# Effectiveness of Homeopathy for Clinical Conditions:

# Evaluation of the Evidence

## Overview Report

**Prepared for the NHMRC Homeopathy Working Committee**

**by Optum**

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# List of Abbreviations

| | |
|---|---|
| ADHD | Attention deficit/hyperactivity disorder |
| CAM | Complementary and alternative medicine |
| CFS | Chronic fatigue syndrome |
| CI | Confidence interval |
| DOMS | Delayed-onset muscle soreness |
| EMBASE | Excerpta Medica Database |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| GRECHO | Groupe de Rechereche et d'Essais Cliniques en Homeopathie |
| HIV | Human immunodeficiency virus |
| HTA | Health Technology Assessment |
| HWC | Homeopathy Working Committee |
| LOC | Level of confidence |
| MDQ | Menstrual Distress Questionnaire |
| NCC-WCH | National Collaborating Centre for Women's and Children's Health |
| NHMRC | National Health and Medical Research Council |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| OA | Osteoarthritis |
| PICO | Population, Intervention, Comparator, Outcome |
| PMS | Premenstrual syndrome |
| RCT | Randomised controlled trial |
| RR | Relative risk |
| SIGN | Scottish Intercollegiate Guidelines Network |
| URTI | Upper respiratory tract infection |
| WHO | World Health Organization |
| WMD | Weighted mean difference |

# Executive Summary


## Introduction

Homeopathy is a 200 year-old form of alternative medicine. The discipline is underpinned by the principle of *similitude* ('like cures like'); meaning substances that cause symptoms in a healthy person have the ability to treat an ill person with the same symptoms (when administered in homeopathic potencies). Homeopathy is also based on the belief that molecules in highly diluted substances retain a 'memory' of the original substance. Specifically, homeopathic remedies are repeatedly diluted and agitated in a process known as '*potentisation*' or '*dynamisation*'.

Homeopathy is included in numerous publicly funded health care systems around the world. It is therefore essential that clinical evidence is regularly reviewed and that the outcomes of these reviews are provided in a format that can (i) facilitate decision-making for policy makers, and (ii) assist the community in making informed decisions about their healthcare. In Australia, the National Health and Medical Research Council (NHMRC) has a statutory responsibility to provide advice on health matters and has identified "claiming benefits for human health not based on evidence" as a major health issue. There have been conflicting reports on the effectiveness of homeopathy; therefore, NHMRC decided to review the literature addressing the effectiveness of homeopathy for any clinical condition.

## Objective

The objective of this review is to summarise the evidence from systematic reviews regarding the effectiveness of homeopathy as a treatment for any clinical condition in humans.

## Methodology

The methodology used to conduct the review was based on that described in Chapter 22 of the *Cochrane Handbook of Systematic Reviews of Interventions.* Literature searches were performed in EMBASE.com (EMBASE and Medline databases), the Cochrane Library, PubMed, and PubMed Health to identify all relevant systematic reviews of controlled clinical trials of homeopathy in humans. From each included systematic review, data was extracted from the individual studies included in the review by a single reviewer and checked by a second reviewer. In addition, the quality of each included systematic review was assessed using the AMSTAR measurement tool by a single reviewer and checked by a second reviewer. The overall conclusion of the systematic review authors was also recorded. The evidence for each clinical condition was summarised and evidence statements were formulated after consultation and agreement with the Homeopathy Working Committee (HWC) of the NHMRC.

## Results

A total of 57 systematic reviews were identified that met the criteria for inclusion within this Overview Report. The relevant reviews tended to have one of three main objectives (i) to review a variety of complementary and alternative medicines (CAM), including homeopathy, for the treatment of a particular clinical condition or specific clinical area, (ii) to review homeopathy for the treatment of one clinical condition, or (iii) to review homeopathy for the treatment of a variety of clinical conditions. The reviews examined the evidence for a total of 68 clinical conditions and included seven clinical conditions for which no relevant primary studies were identified. Of the remaining 61 clinical conditions, the total number of participants included in the trial(s) was less than 150 for 36 of the clinical conditions examined. The total number of participants included in the

trial(s) was between 150 and 499 for 15 clinical conditions. The evidence base for 10 clinical conditions collectively comprised 500 or more participants. There were 31 clinical conditions for which only one Level II or Level III-2 study was identified.

