD001957. DOI: 10.1002/14651858.CD001957.pub4
Witt, C. M., M. Bluth, et al. (2007). "The in vitro evidence for an effect of high homeopathic potencies--a systematic review of the literature." Complementary therapies in medicine 15(2): 128-138.	Found independently in initial iCAHE search

McCarney et al. 2004	McCarney, R. W., K. Linde, et al. (2004). "Homeopathy for chronic asthma." Cochrane Database of Systematic Reviews(1).	Found in iCAHE search as: McCarney, R. W., K. Linde, et al. (2009). "Homeopathy for chronic asthma." Cochrane Database of Systematic Reviews(1).
O'Meara et al. 2002	Barnes, J., Resch, K.L., & Ernst, E. (1997). Homoeopathy for postoperative ileus? A meta-analysis. Journal of Clinical Gastroenterology, 25: 628-633.	New systematic review to iCAHE search
	Cucherat, M., et al. (2000), 'Evidence of clinical efficacy of homeopathy: A meta-analysis of clinical trials', European Journal of Clinical Pharmacology, 56 (1), 27-33.	*Found in Bornhoft 2006*
	Ernst, E. (1999), 'Classical homoeopathy versus conventional treatments: a systematic review (Structured abstract)', PERFUSION, (1), 13-15. <http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11999000356/frame.html>.	*Found in Bornhoft 2006*
	Ernst, E. (1999), 'Homeopathic prophylaxis of headaches and migraine: a systematic review (Structured abstract)', Journal of Pain and Symptom Management, (5), 353-57. <http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-11999002258/frame.html>.	Found independently in initial iCAHE search
	Ernst, E. and Barnes, J. (1998), 'Are homoeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo-controlled trials', PERFUSION, 11 (1), 4-4.	*Found in Bornhoft 2006*
	Ernst, E. and Pittler, M. H. (1998), 'Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials', Archives of surgery (Chicago, Ill. : 1960), 133 (11), 1187-90.	*Found in Bornhoft 2006*
	Linde, K., Jobst, K. (2001) 'Homeopathy for chronic asthma', Cochrane Library, Issue (4).	Found in iCAHE search as: McCarney, R. W., Linde, K., and Lasserson, T. J. (2009), 'Homeopathy for chronic asthma', Cochrane Database of Systematic Reviews, (1).
	Linde, K. and Melchart, D. (1998), 'Randomized controlled trials of individualized homeopathy: A state-of-the-art review', Journal of Alternative and Complementary Medicine, 4 (4), 371-88.	Found independently in initial iCAHE search
	Linde, K., et al. (1997), 'Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials', Lancet, 350 (9081), 834-43.	Found independently in initial iCAHE search

	Long, L. and Ernst, E. (2001), 'Homeopathic remedies for the treatment of osteoarthritis: a systematic review (Structured abstract)', British Homoeopathic Journal, (1), 37-43. <http://www.mrw.interscience.wiley.com/cochrane/cldare/articles/DARE-12001003447/frame.html>.	Found independently in initial iCAHE search
	Smith, C. A. (2001), 'Homoeopathy for induction of labour', Cochrane Database of Systematic Reviews, (4).	Found in iCAHE search as: Smith, C.A. (2010). Homoeopathy for induction of labour (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD003399
	Vickers, A. J. and Smith, C. (2001), 'Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes', Cochrane database of systematic reviews, (4).	New systematic review to iCAHE search
Linde 2001	Barnes, J., K.-L. Resch, et al. (1997). "Homeopathy for Postoperative Ileus?: A Meta-analysis." Journal of Clinical Gastroenterology 25(4): 628-633.	*Found in O'Meara 2002*
	Cucherat, M., M. C. Haugh, et al. (2000). "Evidence of clinical efficacy of homeopathy: A meta-analysis of clinical trials." European Journal of Clinical Pharmacology 56(1): 27-33.	*Found in Bornhoft 2006*
	Ernst, E. (1999) "Classical homoeopathy versus conventional treatments: a systematic review (Structured abstract)." PERFUSION, 13-15.	*Found in Bornhoft 2006*
	Ernst, E. (1999) "Homeopathic prophylaxis of headaches and migraine: a systematic review (Structured abstract)." Journal of Pain and Symptom Management, 353-357.	Found independently in initial iCAHE search
	Ernst, E. and J. Barnes (1998). "Are homoeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo-controlled trials." PERFUSION 11(1): 4-4.	*Found in Bornhoft 2006*
	Ernst, E. and M. H. Pittler (1998). "Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials." Archives of surgery (Chicago, Ill. : 1960) 133(11): 1187-1190.	*Found in Bornhoft 2006*
	Linde, K. and D. Melchart (1998). "Randomized controlled trials of individualized homeopathy: A state-of-the-art review." Journal of Alternative and Complementary Medicine 4(4): 371-388.	Found independently in initial iCAHE search

	Linde, K. Jobst, K. (1998) "Homeopathy for asthma." (Cochrane review) Cochrane Library Issue 4.	Found in iCAHE search as: McCarney, R. W., K. Linde, et al. (2009). "Homeopathy for chronic asthma." Cochrane Database of Systematic Reviews(1).
	Linde, K., N. Clausius, et al. (1997). "Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials." Lancet 350(9081): 834-843.	Found independently in initial iCAHE search
	Vickers, A. J. and C. Smith (2000). "Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes." Cochrane Library, issue 1	Found in iCAHE search as: Vickers, A. J. and C. Smith (2009). "Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes." Cochrane database of systematic reviews (Online)(3): CD001957.
Ulbricht 2011	Ernst, E. (2002). "A systematic review of systematic reviews of homeopathy." British Journal of Clinical Pharmacology 54(6): 577-582.	Found independently in initial iCAHE search
	Linde, K., M. Hondras, et al. (2001) "Systematic reviews of complementary therapies - an annotated bibliography. Part 3: Homeopathy." BMC Complementary and Alternative Medicine 1, 1-5 DOI: doi: 10.1186/1472-6882-1-4.	Found independently in initial iCAHE search
	Vickers, A. J. and C. Smith (2009). "Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes." Cochrane database of systematic reviews (Online)(3): CD001957.	Found independently in initial iCAHE search
Terry 2012	Baranowsky, J., P. Klose, et al. (2009). "Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia." Rheumatology International **30**(1): 1-21.	New systematic review to iCAHE search
	Linde, K., et al. (1997), 'Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials', Lancet, 350 (9081), 834-43.	Found independently in initial iCAHE search
	Perry, R., R. Terry, et al. (2010) A systematic review of homoeopathy for the treatment of fibromyalgia (Provisional abstract). Clinical Rheumatology 457-464	Found independently in initial iCAHE search
ENHR 2007	Jonas, W.B. (2003). A critical overview of homoeopathy. Ann Int Med 138: 393-399.	Found independently in initial iCAHE search

	Shang, A., K. Huwiler-Müntener, et al. (2005). "Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy." Lancet 366(9487): 726-732.	Found independently in initial iCAHE search
	Cucherat, M., et al. (2000), 'Evidence of clinical efficacy of homeopathy: A meta-analysis of clinical trials', European Journal of Clinical Pharmacology, 56 (1), 27-33.	Found independently in initial iCAHE search
	Mathie, R. (2003). The research base of homeopathy: a fresh assessment of the literature. Homeopathy, 92: 84-91.	Found independently in initial iCAHE search
	Linde, K., Clausius, N., Ramirez, G., Melchart, D., Eitel, F., Hedges, L.V. & & Jonas, W.B. (1997). Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo controlled trials. Lancet, 350: 834-843.	Found independently in initial iCAHE search
	Kleijnen, J., P. Knipschild, et al. (1991). "CLINICAL-TRIALS OF HOMEOPATHY." BRITISH MEDICAL JOURNAL **302**(6772): 316-323.	Found independently in initial iCAHE search
	Ullman D. (2003). Controlled clinical trials evaluating the homeopathic treatment of people with human immunodeficiency virus or acquired immune deficiency syndrome. Journal of Alternative and Complementary Medicine, 9: 133-141.	Found independently in initial iCAHE search
Hunt 2010	Jacobs, J. Jonas, W.B. Jimenez-Perez, M. Crothers, D. (2003). Homeopathy for childhood diarrhea: combined results and meta-analysis from three randomized, controlled clinical trials. Pediatric Infectious Disease Journal, 22: 229-234.	Found independently in initial iCAHE search
	Altunç, U, Pittler, MH, Ernst, E. (2007). Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic Proceedings*, 82: 69-75.	Found independently in initial iCAHE search

	Shang, A., K. Huwiler-Müntener, et al. (2005). "Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy." Lancet 366(9487): 726-732.	Found independently in initial iCAHE search

Appendix 5. Systematic review objectives

Author, year	Category	Cited objective
Altunc 2007	3	'To assess the evidence for any type of therapeutic or preventative intervention testing homeopathy for childhood and adolescent ailments' (p 69)
Alraec 2011	2	'The aim of our review was to systematically summarise and critically evaluate the data from RCTs of CAM treatment for patients with CFS' (p 2)
Bagnell 2007	2	'Our objective was to determine whether any particular intervention or combination of interventions is effective in the treatment, management and rehabilitation of adults and children with a diagnosis of CFS/ME.' (p. V)
Baranowsky 2009	3	'The objectives were identification, quality evaluation and summary of RCTs on complementary and alternative medicine as defined by the National Institute of Health with the exception of dietary and nutritional supplements' (p1)
Barnes 1997	1	'To determine whether homeopathic treatment has any greater effect than placebo administration on the restoration of intestinal peristalsis in patients after abdominal or gynecologic surgery' (p628)
Bellavite 2011 (NB subsuming three earlier reviews by the same authors, with similar objectives and included literature 2006a,b, 2008)	3	'To evaluate the effectiveness of homeopathy for the treatment of respiratory allergies, common upper respiratory tract infections, otorhinolaryngologic complaints and rheumatic diseases' (p 1363)
Cooper 2010	1	To systematically review research evidence for effectiveness of homeopathy in the management of insomnia (p 329)
Cucherat 2000	3	'To establish, using a systematic review and meta-analysis, whether there is any evidence from randomised controlled clinical trials of the efficacy of homeopathic treatment in patients with any disease' (p. 27)
Dantas 2000	4	'To evaluate the safety of homeopathic medicines by critically appraising reports of adverse effects published in English from 1970 to 1995' (p. S35)
Davidson 2011	3	'To systematically review placebo-controlled randomised controlled trials of homeopathy for psychiatric conditions' (p. 795)
De Silva 2010	2	'To critically evaluate the evidence regarding complementary and alternative medicines (CAMs) taken orally or applied topically for the treatment of fibromyalgia' (p. 1063)
De Silva 2011	2	'To critically evaluate the evidence regarding complementary and alternative medicine (CAM) taken orally or applied topically (excluding

		glucosamine and chondroitin) in the treatment of OA' (p. 911)
Ernst & Barnes 1998	1	'To systematically review the literature to determine whether or not homeopathic remedies are more effective than placebo in reducing the signs and symptoms of delayed onset muscle soreness' (p. 4)
Ernst & Pittler 1998	1	'To systematically review the clinical efficacy of homeopathic arnica' (p. 1187)
Ernst 1999a	1	'To evaluate the clinical trials, testing the efficacy of homeopathy for these indications (prophylaxis of migraine and headaches)' (p. 353)
Ernst 1999b	3	'To summarise the data from all trials of classic homeopathy (individualised homeopathic prescriptions based on the <like cure like> principle) versus allopathic medications' (p. 13)
Ernst 2004	4	'To summarise and critically evaluate the evidence from rigorous clinical trials of (homotoxicology)' (p. 299)
Ernst 2011	1	'To systematically review the evidence from randomised placebo-controlled trials for or against the notion that *Galphimia glauca (*GG) is effective for hay fever, and (2) critically evaluate the reliability of the published meta-analysis of GG for hay fever' (p. 200)
Ernst 2011	3	'To evaluate all RCTs investigating the effectiveness of homeopathy for insomnia and sleep-related disorders' (p. 196)
Grabia	5	(to) 'compare the frequency of homeopathic aggravations in the placebo and verum groups of double-blind, randomised clinical trials' (p. 92)
Heirs 2009 [Cochrane review]	1	'To assess the safety and effectiveness of homeopathy as a treatment for attention deficit/hyperactivity disorder' (p. 2)
Holdcraft 2003	2	'A systematic review of randomized controlled trials (RCTs) and non-RCTs on CAM studies for Fibromyalgia Syndrome was conducted to evaluate the empirical evidence for their effectiveness' (p. 667)
Huang 2011 [Cochrane review]	2	'To assess the effects of complementary interventions and others such as surgery or diet on nocturnal enuresis in children, and to compare them with other interventions' (p. 1).
Jorm 2004	2	'To review the evidence for the effectiveness of complementary and self-help treatments for anxiety disorders' (p. S29)
Kassab 2011 [Cochrane Review]	3	'To evaluate effectiveness and safety of homeopathic medicines used to prevent or treat adverse effects of cancer treatments' (p. 1).
Linde 1997	4	'To assess whether the clinical effect reported in RCTs of homeopathic remedies is equivalent to that reported for placebo' (p. 9081)
Linde 1998	4	'To summarize the actual state of clinical efficacy research on individualized homeopathy' (p. 371)
Long 2001	1	'To review the clinical evidence for and against the effectiveness of homeopathic medicines in the treatment of patients with osteoarthritis' (p. 37)
Mathie 2003	4	(to) 'examine the cumulative research from randomised and/or double-blind clinical trials (RCTs) in homeopathy for individual medical conditions reported since 1975, and asks the question: What is the weight of the original evidence from published RCTs that homeopathy has an effect that is statistically significantly different from that in a comparative group?' (p. 84)

McCarney 2008 [Cochrane review]	1	'To assess the effects of homeopathy in people with chronic stable asthma' (p. 1).
McCarney 2009 [Cochrane review]	1	'To evaluate the effectiveness and safety profile of homeopathically prepared medications used in treating dementia, as established by randomized controlled trials' (p. 1)
Milazzo 2006	1	'To summarize and critically evaluate the efficacy of homeopathic remedies used as a sole or additional therapy in cancer care' (p. 282)
Mills 2005	1	'To assess the effectiveness of complementary therapies for HIV and HIV-related symptoms' (p. 395)
Owen 2004	1	'To systematically review published prospective trials relating to the homeopathic treatment of tension type, cervicogenic, and migraine headache' (p. 45)
Passalacqua 2006	2	To provide 'a detailed analysis of the experimental evidence concerning the clinical use of CAMs in asthma and rhinitis' (p. 1055)
Perry 2010	1	'To evaluate whether homoeopathic treatments can have a therapeutic effect on the symptoms of fibromyalgia' (p. 457)
Pilkington 2005	1	'To systematically review the research evidence on the effectiveness of homeopathy for the treatment of depression and depressive disorders' (p. 153)
Pilkington 2006	1	'To conduct a systematic review of the clinical research evidence on homeopathy in the treatment of anxiety and anxiety disorders' (p. 151)
Pittler 2005	1	'To critically assess the evidence from randomized controlled trials (RCTs) and systematic reviews of complementary therapies for reducing body weight' (p. 1030)
Porter 2010	2	'To systematically review and evaluate the current literature related to alternative and complementary treatments for ME=CFS and FM' (p. 235)
Rada 2010	2	'To assess the efficacy of non-hormonal therapies in reducing hot flushes in women with a history of breast cancer.' (p. 1)
Quinn 2006	2	'To summarise and evaluate the available literature on the effectiveness of complementary and alternative medicine (CAM) for the management of low back pain' (p. 107).
Roberts 2012	5	'To determine which analgesic modalities used following discharge have the greatest efficacy in reducing postoperative pain after elective non-axial orthopedic surgery' (p. 1)
Sarris 2011	2	To conduct 'a rigorous systematic review of hypnotic CAM interventions, including herbal and nutritional medicine, acupuncture, acupressure, yoga, tai chi, massage, aromatherapy and homoeopathy [for insomnia]' (p. 99)
Schneider, Klein, & Weiser 2005	1	To present the results of a meta-analysis of four recent clinical trials evaluating the effectiveness of homeopathic preparations for tinnitus
Seidl 1998	2	'To review the scientific literature on common alternative remedies for treatment of symptoms attributed to menopause and to contrast this with available lay literature' (p. 1299)

Shang 2005	4	(To) 'examine the effects of homoeopathy and conventional medicine observed in matched pairs of placebo-controlled trials, assess trial quality and the probability of publication and related biases, and estimate results of large trials least affected by such biases' (p. 726).
Simonart 2011	3	'To assess the evidence for the efficacy of homoeopathic treatments in dermatology' (p. 897).
Smith 2010 [Cochrane Review]	1	'To determine the effects of homoeopathy for third trimester cervical ripening or induction of labour' (p. 1)
Stevinson 2001	2	'To determine whether use of complementary and alternative therapies (for women with premenstrual syndrome) is supported by evidence of effectiveness from rigorous clinical trials' (p. 227)
van der Wouden 2012 [Cochrane review]	5	'To assess the effects of management strategies (including waiting for natural resolution) for cutaneous, non-genital molluscum contagiosum in otherwise healthy people' (p. 1).
Vernon 1999	2	'To conduct a systematic review of the randomized controlled clinical trials (RCTs) of complementary/alternative (CAM) therapies in the treatment of non-migrainous headache (i.e. excluding migraine, cluster and organic headaches)' (p. 142)

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Appendix 6 Critical appraisal of the methodological quality of the reviews

A summary of the CEBM scores per included study is provided in Table 5 in the body of the main report.

Critical appraisal elements of the potentially-relevant systematic reviews (N=55)

a. ***CEBM Q1.*** Nine reviews did not ask clearly articulated a focused review question. The reviews in which the main question was not clearly articulated in terms of a focused clinical research question, and/or a comprehensive underpinning search strategy were Altunc (2007), Cucherat (2000), Davidson (2011), Ernst (1999b), Grabia (2003), Linde (1997, 1998), Mathie (2003), Shang (2005).

b. ***CEBM Q2.*** This critical appraisal question raised a number of matters related to the sensitivity and comprehensiveness of searching approaches. To understand the answers to this question better, we considered the databases searched, the search terms, the use of expert input to assist searching, hand-searching, language and date restrictions.

Databases searched: Each systematic review considered at least one comprehensive database in its search strategy (the most common being Medline (88.5% reviews), and therefore one could respond in the affirmative that it was unlikely that important, relevant studies were missed. However the number and type of additional databases searched to identify the component studies in each systematic review varied widely. Some authors reviewed only the mainstream databases, whilst others incorporated searches through many homeopathic databases. Appendix 5 summarises the databases searched for each systematic review into mainstream and complementary medicine, and provides the total number of databases searched (of each). The number of databases searched ranged from 1-17. An arbitrary decision was made regarding the number of databases searched, related to comprehensiveness of searching, and whether searching occurred in both mainstream and complementary research data repositories. The literature was divided into reviews that included findings from 10 or more database searched (N=7, 14.6%), studies that included findings from 5-9 databases (N=32 66.7%), and studies which included fewer than 5 databases (see Table A6.1) (N=10, 20.8%).

All reviews included searches of at least one mainstream database. Searching of complementary medicine databases was more variable. The studies which did not include complementary medicine database searches are highlighted in Table A6.1 with ++.