In rating the body of evidence, the overall size, quality and precision of the evidence was considered and a level of confidence (LOC) was assigned to the body of evidence for each clinical condition. Overall, there was no condition for which there was a high LOC in the body of evidence. One condition was associated with a moderate LOC and four conditions were associated with a moderate-low LOC. Fifty-six clinical conditions were associated with a low or very low LOC (14 conditions with a low LOC; 11 conditions with a low-very low LOC; 31 conditions with a very low LOC). The remaining seven clinical conditions could not be assigned a LOC as there were no relevant primary studies identified.

### Discussion

The quality and comprehensiveness of the systematic reviews included in this Overview Report were limited by the inclusion of many poorly designed, conducted and reported primary studies. Importantly, most of the primary studies were small in size and likely to be insufficiently powered to detect a statistically significant outcome. Also, this Overview Report was reliant upon the reporting within the included systematic reviews, which was not always high quality. In addition, several systematic reviews did not provide specific conclusions relating to each clinical condition included in the review.

### Conclusion

There is a paucity of good-quality studies of sufficient size that examine the effectiveness of homeopathy as a treatment for any clinical condition in humans. The available evidence is not compelling and fails to demonstrate that homeopathy is an effective treatment for any of the reported clinical conditions in humans.

# 1 Background

Homeopathy is a form of complementary and alternative medicine (CAM) that is commonly used to treat or manage a wide variety of clinical conditions. Developed by Samuel Christian Hahnemann in the late 18th century, homeopathy is founded on two fundamental principles: similitude ('like cures like') and potentisation (or 'dynamisation'), whereby a substance is repeatedly diluted and agitated ('succussion'). The principle of similitude is known as '*similia similibus curantur'* and 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). 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 to be more active. The serial dilution of various animal, plant, mineral or synthetic substances to create a homeopathic remedy often occurs to a point at which it is highly unlikely that a single molecule of the original substance remains (Ernst and Barnes, 1998). The principle of potentisation is based on the belief that even though it is highly diluted, the solvent retains a 'memory' of the original substance.

Globally, homeopathy is one of the most extensively used forms of CAM (Linde et al, 1997) and is included in numerous publicly funded health care systems around the world. In Australia, herbal products, vitamins, minerals and nutritional supplements, some aromatherapy products and certain homeopathic products are regulated as complementary medicines under the *Therapeutic Goods Act 1989* by the Therapeutic Goods Administration (TGA). Homoeopathic preparations are currently exempt from inclusion on the Australian Register of Therapeutic Goods (ARTG) prior to supply, providing they contain ingredients more dilute than a 1,000 fold dilution of a mother tincture, do not contain substances of human origin or certain animal parts, and do not make therapeutic claims that refer to serious conditions or diseases.

It is estimated that Australians spent US $7.3 million dollars on homeopathic medicines in 2008 (WHO, 2009). Despite its widespread use, homeopathy remains highly controversial due to a large discordance between its underlying principles and those of biomedical science (Davidson et al, 2011). Still, homeopathy is often adopted as a treatment strategy, particularly by patients with difficult-to-treat conditions who are frustrated with conventional therapeutic options or their side effects.

Given the prevalence of its use, there is a strong incentive for policy makers and consumers to understand the existing evidence base for homeopathy but consensus across various government reports and systematic reviews has not been reached. For example, in 2009 the UK House of Commons Science and Technology Committee released a report entitled *Evidence Check 2: Homeopathy*, in which they argued "there has been enough testing of homeopathy and plenty of evidence showing that it is not efficacious" and surmised that "systematic reviews and meta-analyses conclusively demonstrate that homeopathic products perform no better than placebo" (House of Commons Science and Technology Committee, 2009). Overall, the report recommended that the National Health Service (NHS) stop funding homeopathy. However, the report has been criticised for inaccurately representing the findings of several key systematic reviews and overstating the findings of reviews or meta-analyses that found no effect for homeopathy (British Homeopathic Association, 2010).