Table 11 Database use for searches in the potentially-relevant reviews

10+ databases searched		5-9 databases searched		<5 databases searched	
Alraek	2011	Altunc	2007	Ernst++	1999b
Bagnell	2007	Baranowsky	2009	Jorm++	2004
Barnes	1997	Bellavite	2006a	McCarnie++	2004
Heirs	2009	Bellavite	2006b	Passalacqua++	2006
Kassab	2011	Bellavite	2008	Porter++	2010
McCarnie	2009	Bellavite	2011	Roberts++	2012
Pilkington	2005	Cooper	2009	Seidl++	1998
Pilkington	2006	Cuhcerat	1999	Smith++	2010
Shang	2005	Dantas	2000	Vernon++	1999
		Davidson	2011		
		De Silva	2010		
		De Silva	2011		
		Ernst & Pittler	1998a		
		Ernst	1998b		
		Ernst	1999a		
		Ernst & Schmidt	2004		
		Ernst++	2011		
		Ernst	2011		
		Grabia	2003		
		Holdcraft++	2004		
		Huang	2011		
		Linde	1997		
		Linde	1998		
		Long&Ernst	2001		
		Mathie	2003		
		Milazzo	2006		
		Mills	2005		
		Owen	2004		
		Pittler	2005		
		Perry	2010		
		Quinn	2005		
		Rada	2010		
		Sarris++	2011		
		Simonart	2011		
		Stevinson	2001		
		Van Der Wouden++	2012		

Data unavailable for Schneider et al (2005) on databases searched

Search terms: 46/52 articles reported the use of descriptive terms for their searching, with many providing the search strings. MESH terms were less commonly used (in 34 reviews). Seven reviews did not provide any detail on the search terms.

Hand-searching: Hand-searching of reference lists occurred in 96% of the included systematic reviews.

Expert opinion: 45% of the reviews incorporated expert opinion when searching for relevant articles. This involved a range of expert input, from expert clinicians, academics and other researchers, and pharmaceutical companies.

Language: Very few reviews imposed language restrictions on their searches. Only three reviews explicitly stated that articles were sought in English language only, and two reviews did not specifically state that there was a language inclusion/exclusion criterion. However in the remaining reviews, few stated how they dealt with translation or interpretation issues, if papers were in languages other than English. One presumes that the authorship team had access to translators, or could read and interpret in other languages. No paper explicitly stated how many non-English articles were found.

Date restrictions: All but three reviews specified the dates within which literature was included. Most reviews (N=37) recruited literature from the date of inception of the databases, either to the year before, or the year when, the review was published. Eight papers stipulated a specific date range (see below).

Baranowsky	2009	1990-2009
Bellavite	2006a	1978-2006
Bellavite	2006b	1978-2007
Bellavite	2008	1978-2006
Bellavite	2011	1978-2010
Dantas	2000	1970-1995
Seidl	1998	1966-1977
Simonart	2011	1962-2011

c. ***CEBM Q3.*** The criteria used to judge whether articles had been identified and included appropriately related to the study designs chosen relevant to the purpose of the review, the clarity of the conditions being investigated, and identification of a population of interest.

Study purpose: Wording varied between reviews regarding investigation of the importance of the outcome of homeopathic interventions. Just over half the potentially-eligible reviews (28, 57%) investigated effectiveness of homeopathic interventions. One study (2%) investigated 'effects', one (2%) investigated 'therapeutic effect', two (4%) investigated 'therapy', three studies (6%) investigated 'efficacy', and 11 (22%) investigated 'treatment'. Combining these terms, treatment effects of homeopathic interventions were investigated in 46 reviews. The remaining reviews investigated adverse events/aggravations, safety and prevention.

Component study designs: The component studies in the included reviews largely favoured controlled trials (Randomised Controlled Trials and Clinical Controlled Trials). However 18% reviews

also included data from prospective observational studies, and case series. Thus overall, the choice of primary research designs was appropriate to the purpose of each review.

Conditions investigated: The included reviews considered the effects of homeopathy interventions for a range of conditions, comprising Anxiety, Asthma, Allergic respiratory conditions (including Hay fever), Bed wetting in children, HIV/AIDS, Cancer, Chronic Fatigue Syndrome & Fibromyalgia, Dementia, Depression, Dermatological conditions, Ear, Nose and Throat conditions, Headache (a range of manifestations), Induction of labour, Infections, Influenza, Insomnia, Osteoarthritis, Low Back Pain, Pre-Menstrual Syndrome/symptoms, Post-operative pain, Post-operative Ileus, Obesity.

A number of reviews dealt with a range of different conditions, or a range of interventions for the one condition, which potentially attenuated the impact of the review findings with respect to homeopathy effectiveness.

Populations of interest: Not all reviews were explicit about the populations addressed in the review question. In most reviews, the population needed to be extrapolated from the tables in the review itself. Even when 'adults' was specified there was usually no age range provided, thus different papers could provide data on different age groups (up to 65 years, 18-72 years, no age restriction etc.) within the one review. This constrained the external generalisability of the review findings. One review (Milazzo et al. 2006) on the use of homeopathy for side effects of cancer provided no age indication, despite the cancers investigated being found in all age groups.

Table A6.2 lists the included study references, the conditions addressed and the populations on which the homeopathic interventions were tested.

Table 12 List of reviews, conditions and populations

The reviews which did not ask a focused clinical question, or did not report specifically on clinical conditions are highlighted in grey.

Study reference	Condition	Population
Alraek, T., M. S. Lee, et al. (2011). "Complementary and alternative medicine for patients with chronic fatigue syndrome: A systematic review." BMC Complementary and Alternative Medicine **11**(1): 87-87.	Chronic Fatigue Syndrome	Adults
Altunç, U, Pittler, MH, Ernst, E. (2007). Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials. *Mayo Clinic Proceedings*, 82: 69-75.	Adenoid vegetation ADHD Asthma Otitis media Conjunctivitis Diarrhoea Postop pain URTI Warts	Children and adolescents
Bagnall A-M, Hempel S, Chambers D, Orton V, Forbes C. The treatment and management of chronic fatigue syndrome (CFS) / myalgic encephalomyelitis (ME) in adults and children. 2007; Update of CRD Report 22. Centre for Reviews and Dissemination University of York ISBN 978-1-900640-43-5	Chronic fatigue syndrome Myalgic encephalomyelitis	Children and adults
Baranowsky, J., P. Klose, et al. (2009). "Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia." Rheumatology International **30**(1): 1-21.	Fibromyalgia	(assume) adults
Barnes, J., Resch, K.L., & Ernst, E. (1997). Homoeopathy for postoperative ileus? A meta-analysis. *Journal of Clinical Gastroenterology*, 25: 628-633.	Postoperative Ileus	(assume) adults
Bellavite., P., R. Ortolani., et al. (2006a). "Immunology and Homeopathy. 4. Clinical Studies—Part 1." eCAM **3**(3): 293-301.	Hay fever and allergic asthma	Children and adults
Bellavite P, Ortolani R, Pontarollo F. (2006b). Immunology and homeopathy. 4. Clinical studies—Part 2. Evidence-based Complementary and Alternative Medicine: eCAM, 3: 397-409	Rhinitis in some form URTI Sinusitis Tonsilitis/pharyngitis Otitis media Chemo-induced symptoms Cough	Children and adults
Bellavite, P., S. Chirumbolo, et al. (2008). "Effectiveness of homeopathy in immunology and inflammation disorders: a literature overview of clinical studies." *Homoeopathic Heritage International* **33**(3): 35-57.	respiratory allergy, common upper respiratory tract infections, otorhinolaryngologic complaints rheumatic diseases	Children and adults
Bellavite., P., M. Marzotto., et al. (2011). "Advances in homeopathy and immunology: a review of clinical research." Frontiers in Bioscience **S3**: 1363-1389.	respiratory allergies, common upper respiratory tract infections & otorhinolaryngologic complaints, Rheumatic diseases	Children and adults
Cooper, K. L. and C. Relton (2010). "Homeopathy for insomnia: A systematic review of research evidence." Sleep Medicine Reviews **14**(5): 329-337.	Insomnia	Adults 19-73 years
Cucherat, M. & Linde, K. (2000). Evidence of clinical effectiveness of	Boils & pyoderma	Children and adults

homeopathy: a meta-analysis of clinical trials. Eur J Clin Pharmacol 56: 27-33.	Dystocia Active Hay Fever Post-surgery ileus Ankle sprain Influenza Postoperative pain Knee joint haematoma Burns Rheumatoid arthritis Headache Childhood diarrhoea Allergic asthma Chronic sinusitis Bronchitis	
Dantas, F. & Rampes, H. (2000). Do Homeopathic Medicines Provoke Adverse Effects? A Systematic Review. British Homeopathic Journal; 89: 70-74.	Adverse effects (across conditions)	Children & adults
Davidson, J. R. T., C. Crawford, et al. (2011). "Homeopathic treatments in psychiatry: A systematic review of randomized placebo-controlled studies." Journal of Clinical Psychiatry **72**(6): 795-805.	Range of psychiatric conditions (eg post-traumatic stress, anxiety, panic, phobia, fibromyalgia, sleep disorders etc)	(assume) adults
De Silva, V., A. El-Metwally, et al. (2010). "Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review." Rheumatology (Oxford) **49**(6): 1063-1068.	Fibromyalgia	(assume) adults
De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GL on behalf of the Arthritis Research UK working group on complementary and alternative medicines (2011): Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review *Rheumatology* 50:911_920	Osteoarthritis	Adults
Ernst, E. & Barnes, A. (1998). Are homeopathic remedies effective for delayed-onset muscle soreness? A systematic review of placebo controlled trials. Perfusion, 11: 4-8	Delayed onset muscle soreness	Adults (Women, marathon runners, healthy volunteers)
Ernst, E. and Pittler, M. H. (1998), 'Efficacy of homeopathic arnica: a systematic review of placebo-controlled clinical trials', Archives of surgery (Chicago, Ill. : 1960), 133 (11), 1187-90.	Delayed onset muscle soreness, prevention of post-surgical complications, acute trauma, experimentally-induced tissue trauma, stroke	(assume) adults
Ernst, E. (1999a). "Homeopathic prophylaxis of headaches and migraine? A systematic review." Journal of Pain & Symptom Management **18**(5): 353-357	Migraine and headache	(assume) adults
Ernst, E. (1999b), 'Classical homoeopathy versus conventional treatments: a systematic review, *PERFUSION*, (1), 13-15.	Rheumatoid arthritis, proctocolitis, irritable bowel disease, malaria, otitis media, tonsillitis	Children and adults
Ernst, E. and K. Schmidt (2004). "Homotoxicology--a review of randomised clinical trials." European Journal of Clinical Pharmacology 60(5): 299-306.	Ankle sprains, knee haemarthrosis, other joint sprains and contusions, prevention of influenza, chemotherapy-induced stomatitis, chronic asthma, chronic sinusitis, common cold	(assume) adults
Ernst, E. (2011a). "Homeopathic Galphimia glauca for hay fever: a	Hay fever	Adults

systematic review of randomised clinical trials and a critique of a published meta-analysis." Focus on Alternative & Complementary Therapies **16**(3): 200-203.		
Ernst, E. (2011b). "Homeopathy for insomnia and sleep-related disorders: a systematic review of randomised controlled trials." Focus on Alternative & Complementary Therapies **16**(3): 195-199.	Insomnia	Adults
Grabia, S. and E. Ernst (2003). "Homeopathic aggravations: a systematic review of randomised, placebo-controlled clinical trials." Homeopathy **92**(2): 92-98	Birch pollen allergy, influenza, skin reactions after treatment for Ca of breast, Benzodiazepine Substitution, delivery, post-operative ileus, post-hysterectomy pain, irritable colon, hay fever, asthma (adult & child), tinnitus, Seborrheic dermatitis, warts in children, migraine, perennial allergic Rhinitis	Children and Adults
Heirs, M. and M. E. Dean (2007 Updated 2009). "Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder." Cochrane Database of Systematic Reviews(4).	Attention deficit disorder	Children
Huang, T., X. Shu, et al. (2011). "Complementary and miscellaneous interventions for nocturnal enuresis in children." Cochrane Database of Systematic Reviews(12).	Bed wetting	Children
Holdcraft, L. C., N. Assefi, et al. (2003). "Complementary and alternative medicine in fibromyalgia and related syndromes." Best Pract Res Clin Rheumatol **17**(4): 667-683.	Fibromyalgia and related symptoms	Adults
Jorm, A. F., H. Christensen, et al. (2004). "Effectiveness of complementary and self-help treatments for anxiety disorders." Medical Journal of Australia **181**(7): S29-46	Anxiety	Adults
Kassab, S. Cummings, M. Berkovitz, S. et al (2011). Homeopathic medicines for adverse effects of cancer treatments (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD 004845.	Adverse effects of chemotherapy for cancer	All ages
Linde, K., Clausius, N., Ramirez, G., Melchart, D., Eitel, F., Hedges, L.V. & Jonas, W.B. (1997). Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo controlled trials. Lancet, 350: 834-843.	Allergic asthma, pollenosis, warts, minor burns, pyodermia, skin lesions, dermatoses, anal fissure, diarrhoea, gastritis, cholecystopathia, irritable bowel syndrome, sprains, haemarthrosis, cramps, dental neuaralgia, migraine, seasickness, stroke, menopausal symptoms, vaginal discharge, menstrual complications, childbirth, mastodynia, cystitis	Children and adults

Linde, K. & Melchart, D. (1998). Randomised controlled trials of individualised homeopathy: a state-of-the-art review. Journal of Alternative and Complementary Medicine 4: 371-388.	Headache (incl migraine), diarrhoea, rheumatology, infectious diseases, pre-menstrual syndrome, post-viral fatigue, ADHD, insomnia, proctocolitis, dental pain, aphasia after stroke, agne vulgaris, dermatoses	Children and adults
Long, L. & Ernst, E. (2001). Homeopathic remedies for the treatment of osteoarthritis: a systematic review. British Homeopathic Journal, 90: 37-43	Osteoarthritis	Adults
Mathie, R. (2003). The research base of homeopathy: a fresh assessment of the literature. Homeopathy, 92: 84-91.	childhood diarrhoea, fibrositis (fibromyalgia), hayfever/allergic rhinitis, influenza, pain (of various origins), side-effects of radio-/chemotherapy, Sprains, upper respiratory tract infections, headache, stroke, wart, hypertension, insect bites, Leg ulcers, Seborrheic dermatitis, Otitis media, influenza, irritable bowel syndrome, Post-operative ileus, female infertility, Menopausal syndrome, pre-menstrual symptoms, Tissue recovery after childbirth, muscle soreness (cramp), osteoarthritis, rheumatoid arthritis, anxiety, Attention Deficit Hyperactivity Disorder (ADHD), stroke, headache (migraine, tension-type, cervicogenic), vertigo, minor burns, cholera, malaria	Children and adults
McCarney RW, Linde K, Lasserson TJ (2008). Homeopathy for chronic asthma (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD000353.	Chronic stable asthma	Children and adults
McCarney RW, Warner J, Fisher P, van Haselen R. (2009). Homeopathy for dementia. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD003803. DOI: 10.1002/14651858.CD003803	Dementia	Adults
Milazzo S, et al. (2006). Efficacy of homeopathic therapy in cancer treatment. European Journal of Cancer, 42: 282-289.	Cancer treatment side effects	Not stated
Mills, E., P. Wu, et al. (2005). "Complementary therapies for the treatment of HIV: in search of the evidence." International Journal of STD & AIDS **16**(6): 395-403.	HIV	(assume) adults
Owen, J.M. Green, B.N. (2004). Homeopathic treatment of headaches: A systematic review of the literature. Journal of Chiropractic Medicine, 3: 45-52.	Headaches	(assume) adults
Passalacqua, G., P. J. Bousquet, et al. (2006). "ARIA update: I--Systematic review of complementary and alternative medicine for	Rhinitis and asthma	Children and adults

rhinitis and asthma." J Allergy Clin Immunol **117**(5): 1054-1062.		
Perry, R., R. Terry, et al. (2010) A systematic review of homoeopathy for the treatment of fibromyalgia (Provisional abstract). Clinical Rheumatology 457-464	Fibromyalgia	Adults
Pilkington, K., G. Kirkwood, et al. (2005). "Homeopathy for depression: a systematic review of the research evidence." Homeopathy **94**(3): 153-163.	Depression	(assume) adults
Pilkington, K, Kirkwood, G, Rampes H, et al (2006). Homeopathy for anxiety and anxiety disorders: A systematic review of the research. Homeopathy, 95: 151-162.	Anxiety and related disorders	(assume) adults
Pittler MH & Ernst E (2005). Complementary therapies for reducing body weight: a systematic review. International Journal of Obesity (2005) 29, 1030–1038	Obesity reduction	(assume) adults
Porter, N. S., L. A. Jason, et al. (2010). "Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia." Journal of Alternative & Complementary Medicine **16**(3): 235-249.	Myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia	(assume) adults
Quinn F, Hughes C, Baxter GD (2006): Complementary and alternative medicine in the treatment of low back pain: A systematic review *Physical Therapy Reviews* **11**: 107–116	Low Back pain	Adults
Rada G, Capurro D, Pantoja T, Corbal·n J, Moreno G, Letelier Luz M, et al. (2010) Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database of Systematic Reviews	Hot Flushes	Adult women with a history of breast cancer
Roberts, M., W. Brodribb, et al. (2012). "Reducing the Pain: A Systematic Review of Postdischarge Analgesia Following Elective Orthopedic Surgery." Pain Medicine.	Post orthopaedic surgery pain	Adults
Sarris, J. and G. J. Byrne (2011). "A systematic review of insomnia and complementary medicine." Sleep Medicine Reviews **15**(2): 99-106.	Insomnia	Adults
Schneider, Klein, & Weiser (2005). "Treatment of vertigo with a homeopathic complex remedy compared with usual treatments. Arzneim.-Forsch./Drug Research 55(1): 23-29	Vertigo	Unable to assess
Seidl, M. M. and D. E. Stewart (1998). "Alternative treatments for menopausal symptoms. Systematic review of scientific and lay literature." Can Fam Physician **44**: 1299-1308.	Menopausal symptoms	Adult women
Shang, A. Huwiler-Mutener, K. Nartey, L. Juni, P. Dorig, S., Sterne, J.A. 2005. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo controlled trials of homoeopathy and allopathy. The Lancet, Vol. 366, pp. 726-732	Respiratory-tract infections Pollinosis and asthma Gynaecology and obstetrics Surgery and anaesthetics Gastroenterology Musculoskeletal disorders Neurology Other	Not stated
Simonart, T., C. Kabagabo, et al. (2011). "Homoeopathic remedies in dermatology: a systematic review of controlled clinical trials." British Journal of Dermatology **165**(4): 897-905.	Atopic eczema, leg ulcers, minor recurrent aphthous ulceration, radiodermatitis, seborrhoeic dermatitis, uraemic pruritus, warts, candidiasis	Children and adults
Smith, C.A. (2010). Homoeopathy for induction of labour (Cochrane Review). In: The Cochrane Library. Chichester, UK: John Wiley & Sons, Ltd. CD003399.	Induction of labour	Pregnant women due to deliver
Stevinson, C. and E. Ernst (2001). "Complementary/alternative therapies for premenstrual syndrome: a systematic review of randomized controlled trials." Am J Obstet Gynecol **185**(1): 227-235.	Premenstrual syndrome	Adolescent and adult women
van der Wouden, J. C., R. van der Sande, et al. (2009). "Interventions for cutaneous molluscum contagiosum." Cochrane database of	Dermatitis (cutaneous molluscum contagiosum)	Not stated

systematic reviews (Online)(4): CD004767 Vernon, H., C. S. McDermaid, et al. (1999). "Systematic review of randomized clinical trials of complementary/alternative therapies in the treatment of tension-type and cervicogenic headache." Complement Ther Med **7**(3): 142-155.	Tension-type and cervicogenic headache	Not stated

Interventions: In many of the reviews, the lack of detail was surprising, on the homeopathic interventions being tested. This lack of detail would constrain replication of the studies by other researchers, and limited the external generalisability of the effect of these interventions to other patient populations. It was not possible to determine, in many of the component studies, the nature or intent of the homeopathic interventions, as no details were given. Table A6.3 lists the included reviews and the homeopathic interventions reported in them.