In contrast to the findings of the UK report, a Swiss Health Technology Assessment (HTA) report in Homeopathy (published in English in February, 2012) concluded that homeopathy is a "valuable addition to the conventional medical landscape" (Bornhöft and Matthiessen, 2012). However, recent reviews of the Swiss report have suggested that it is "scientifically, logically and ethically flawed", "misinterprets studies previously exposed as weak" and "attempts to discredit randomised controlled trials as the gold standard of evidence" (Shaw, 2012).

In view of the inconsistency among published reviews, as well as the fact that neither of the above reviews addressed homeopathy in the Australian context, the National Health and Medical Research Council (NHMRC) recognised that an updated systematic review of systematic reviews (an overview) on this topic was needed to critically appraise and summarise the evidence on homeopathy. As part of this decision, NHMRC established the Homeopathy Working Committee (HWC), which comprises experts in evidence-based medicine and CAM. NHMRC contracted Health Technology Analysts Pty Ltd (the evidence reviewer, trading as Optum) to conduct an overview that would examine the effectiveness of homeopathy for the specific treatment of any clinical condition in humans, including treating the clinical side effects of another treatment or intervention. NHMRC is also evaluating and considering published guidelines, other government reports and evidence submitted to the NHMRC.

This Overview Report provides a comprehensive description of the methods used to assess the evidence and includes a summary of the findings of the systematic review(s) and an evidence statement for each clinical condition.

## 1.1 The purpose of this overview

It is important that accurate information regarding the effectiveness of available healthcare options is provided to the community so they can make informed decisions underpinned by the best available evidence. A major function of NHMRC under the *National Health and Medical Research Council Act 1992* is to inquire into and advise the community on matters relating to the improvement of health and treatment of disease (section 7(1)(a)). A recurring theme in the National Health and Medical Research Council Strategic Plan 2013-2015 is the importance of health advice and care that is evidence-based.

The findings of this homeopathy review will inform the development of an NHMRC Information Paper and Position Statement on homeopathy which will be made available to the Australian community to assist people in making informed health care choices (Figure 1).

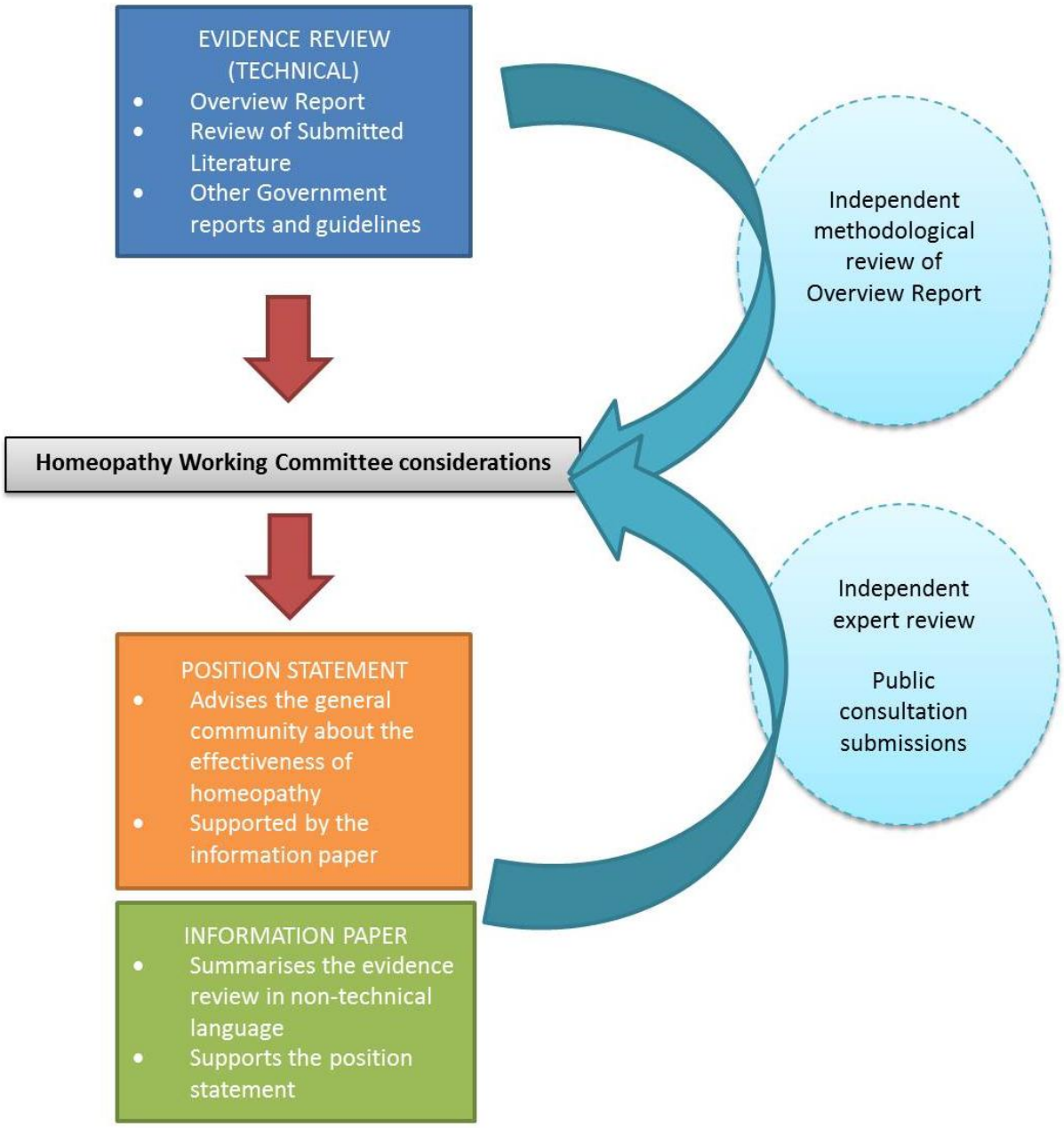


**Figure 1 Flow chart outlining the purpose of the Overview Report in the context of the broader project**

# 2 Objective

The objective of this overview is to summarise the evidence from systematic reviews regarding the effectiveness of homeopathy as a treatment for any clinical condition in humans.

In considering the effectiveness of homeopathy for this review, the HWC determined the following uses are also within scope (i) homeopathy used to treat the side effects of another treatment/intervention; and (ii) homeopathy used in conjunction with another treatment/intervention, where the design of the study does not confound the results (i.e. where the specific effect of homeopathy can be determined). For example, studies that examined *homeopathy plus other intervention* versus *other intervention* were included. The use of homeopathy as a preventative/prophylactic intervention was considered out of scope. In addition, the report did not include studies that exclusively examined safety or homeopathic aggravations, defined as a temporary worsening of existing symptoms following the administration of a homeopathic remedy (Grabia and Ernst, 2003); however safety results reported in otherwise included studies were presented in the report.

# 3 Overview methodology

Prior to conducting the evidence evaluation of the effectiveness of homeopathy for the treatment of any clinical condition in humans, a research protocol was developed through active consultation between the members of the HWC and the evidence review team. This research protocol specified the methodology to be used in the review and was approved by NHMRC before the review commenced. The methods used were derived from Chapter 22 of the *Cochrane Handbook of Systematic Reviews of Interventions*, which is designed to compile evidence from multiple systematic reviews into a single document. This overview does not aim to repeat the searches of the systematic reviews, or repeat the assessments of eligibility or risk of bias conducted by the included systematic reviews.

This section outlines:

- The primary clinical research question used to define the systematic evidence review
- The literature search strategies used to identify studies relevant to the primary clinical research question
- The study eligibility criteria used to determine the inclusion or exclusion of studies for this overview
- A description of the quality assessment and critical appraisal process and the data extraction forms used to capture information from the systematic reviews
- A description of the process used to assess the body of evidence relative to the primary clinical research question, including the development of evidence summaries and evidence statements
- A brief description of how comments from the independent methodological review have been addressed

## 3.1 Research question development

The clinical research question for the overview was structured and scoped according to the PICO criteria (Population, Intervention, Comparator, Outcomes). Use of the PICO framework facilitates the systematic review process as it improves conceptual clarity of the clinical problem, allows more complex search strategies, results in more precise search results, and allows evidence to be selected appropriately.