Table 13 Details of homeopathic interventions reported in the included reviews

Study	Intervention
Alraek 2011	Homeopathy intervention not stated
Altanc 2007	Individualised or formulaeic homeopathic agents
Barnes 1997	Homeopathic remedies of <12C potency versus placebo; homeopathic remedies of >=12C potency versus placebo (combinations of *Opium* 15C, *Opium* 15C+, *Opium* 9C, *Raphanus Satinus* 7C, *Raphanus Satinus* 5C, *Arnica Montana* 9C+, *China regia* 5C)
Baranovsky 2009	Daily, flexibly dosed LM potencies. Homeopaths were permitted to change prescription after a homeopathic visit at 2 months.
Bellavite 2006a	Any type of homeopathic approach to address inadequacy of efficiency of the immune system in the rejection of an extraneous aggressor
Bellavite 2006b	*Galphimia glauca* (low dilutions/potencies) or classical individualised homeopathy or low-potency homeopathic complexes
Bellavite 2008	Classic individualised homeopathy, isopathy
Bellavite 2010	All forms of homeopathic therapy a) classical individualised homeopathy b) ailment-specific remedies and complexes c) isotherapy
Cooper 2010	Individualised *Rx* by Homeopath or Formulaic homeopathic remedies
Cucherat 2000	A preparation was considered to be homeopathic if the dilution was greater than 3C (one molecule of the original principle in 106 molecules of solvent) or if it was presented as homeopathic by the manufacturer
Dantas 2000	Homeopathy Medicine is a substance which is potentially toxic or pathogenic that was prepared according to the specifications of homeopathic pharmacopoeias (excluding herbal preparations and non-homeopathic medicines). This includes combination remedies and isopathy but excludes mixed preparations with non-homeopathic components
Davidson 2011	Individualised or formulaic
De Silva 2010	1. *Rhus toxicodendron* (6c potency) put up on 125mg lactose 2. *Arnica montana, Bryonia alba* and *R. toxicodendron* (all of 6c potency) based on a homeopathic consultation 3. Individually selected homeopathic remedy
De Silva 2011	1. *Rhus toxicodendron 12x, 6x, Causticum 12x, Lac Vaccinum 12x* 2. *Rhus toxicodendron 6x* 3. *Spiroflor*, which contains *Symphytum officinale, R. toxicodendron and Ledum palustre*
Ernst & Pittler 1998a	Homeopathic *Arnica*
Ernst 1998b	Various combinations of *Rhus Toxicodendron D4, Arnica, Arnica Montana D30, Arnica Montana 30C, Sarcolactic acid 30C*
Ernst 1999a	Individualised homeopathic remedies
Ernst 1999b	Classic, individualised homeopathic remedies vs conventional (allopathic) treatments
Ernst 2011	Homeopathic *Galphimia* glauca
Ernst 2011	Individualised or formulaic

Heirs 2009	individualised, clinical or formula homeopathy
Holdcraft 2004	*Rhus toxicodendron*
Huang 2011	No homeopathic interventions identified
Jorm 2004	Homeopathy (not specified)
Kessab 2011	Topical *Calendula* or *Traumeel S* (a proprietary complex homeopathic medicine)
Linde 1997	Classical, Complex, Isopathy, Clinical *low dilution = 10^{-5} to 10^{-12} mol/L* *medium dilution = 10^{-13} to 10^{-27} mol/L* *high dilution = <=10^{-27} mol/L* *mixed dilution*
Linde 1998	Individualised homeopathy
Long & Ernst 2001	Formulaic (injections, oral or topical)
McCarnie 2004	Homeopathically prepared remedies. Incl. classical homeopathy (tailored to an individual's symptoms) or isopathy (using a dilution of an agent that causes an allergy eg pollen)
McCarnie 2009	Homeopathically prepared medications
Milazzo 2006	Single or combined homeopathic interventions used as a sole or additional therapy
Mills 2005	Homeopathy (unstated) or Dronabinol (delta-9-tetrahydrocannabinol)
Owen 2004	Single dose, and individualised interventions
Passalacqua 2006	Generally Isopathy or individual homeopathic preparations
Perry 2010	Different homeopathic approaches
Pilkington 2005	All forms of homeopathy including individualised and complex
Pilkington 2006	All forms of homeopathy including individualised and complex
Pittler 2005	*Helianthustuberosus* D1 or *thyroidinum* 30cH
Porter 2010	All forms of alternative and complementary Rx
Quinn 2006	Spiroflor SRL compared to Cremor Capsici Compositus (CCC) (capsicum-based gel (herbal))
Rada 2010	Individualised homeopathy or single or combination homeopathic therapy (not specified)
Roberts 2012	Homeopathic *Arnica*
Sarris 2011	Different CAM approaches (incl homeopathy)
Schneider, Klein, & Weiser 2005	Vertigoheel compared with usual therapies (betahistine, Ginkgo biloba extract, dimenhydrinate)
Seidl 1998	*lachesis* (derived from South American bushmaster snake venom), *pulsatilla* (derived from the perennial windflower, Anemone pulsatilla), and *sepia* (derived from cuttlefish ink)
Simonart 2011	Individual, classical homeopathic approaches
Smith 2010	1. *Caulophyllum* 2. 5 homoeopathic therapies (not stated)
Stevinson 2001	Formulaeic dose
Van der Wouden 2012	*calcarea carbonica*
Vernon 1999	individualised homeopathic remedy

Comparators: Comparators were often not well described. Where information was available, they variably comprised inactive solutions or tablets that looked similar to the homeopathic intervention, but contained no homeopathic ingredients (such as un-medicated granules (usually lactose) or drops (alcohol diluted in water, or saline). The control intervention could also be another complementary medicine approach (acupuncture, relaxation, hydrotherapy, herbal medicines etc), a mainstream medical approach or no treatment at all.

d. CEBM Q4. We assessed the believability of the findings provided in the reviews using four component criteria.

Critical appraisal of the component primary studies: 86% of the reviews used a formal critical appraisal approach to assess the methodological quality of the component studies. The most common critical appraisal instruments were Jadad[8], Kleinen[9], Cochrane risk of bias approach[10], SIGN

[8] Jadad AR, Moore RA, Carrol D, et al. Assessing the quality of reports of randomised clinical trials: is blinding necessary?

checklist[11], GRADE[12], York/CASP[13], NHMRC hierarchy[14], CRDR[15], Oxford Quality Score (a specific version of the Jadad tool[5]) and van Tulder[16] Five studies used purpose-built instruments along the lines of the Cochrane approach to measurement of bias (reflecting elements such a 'good' sample size, randomisation procedures, blinding, sampling procedures etc).

The most common finding reported in the reviews was that the methodological quality of the component primary studies was poor, and this restricted the review authors' capacity to infer stronger findings from the review process. Irrespective of the critical appraisal instrument used by the review authors, average study quality approximated 50% of the possible critical appraisal scores.

Common criticisms of the methodological quality of component studies which were expressed by the authors of the systematic reviews were (in no order):

- differences identified at baseline but not adjusted for in analysis
- failure to apply intention to treat analysis
- small sample sizes (underpowered)
- no evidence of sample size calculations
- poor sampling frames (convenience or volunteer sampling)
- sample reference groups reflecting individuals who may or may not have had a belief in homeopathy (influencing the likely placebo effect)
- low quality trials tended to overestimate treatment effects
- inadequate blinding
- inadequate allocation concealment
- inadequate or unexplained methods of sequence generations in randomised studies
- lack of replication of treatment effects
- the need for independent replication of the homeopathic decision-making regarding the interventions
- the individual nature of homeopathic intervention was frequently undermined by the necessity of rigour of RCT design
- homeopathic intervention was not adequately described
- inadequate follow-up

Independence of decision-making: 76% reviews used independent reviewers for critical appraisal and data extraction, and had a formal process for resolving disputes.

Consort diagram: Only 14 of the reviews (26%) reported a consort diagram or study flowchart, describing the processes and outcomes of study inclusion/ exclusion.

Sensitivity analysis: Only two Category 1-3 reviews conducted some form of sensitivity analysis (comparing the findings of low and high quality trials, or using multivariate modelling procedures to test the effect on overall pooled data by the removal of lower quality studies, or studies with low

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Control Clin Trials 1996; 17: 1 ± 12.

[9] Kleijnen J, Knipschild P, ter Riet G. Clinical trials of homoeopathy. *Br Med J* 1991;302:316-23.

[10] http://smg.cochrane.org/whats-new (accessed May 7th 2012)

[11] http://www.sign.ac.uk/(accessed May 7th 2012)

[12] http://www.gradeworkinggroup.org/(accessed May 7th 2012)

[13] www.phru.nhs.uk/casp/casp.htm(accessed May 7th 2012)

[14] www.nhmrc.gov.au (accessed May 7th 2012)

[15] NHS Centre for Reviews and Dissemination (CRD). Undertaking Systematic Reviews of Research on Effectiveness, 2nd ed.York: CRD, 2001 Report Number 4.

[16] van Tulder MW, Assendelft WJJ, Koes BW, Bouter LM. Method guidelines for systematic reviews in the Cochrane Collaboration back review group for spinal disorders. *Spine* 1997;**22**:2323–30

sample sizes (to test for Type 1 errors). These studies were Barnes (1997) and Heirs (2009). Opportunities to conduct sensitivity analyses were limited by the nature of the data synthesis reported in the reviews (for instance there were only six reviews which attempted data pooling).

e. ***CEBM Q5.*** The results were dissimilar between the primary studies included in most of the reviews. This related to study quality, interventions, variability in outcome measures, study sample size and sampling frames, the number (and replication) of studies included in the reviews, and the number of subjects included in the studies. We found few examples of subgroup analysis within reviews, to identify groups of subjects who may have had different outcomes from others in the study. Table A6.4 reports on the included secondary evidence in this overview review, the number of included primary studies relevant to the review questions, the total number of participants relevant to the studies which answered the review questions and the study designs included in the reviews.

Table 14 Included systematic reviews with total number of component studies included in the review, total subject numbers (where available) and study design types.