One primary clinical research question was developed for the overview:

1. For patients with a specific clinical condition, is homeopathy an effective treatment, compared with no homeopathy/other treatments?

The agreed PICO criteria for the primary clinical research question are detailed in Table 1.

**Table 1 PICO criteria for the primary clinical research question developed for the overview**

| **For patients with a specific clinical condition, is homeopathy an effective treatment, compared with no homeopathy/other treatments?** | | | | |
|---|---|---|---|---|
| **Population** | **Intervention** | **Comparator** | **Outcomes** | **Other systematic review considerations** |
| People with any clinical condition<br><br>Stratified by:<br>• Age (adults; children or adolescents)<br>• Indigenous/non-indigenous | (1) Homeopathy for the treatment of any clinical condition<br>(2) Homeopathy for the treatment of clinical side effects of another treatment or intervention<br>(3) Homeopathy used in conjunction with another intervention, where the specific effects of homeopathy can be determined<br><br>Stratified by practitioner prescribed and self-prescribed where applicable | • No homeopathy<br>• Standard or usual care<br>• Any other active treatment | Any clinical outcome<br><br>Adverse events[a] | Limits:<br>• Search period: January 1997-3 January 2013<br>• Full length publications only<br>• English only publications[b] |

[a] Adverse events were only considered if they were included within a systematic review that also considered effectiveness.

[b] Studies were excluded if they were not published in the English language. Non-English publications that otherwise fulfilled the eligibility criteria were brought to the attention of the HWC, noted and excluded.

### 3.1.1 Description of conditions examined

The HWC agreed that a 'clinical condition' is defined as a stage in the history of a pathologic condition that begins with anatomic or physiologic changes that are sufficient to produce recognisable signs and/or symptoms of a disease. For the purpose of this overview, 'any clinical condition' also included the clinical side effects of another treatment or intervention. The literature search was not limited by population, so all potentially relevant clinical conditions could be

identified. Where there was ambiguity about what constitutes a clinical condition, this was clarified through consultation with the HWC.

To maximise the generalisability and applicability of the review findings, the evidence evaluation included any clinical condition for which there was at least one systematic review that searched for prospectively designed and controlled studies conducted in humans.

### 3.1.2 Description of the interventions examined

For the purposes of this overview, the HWC agreed that 'homeopathy' is defined as an alternative medical system based on two central hypotheses ('similitude' and 'potentisation'), as described by the National Center for Complementary and Alternative Medicine (NCCAM, National Institutes of Health, United States). There are two major homeopathic approaches to treatment, both of which were included for this review. The traditional approach is known as *individualised homeopathy* in which a single homeopathic medicine is selected and prescribed on the basis of all of a patient's symptoms. Another approach is *clinical homeopathy* in which one or more homeopathic medicines are used for standard clinical situations or conventional diagnoses and are prescribed based on the presenting disease state rather than the totality of symptoms. It is not uncommon for different people with the same condition to receive different treatments.

Homeopathic products are derived from substances that come from plants, minerals, or animals and can come in different oral (by mouth) or topical (on the skin) forms. Remedies are often formulated as sugar (soft) pellets to be placed under the tongue; but may also be in other forms, such as hard tablets, liquids, ointments, sprays and creams. The homeopathic products are prescribed in either low dilutions, where the original substance is physically present, or in high dilutions, in which material quantities of the original substance are unlikely to be present.

### 3.1.3 Description of the comparators examined

The comparators for this evidence evaluation are no homeopathy, standard or usual care, or any other active treatment. Where active comparators were reported, their appropriateness was not assessed by the evidence reviewer. The appropriateness of active comparators was also generally not reported or commented on in the included systematic reviews.