		N. included studies relevant to homeopathic interventions	Total N subjects relevant to homeopathic intervention, or condition of interest, or both	RCT	CCT	Other exp	Obs	Case series
Alraek	2011	2	77	Y				
Altunc	2007	16	2562	Y				
Bagnell	2007	2	167	Y				
Barnes	1997	7	537	Y				
Baranowsky	2009	1	62	Y				
Bellavite	2006a	23	5026	Y	Y	Y		
Bellavite	2006b	27	2237	Y	Y	Y		
Bellavite	2008	40	4206	Y	Y	Y	Y	Y
Bellavite	2011	80	12249	Y	Y	Y	Y	Y
Cooper	2009	9	656	Y	Y	Y	Y	Y
Cucherat	1999	16	Not reported	Y				
Dantas	2000	53	Not reported	Y	Y	Y	Y	Y
Davidson	2011	25	1048	Y				
De Silva	2010	3	116	Y				
De Silva	2011	3	285	Y				
Ernst & Pittler	1998a	8	338	Y	Y			
Ernst	1998b	8	468	Y	Y			
Ernst	1999a	4	284	Y				
Ernst	1999b	6	607	Y	Y			
Ernst	2011	4	1324	Y				
Ernst	2011	6	263	Y				
Heirs	2009	4	196	Y	Y	Y	Y	Y
Holdcraft	2004	1	30	Y	Y	Y		
Huang	2011	24	2334	Y	Y			

Jorm	2004	2	Not reported	Y	Y	Y	Y	Y
Kassab	2011	8	664	Y				
Linde	1997	119	9277	Y	Y			
Linde	1998	31	1778	Y	Y			
Long&Ernst	2001	4	406	Y				
McCarnie	2009	0	0	Y	Y			
McCarnie	2004	6	556	Y				
Milazzo	2006	6	336	Y	Y			
Mills	2005	2	112	Y				
Owen	2004	6	362	Y			Y	
Passalacqua	2006	10	907	Y				
Pilkington	2005	9	1735	Y	Y	Y	Y	Y
Pilkington	2006	11	685	Y	Y	Y	Y	Y
Pittler	2005	2	377					
Perry	2010	4	163	Y				
Porter	2010	4	259	Y	Y			
Quinn	2005	1	161	Y				
Rada	2010	2	395	Y				
Roberts	2012	3	191	Y	Y			
Sarris	2011	0	0	Y	Y			
Schneider et al	2005	4	1388		Y			
Seidl	1998	5	Not reported	Y	Y	Y	Y	Y
Simonart	2011	12	Not reported	Y	Y			
Smith	2010	2	133	Y				
Stevinson	2001	1	10	Y	Y	Y		
Van Der Wouden	2012	1	103	Y				
Vernon	1999	1	98	Y				

Component studies: The total number of times that component (primary) studies were reported in the secondary evidence potentially-relevant to this review was 942. Whilst cross-checking the reports of the component studies in the systematic reviews for sample sizes, interventions and quality scores, it because apparent that many component studies had been used in more than one review. After summarising them, we identified 306 individual component studies which had been cited (and re-cited). The list of component primary studies cited in the potentially-relevant systematic reviews and meta-analyses, collated across the secondary evidence as a way of considering the potential for bias if the same study was cited multiple times, is provided as a separate file (see *Studies in SRs.xls).*

The component studies cited in the potentially-relevant reviews are listed in Appendix 6, with the number of times the study had been cited in the secondary evidence included in this review, the sample size of each study and the quality score (where available) expressed as a risk of bias (HR = high risk, MR = moderate risk, LR = low risk, U = unclear). Where no sample size or risk of bias is reported, this denotes the situation where this information was not provided in any of the systematic review(s) which cited the component study. No attempt was made to find the individual

study to verify this information. The systematic reviews which cite the component studies are also listed.

Discrepancies were frequently noted in the reporting of sample size and quality of the component studies, when one study was cited in more than one review. Some reviews only reported on the number of subjects in the active (homeopathic) arm, and others only reported on the number which completed the study, not the number which entered. Other reviews reported (appropriately) on the total number which entered the study (across all arms). The quality rankings given to the component studies also often differed, not so much (as we initially believed) through the use of different tools, rather different perspectives on assessing study quality. In approximately 15% component studies with two or more quality appraisals in different reviews, we could find the same study reported with High and with Low risk of bias. When there were discrepancies, we reported the poorest score. Discrepancies could only be identified when there were two or more systematic reviews which provided component study details (N, quality ratings). Thus there may well be errors in our recording of component study N and quality scores, where the study was cited only once. There was no attempt to go to each component study to verify the study details.

CEBM Q6. Synthesised information from the component studies was mostly reported qualitatively, in text, or occasionally in summary tables. This approach was largely taken because of non-homogeneity of included studies in terms of subjects, conditions and type of homeopathic intervention. Six reviews of clinical conditions attempted pooling and/ or meta-analysis (Barnes 1997, Heirs 2009, Kassab 2011, McCarnie 2008, Schneider 2005, Smith 2010).

This table suggests that only about 28% of the primary studies within the included systematic reviews had a low risk of bias. And conversely, as many as approximately 72% of primary studies were either medium or high risk of bias , or the authors could not attribute a score on the quality of the study .

Appendix 7. Authors and year of component studies, number of times cited (and in which systematic reviews), sample size (best estimate of total entering study) and quality measure

Table 15 Authors and year of component studies, number of times cited (and in which systematic reviews), sample size (best estimate of total entering study[17]) and Risk of Bias score[18]

Component studies	N times cited	N	Risk of bias	SRs in which study was cited					
Aabel 2000	4	74	LR	Bellavite 2006b	Grabia	Passalacqua	Shang		
Aabel 2001	4	51	LR	Bellavite 2006b	Bellavite 2011	Mathie	Shang		
Aabel et al 2000	4	66	LR	Bellavite 2006b	Grabia	Passalacqua	Bellavite 2011		
Adler 1999	2	119	HR	Bellavite 2006a	Bellavite 2011				
Albertini 1984	1	60	HR	Linde 1997					
Alibeu and Jobert 1990	5	40	HR	Altunc	Cucherat	Linde 1997	Pilkington 2006	Shang	
Ammerschlager et al. 2005	2	739	HR	Bellavite 2006a	Bellavite 2011				
Andrade et al 1991	5	77	LR	Bellavite 2011	Linde 1998	Grabia	Mathie	Shang	
Attena et al 1995	2	1595	MR	Grabia	Shang				
Aulagnier 1985	4	100	LR	Barnes	Linde 1997	Mathie	Shang		
Awdry 1996	6	125	MR	Alraek	Davidson	Linde 1998	Porter	Shang	Bagnell
Baker et al 2003	2	70	LR	Davidson	Pilkington 2006				
Bakshi 1990	1	120	HR	Linde 1998					
Balzarini et al 2000	6	66	LR	Grabia	Kassab	Mathie	Milazzo	Shang	Simonart
Bannerjee 1993	1	50	HR	Huang					
Barbach 1994	1	na	N/S	Seidl					
Beer 1999	2	40	HR	Shang	Smith				
Beer AM 1995	1	na	N/S	Mathie					
Bekkering 1993	1	10	MR	Linde 1997					
Bell IR , Lewis DA & Brooks 2004	5	62	LR	Baranowski	Davidson	de Silva	Perry	Porter	
Bignamini M 1987	1	na	N/S	Mathie					
Bignamini M 1991	2	31	HR	Linde 1997	Shang				
Bohmer and Ambrus 1992	5	102	LR	Ernst 2004	Grabia	Linde 1997	Mathie	Shang	

[17] This is an estimate, as many of the reviews reported different sample sizes.

[18] This is a general quality score as the systematic reviews reported different methods of quality scoring, thus the score has been recorded as Low, Medium or High risk, depending on the category each score fell into on the quality scale it was originally measured with.

Bonne et al 2003	2	44	MR	Davidson	Pilkington 2006				
Borders LR 1986	1	na	N/S	Mathie					
Bordes and Dorfman 1986	4	60	LR	Bellavite 2006a	Bellavite 2011	Mathie	Shang		
Bourgeois 1984	4	29	MR	Grabia	Kassab	Linde 1997	Shang		
Brewitt et al. 2000	1	77	HR	Ullman					
Brewitt et al. 2002	1	27	HR	Ullman					
Brigo 1991	6	120	HR	Ernst 1999	Linde 1998	Linde 1997	Mathie	Owen	Shang
Brinkhaus et al 2006	1	82	LR	Roberts					
Brydek 1999	1	na	N/S	Shang					
Campbell et al. 1990	2	28	LR	Bellavite 2006b	Bellavite 2011				
Campbell, A 1976	3	13	HR	Ernst & Pittler	Linde 1997	Mathie			
Carey 1986	2	40	N/S	Linde 1997	Shang				
Carlini et al . 1987	3	62	MR	Cooper	Ernst 2011 (sleep)	Linde 1998			
Casanova 1981	2	na	UR	Linde 1997	Shang				
Casanova & Gerard 1988	1	300	LR	Bellavite 2011					
Casanova & Gerard 1992	1	300	LR	Linde 1997					
Castelin 1979	1	10	HR	Barnes					
Castellsagu 1992	2	26	HR	Bellavite 2006b	Bellavite 2011				
Cavalcanti et.a l. 2003	1	28	MR	Simonart					
Chapman 1994	6	20	MR	Davidson	Linde 1997	Linde 1998	Mathie	Shang	Stevinson
Chapman 1997	1	20	LR	Linde 1998					
Chapman 1999	3	61	N/S	Davidson	Mathie	Shang			
Chevel 1984	2	50	MR	Barnes	Shang				
Chung 2007	1	62	HR	Huang					
Cialdella et al . 2001	5	96	UR	Cooper	Ernst 2011 (sleep)	Grabia	Jorm	Shang	
Ciotti 1983	1	21	HR	Huang					
Clover et al 1995	2	50	MR	Pilkington 2005	Pilkington 2006				
Colin 2006	2	147	HR	Bellavite 2006b	Bellavite 2011				
Connert and Maiwald 1991	3	26	HR	Bellavite 2006a	Bellavite 2008	Bellavite 2011			
Coudert 1981	2	186	HR	Cucherat	Linde 1997				
Cupalova 1988	1	50	HR	Huang					

Daub 2005	1	65	HR	Kassab							
Davidson et al 1997	2	12	LR	Pilkington 2005	Pilkington 2006						
De Lange de klerk 1994	6	330	MR	Altunc	Bellavite 2011	Linde 1997	Linde 1998	Mathie	Shang		
De Lange de klerk 1999	2	170 (children)	HR	Bellavite 2006a	Bellavite 2008						
Deifenbach et al 1997	2	209	HR	Mathie	Shang						
Dexpert 1987	2	55	LR	Linde 1997	Shang						
Dorfman 1992	2	80	LR	Grabia	Linde 1997						
Dorfman 1987	4	93	LR	Grabia	Linde 1997	Mathie	Smith 2010				
Dorfman 1988	2	39	HR	Mathie	Linde 1997						
Edwards 1985	1	48	UR	Huang							
Egger 1992	1	21	N/S	Huang							
Eizayaga 1996	2	na	UR	Bellavite 2006b	Bellavite 2011						
Ernst & Saradeth 1990	2	na	N/S	Mathie	Shang						
Feng 1999	1	51	UR	Huang							
Feng 2008	1	76	LR	Huang							
Ferley 1989	5	478	LR	Bellavite 2011	Cucherat	Linde 1997	Mathie	Shang			
Feuchter et al. 2001	1	97	N/S	Altunc							
Fingerhut 1990	1	na	MR	Linde 1997							
Fisher et al. 1980	1	60	LR	Linde 1998							
Fisher et al. 1989	8	30	MR	Bellavite 2011	Davidson	De Silva 2010	Holdcraft	Linde 1997	Mathie	Perry	Porter
Fisher P 1986	5	24	N/S	Bellavite 2011	Davidson	De Silva	Mathie	Perry	Porter		
Fisher P 2001	1	112	LR	Bellavite 2011	Mathie						
Frass, Dielacher et al. 2005	1	50	LR	Bellavite 2011							
Frei 2005	2	62	HR	Altunc	Davidson	Heirs					
Frei and Thurneysen 2001	3	230	LR	Bellavite 2006a	Bellavite 2011	Bellavite 2008					
Freitas 1995	6	62	LR	Altunc	Bellavite 2008	Linde 1997	Mathie	McCarney 2009a	Shang		
Frenkel and Hermoni 2002	2	86	LR	Bellavite 2006b	Bellavite 2011						
Friese et al. 1997	4	131	N/S	Bellavite 2006a	Bellavite 2011	Bellavite 2008	Shang				
Furuta et al. 2003	1	131	LR	Altunc							
Garrett et al. 1997	2	40	MR	Mathie	Simona						

					rt			
Gassinger et al. 1981	4	23	N/S	Bellavite 2006a	Bellavite 2011	Bellavite 2008	Mathie	
Gaucher 1994	1	53	HR	Linde 1998				
Gaus W 1993	2	44	N/S	Cucherat	Linde 1997			
Gaus W 1997	1	176	N/S	Mathie				
Gauthier JE 1983	1	na	MR	Linde 1997				
Gerhard I 1997	1	48	N/S	Mathie				
Gibson 1978	3	20	HR	Bellavite 2011	Ernst 1999b	Linde 1998		
Gibson 1980	5	241	MR	Bellavite 2011	Linde 1997	Linde 1998	Mathie	Shang
Gibson 1991	1	na	HR	Ernst & Pittler				
Gmunder 2002	1	89	N/S	Mathie				
Goosens Laekeman et al. 2009	1	na	N/S	Bellavite 2011				
GRECHO 1987	1	150	LR	Cucherat	Linde 1997			
Groupe de Recherches et d'Essais Cliniques en Hom!eopathie (GRECHO) 1989	1	300	LR	Barnes	Cucherat		Mathie	
Haidvogl,Riley et al. 2007	3	na	LR	Bellavite 2006b	Bellavite 2011	Bellavite 2008		
Hardy 1984	3	1557	N/S	Bellavite 2006a	Bellavite 2006b	Bellavite 2011		
Hariveau 1991	1	70	HR	Pilkington 2006				
Hariveau E 1987	2	87	N/S	Linde 1997	Mathie			
Harrison H 1999	1	na	N/S	Mathie				
Hart et al. 1997	3	73	LR	Grabia	Mathie	Shang		
Heilmann 1992	3	73	HR	Ernst 2004	Linde 1997	Shang		
Heilmann 1994	2	102	N/S	Bellavite 2006a	Bellavite 2011			
Heulluy 1985	2	60	HR	Pilkington 2005	Pilkington 2006			
Hildelbrandt 1983a	1	42	HR	Ernst 1998				
Hildelbrandt 1983b	1	na	HR	Ernst 1998				
Hidelbrandt 1983c	1	60	HR	Ernst 1998				
Hidelbrandt 1983d	1	na	HR	Ernst 1998				
Hidelbrandt 1984	2	na	HR	Ernst 1998	Ernst & Pittler 1998			
Hill N 1995	1	na	N/S	Mathie				
Hill N 1996	1	na	N/S	Mathie				

Hitzenberger G 1982	1	na	N/S	Mathie					
Hofmeyer GJ 1990	3	na	LR	Linde 1997	Mathie	Shang			
Hu 2008	1	244	UR	Huang					
Hui 2006	1	473	LR	Huang					
Jacobs & Springer 2001	6	75	LR	Altunc	Bellavite 2006a	Bellavite 2008	Bellavite 2011	Mathie	Shang
Jacobs 1994	5	75	LR	Altunc	Cucherat	Linde 1998	Mathie	Shang	
Jacobs 2000	3	173	LR	Altunc	Mathie	Shang			
Jacobs et al 1997	1	126	MR	Linde 1998					
Jacobs et al. 1993	5	34	UR	Altunc	Linde 1997	Linde 1998	Mathie	Shang	
Jacobs et al. 2005	6	342	LR	Altunc	Davidson	Heirs	Kassab	Milazzo	Rada
Janssen G 1992	2	83	LR	Ernst 1999b	Linde 1998				
Jawara 1997	3	38	LR	Ernst 1998	Mathie	Shang			
Jeffrey and Belcher 2002	2	na	UR	Roberts	Shang				
Jiang 2000	1	37	UR	Huang					
Kahan 1998	1	100	N/S	Huang					
Kainz et al. 1996	5	228	LR	Altunc	Linde 1998	Mathie	Shang	Simonart	
Katz et al 2005	1	11	HR	Pilkington 2005					
Kaziro 1984	2	77	MR	Linde 1997	Shang				
Keil 2008	1	11	N/S	Siomonart					
Kennedy 1971	1	128	MR	Linde 1997					
Khosroshaha 1989	1	73	UR	Huang					
Kim et al. 2005	3	73	LR	Bellavite 2006b	Bellavite 2011	Passalacqua			
Kirtland 1994	1	40	N/S	Davidson					
Kohler T 1991	2	176	MR	Linde 1997	Mathie				
Kolia -Adam et al. 2008	3	48	HR	Cooper	Davidson	Ernst 2011 (Hay fever)			
Kruse 1998	4	126	N/S	Bellavite 2006a	Bellavite 2008	Bellavite 2011	Ernst 1999b		
Kubista E 1986	1	126	HR	Linde 1997					
Kulkarni 1988	3	238	N/S	Kassab	Mathie	Milazzo			
Kumar	1	23	N/S	Davidson					
Kuzeff 1998	1	82	MR	Linde 1998					
La Pine et al 2006	2	72	N/S	Davidson	Ernst 2011				

					(sleep)			
Labrecque et al. 1992	4	34	LR	Linde 1997	Mathie	Shang	Simonar t	
Laister 2008	1	174	N/S	Davidso n				
Lamont 1997	3	39	HR	Heirs	Linde 1998	Mathie		
Langer 1995	1	45	LR	Seidl				
Lara- Marquez et al. 1997	3	na	N/S	Bellavit e 2006b	Bellavit e 2011	Linde 1998		
Leaman AM 1989	3	19	HR	Linde 1997	Mathie	Shang		
Leboeuf 1991	1	34	LR	Huang				
Lecoq 1985	5	171	MR	Bellavit e 2006a	Bellavit e 2011	Linde 1997	Mathie	Shang
Lecoyte T 1993	2	60	HR	Ernst 1999b	Linde 1998			
Lepaisant 1994	2	43	MR	Linde 1997	Shang			
Lewith et al. 2002	5	45	HR	Bellavit e 2006b	Bellavit e 2011	Mathie	McCarn ey 2009a	Passalac qua
Li et al. 2003	2	48	LR	Bellavit e 2006b	Bellavit e 2011			
LieÂvre 1992	2	12	N/S	Cuchera t	Linde 1997			
Lipman et al. 1999	1	103	N/S	Davidso n				
Livingston 1991	1	101	MR	Ernst & Pittler 1998				
Lockie A 1992	1	40	N/S	Seidl				
Lokken et al. 1994	1	na	LR	Linde 1998				
Lokken et al. 1995	2	67	LR	Linde 1997	Mathie			
MacEoin 1996	3	na	LR	Seidl				
Maiwald et al. 1988	3	na	HR	Bellavit e 2006a	Bellavit e 2011	Mathie		
Manchanda RK 1997	1	170	UR	van der Woude n				
Mao 1998	1	14	N/S	Haung				
Master 1987	3	111	HR	Linde 1997	Linde 1998	Shang		
Matusiewicz 1995	3	72	HR	Bellavit e 2006b	Bellavit e 2011	McCarn ey 2009a		
Matusiewicz and Wasniewski 1999	5	40	HR	Bellavit e 2006b	Bellavit e 2011	Ernst 2004	McCarn ey 2009a	Shang
Matusiewicz 1996	2	84	LR	Bellavit e 2006b	Bellavit e 2011			
Matusiewicz 1997	4	40	N/S	Bellavit e 2006b	Bellavit e 2011	Mathie	Shang	
Mayaux et al 1988	1	40	N/S	Linde 1997				

McCutcheon 1996	5	60	LR	Davidson	Jorm	Mathie	Pilkington 2006	Shang		
McDavid 1994	1	na	HR	Linde 1998						
McKendry 1975	1	77	HR	Huang						
Micciche et al. 1998	2	222	N/S	Bellavite 2006b	Bellavite 2011					
Michaud J 1981	1	70	HR	Linde 1997						
Mokkapatti 1992	3	306	HR	Altunc	Linde 1997	Shang				
Molvik D 1995	1	130	HR	Seidl						
Mosquera 1990	2	na	N/S	Bellavite 2006b	Bellavite 2011					
Mossinger P 1980	3	120	HR	Cucherat	Linde 1997	Shang				
Mossinger 1984	2	144	HR	Linde 1997	Shang					
Mossinger P 1976	3	14	N/S	Linde 1997	Mathie	Shang				
Mossinger P 1982	3	na	MR	Linde 1997	Mathie	Shang				
Mousavi et.al. 2009a	2	100	MR	Bellavite 2011	Simonart					
Mousavi et.al. 2009b	1	30	MR	Bellavite 2011						
Muscari- tomaioli 2001	1	100	MR	Owen						
Nahler 1998	1	53	N/S	Mathie						
Naude et al 2010	2	30	HR	Davidson	Ernst 2011 (sleep)					
Ngobese 2006	1	31	HR	Davidson						
Nolleveaux 1992	2	108	N/S	Bellavite 2006b	Bellavite 2011					
Nusche 1998	1	51	HR	Ernst 1999b						
Oberbaum 1998	1	27	LR	Milazzo						
Oberbaum et al. 2001	7	30	N/S	Bellavite 2006a	Bellavite 2011	Ernst 2004	Kassab	Mathie	Milazzo	Shang
Papp et al. 1998	4	372	LR	Bellavite 2011	Cucherat	Mathie	Shang			
Pinsent 1984	1	59	N/S	Ernst & Pittler 1998						
Pommier 2004	1	254	HR	Kassab						
Ponti 1986	2	93	UR	Linde 1997	Shang					
Rabe et al 2004	2	485	N/S	Bellavite 2006a	Bellavite 2011					
Radmayr 2001	1	40	N/S	Huang						
Rahlfs and Mossinger 1978	1	91	LR	Grabia						
Rahlfs et al 1976	3	72	HR	Linde 1997	Mathie	Shang				
Rahlfs VW 1979	3	119	HR	Linde 1997	Mathie	Shang				

Ramchandani 2010	1	30	N/S	Bellavite 2011					
Ramelet 2000	1	118	LR	Shang					
Rastogi 1999	2	100	LR	Mills	Ullman				
Reed 1994	1	57	LR	Huang					
Reilly 1986	5	162	LR	Cuchera t	Grabia	Mathie	Passalac qua	Shang	
Reilly 1994	7	28	LR	Bellavite 2011	Cucher at	Grabia	Linde 1997	Mathie	Passalac qua	Sha ng
Reilly DT 1985	3	39	HR	Linde 1997	Mathie	Shang			
Reilly et al. 1986	3	144	N/S	Bellavite 2006b	Cucher at	Linde 1997			
Relton et al. 2009	1	47	HR	Perry					
Riley et al . 2001	3	456	HR	Bellavite 2006a	Bellavite 2008	Bellavite 2011			
Ritter H 1966	2	147	UR	Linde 1997					
Riveron-Garrote et al. 1998	2	80	N/S	Bellavite 2006b	Bellavite 2011				
Ronen 1992	1	77	N/S	Huang					
Sacks 1994	1	83	N/S	Huang					
Saul 2005	1	37	MR	Davidson					
Savage RH 1977	3	na	MR	Linde 1997	Mathie	Shang			
Savage RH 1978	4	40	HR	Ernst & Pittler 1998	Linde 1997	Mathie	Shang		
Schirmer 2000	1	104	N/S	Bellavite 2011					
Schmidt 2002	2	211	N/S	Pittler	Shang				
Schmidt C 1996	1	na	MR	Mathie					
Schmiedel and Klien et al. 2006	1	397	N/S	Bellavite 2011					
Schneider, Klein, & Weiser 2005	4	Lack of data on included studies precludes reporting							
Schwab 1990	1	45	N/S	Linde 1998					
Seabrook 2005	1	74	HR	Huang 2011					
Shealey CN 1998	3	65	MR	de Silva 2011	Long	Mathie			
Shipley M 1983	5	36	MR	de Silva 2011	Grabia	Linde 1997	Long	Mathie	
Siebenwirth et. al. 2009	1	24	MR	Simonart					
Simpson et al 1998	1	28	MR	Grabia					
Singh et al. 1994	1	34	MR	Ullman					
Smith et al 2002	3	45	MR	Grabia	Mathie	Simonart			
Smolle et al 1998	1	67	N/S	Grabia					
Solanki and Gandhi 1995	2	68	N/S	Linde 1998	Shang				
Sprenger 1989	2	65	MR	Bellavite 2006a	Bellavite 2011				

Stam C 2001	2	161	LR	Mathie	Quinn			
Stanton 1981	1	40	LR	Pilkington 2006				
Steinsbekk et al. 2005A	3	169 (children)	LR	Bellavite 2006a	Bellavite 2008	Bellavite 2011		
Steinsbekk et al. 2005B	4	251 (children)	MR	Altunc	Bellavite 2006a	Bellavite 2008	Bellavite 2011	
Steinsbekk Lewitt et al. 2007	1	251 (208 children)	MR	Bellavite 2011				
Stevinson et al 2003	2	62	LR	Roberts	Shang			
Straumsheim 1997	3	141	HR	Ernst 1999	Linde 1998	Owen		
Straumsheim 2000	3	68	LR	Grabia	Mathie	Shang		
Strauss 2000	3	20	LR	Altunc	Davidson	Heirs		
Struwe 1993	1	12	HR	Mills				
Taylor and Reilly et al. 2000	5	50	LR	Bellavite 2006b	Bellavite 2011	Grabia	Mathie	Shang
Teitelbaum 2001	2	72	LR	Alraek	Porter			
Theil 1999	2	80	LR	Ernst 2004	Linde 1997			
Theil & Borho 1991	2	73	LR	Cucherat	Shang			
Thiel 1991	1	na	HR	Linde 1997				
Thompson 2005	4	53	HR	Kassab	Millazzo	Pilkington 2006	Rada	
Thompson and Reilly 2002	2	100	HR	Pilkington 2005	Pilkington 2006			
Thompson and Reilly 2003	2	45	N/S	Pilkington 2005	Pilkington 2006			
Traub 2000	1	47	LR	Davidson				
Trichard et al. 2005	3	499	N/S	Bellavite 2006a	Bellavite 2008	Bellavite 2011		
Tveiten 1991	2	36	LR	Ernst 1998	Ernst & Pittler 1998			
Tveiten 1998	2	na	LR	Mathie	Shang			
Ustianowski PA 1974	2	400	N/S	Linde 1997	Shang			
Vaithilingam 2005	1	28	LR	Davidson				
Valerin 1981	1	37	HR	Barnes				
Valero E 1981	2	na	LR	Linde 1997	Shang	Barnes 1997		
Van Erp 1996	3	129	N/S	Ernst 1999b	Linde 1998	Mathie		

Van haselen 2000	3	184	MR	de Silva 2011	Long	Mathie			
Vickers 1997	2	na	MR	Ernst 1998	Shang				
Vickers AJ 1998	2	na	HR	Mathie	Shang				
Villeda et al. 2001	1	26	N/S	Simonart					
Walach 1997	4	98	LR	Linde 1998	Mathie	Owen	Shang		
Walach 2001	1	18	HR	Owen					
Walach et al 1997	1	190	LR	Vernon					
Waldshutz and Klein 2008	1	409	MR	Cooper					
Wang 2009	1	70	LR	Huang					
Weatherley -Jones 2004	4	103	LR	Alraek	Davidson	Porter	Bagnell		
Wiesenauer 1998	1	107	N/S	Bellavite 2008	Bellavite 2011				
Wiesenauer & Gaus 1989	4	146	N/S	Bellavite 2006a	Bellavite 2008	Bellavite 2011	Mathie		
Wiesenauer and Gaus 1990	5	296	MR	Bellavite 2006b	Ernst 2011 (hay fever)	Linde 1997	Mathie	Shang	
Wiesenauer and Ludke 1987	2	176	HR	Bellavite 2006b	Bellavite 2011				
Wiesenauer and Ludke 1995	5	134	HR	Bellavite 2006b	Bellavite 2011	Ernst 2011 (hay fever)	Linde 1997	Mathie	
Wiesenauer & Gaus 1985	3	152	LR	Linde 1997	Mathie	Passalacqua			
Wiesenauer & Hausler 1983	2	164	LR	Linde 1997	Mathie				
Wiesenauer & Gaus 1991	3	39	N/S	Bellavite 2011	Linde 1997	Mathie			
Weiser and Clasen 1994	6	155	MR	Bellavite 2006a	Bellavite 2008	Bellavite 2011	Ernst 2004	Linde 1997	Shang
Weiser Gegenheimer et al 1999	4	155	N/S	Bellavite 2006b	Bellavite 2011	Mathie	Passalacqua		
Weiser M 1995	2	60	LR	Cuchera t	Mathie				
Weiser, Strasser et al. 1998	1	166	LR	Mathie					
Werk 1994	2	93	N/S	Pittler	Shang				
Werry 1965	2	123	N/S	Huang					
White 2002	1	60	LR	Grabia					
White et al. 2003	5	na	LR	Altunc	Bellavite 2006b	Bellavite 2011	McCarney 2009a	Passalacqua	
Whitmarsh 1993	2	207	HR	Cuchera t	Linde 1997				
Whitmarsh 1997	6	na	HR	Ernst 1999	Grabia	Linde 1998	Mathie	Owen	Shang
Wieser 1994	1	178	LR	Linde 1997					

Witt & Ludke 2009	2	19	HR	Bellavite 2011	Simonart			
Witt et al. 2005	1	113	HR	Bellavite 2006b				
Wolf 1992	2	73	N/S	Cooper	Ernst 2011 (sleep)			
Yakir 2001	4	na	HR	Davidson	Linde 1998	Mathie	Shang	
Zabolotnyi 2007	1	594	N/S	Bellavite 2011				
Zell J 1988	5	269	N/S	Cucherat	Ernst 2004	Linde 1997	Mathie	Shang
Zell J 1990	1	72	N/S	Linde 1997				
Zenner and Metelmann 1990	2	na	N/S	Bellavite 2006a	Bellavite 2011			
Zenner and Weiser 1999	1	269	HR	Pilkington 2005				
Zhu 2005	1	na	N/S	Huang				