### 3.1.4 Description of the outcomes examined

Due to the broad nature of the overview and the inclusion of any clinical condition, the review was not limited to any particular outcome provided that the outcome was related to the effectiveness of homeopathy.The HWC agreed that 'effectiveness' is defined as a statistically significant improvement in a clinically relevant outcome. Clinically relevant outcomes varied depending on the clinical condition being considered. The literature search was not limited by outcome, so all potentially relevant outcomes could be identified.

## 3.2 Literature searches

A systematic literature search was conducted for the primary clinical research question. According to the NHMRC standards for evidence review, Level I evidence refers to a systematic review of Level II studies and is considered to be the highest level of evidence for intervention and screening intervention questions. Level II evidence refers to randomised controlled trials (RCTs) (Table 2). The current systematic review, however, is intended to identify all systematic reviews of prospectively designed and controlled studies (i.e. Level II, Level III-1 and some types of Level III-2 studies). Thus,

for the purposes of this review, systematic reviews were eligible if they contained one or more of the following study types: RCT, pseudo-randomised controlled trial, non-randomised controlled trial or prospective cohort study. Furthermore, if a systematic review identified no studies for a particular clinical condition, this information was included in the evidence review.

**Table 2 NHMRC levels of evidence hierarchy**

| Level | Intervention[b] |
|---|---|
| I[a] | A systematic review of Level II studies |
| II | A randomised controlled trial |
| III-1 | A pseudo-randomised controlled trial<br>(i.e. alternate allocation or some other method) |
| III-2 | A comparative study with concurrent controls:<br>• Non-randomised, experimental trial[c]<br>• Cohort study<br>• Case-control study<br>• Interrupted time series with a control group |
| III-3 | A comparative study without concurrent controls:<br>• Historical control study<br>• Two or more single arm study[d]<br>• Interrupted time series without a parallel control group |
| IV | Case series with either post-test or pre-test/post-test outcomes |

Source: Merlin T et al (2009)

[a] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of Level II evidence. Systematic reviews of Level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

[b] Definitions of these study designs are provided on pages 7–8 of the NHMRC toolkit, How to use the evidence: assessment and application of scientific evidence (NHMRC 2000).

[c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs. B and B vs. C, to determine A vs. C).

[d] Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilise A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

The literature search strategies used to identify publications relevant to the primary clinical research question are shown in Table 3. The literature searches were conducted using EMBASE.com (which searches EMBASE and Medline databases concurrently), the Cochrane Library, PubMed and PubMed Health. After reviewing the initially retrieved citations, a manual search of the reference lists of included papers was also performed to identify other potential reviews that may have met the criteria for inclusion in this overview, but were missed by the initial search strategy.

**Table 3 Literature search strategy for the systematic review of systematic reviews**

| Database | # | Search terms | Citations retrieved | Total number of citations |
|---|---|---|---|---|
| Medline and EMBASE (using EMBASE.com interface)[a]<br><br>Search date:<br>3 January 2013 | #1 | homeop* OR homoeop* OR homöop* OR omeop* OR 'homeopathy'/exp | 7846 | 436 |
| | #2 | 'meta analysis'/exp OR 'meta analysis' OR 'systematic review'/exp OR 'systematic review' OR 'pooled analysis' OR ('review'/exp OR 'review' AND (systemat* OR pool*)) | 172,931 | |
| | #3 | #1 AND #2 | 436 | |
| PubMed<br><br>Search date:<br>3 January 2013 | #1 | ((review OR meta-analysis[Publication Type]) OR (systematic review OR meta analysis OR pooled analysis[Title/Abstract])) AND (homeopath* OR homoeopath*[Title/Abstract] | 711 | 711 |
| PubMed Health<br><br>Search date:<br>10 January 2013 | #1 | homeopath* OR homoeopath* | 169 | 169 |
| Cochrane Library (systematic reviews, other reviews and health technology assessments)<br><br>Search date:<br>3 January 2013 | #1 | Title/abstract/keyword: homeop* or homoeop* | 50 | 50 |
| Citations identified through manual check of reference lists | | | 1 | 1 |
| Total number of citations identified | | | | 1367 |

[a] Records are included in EMBASE.com as soon as the citation and abstract is available from the publisher. Although the full indexing is not yet available, In-Process records are enriched with index terms automatically generated from title and abstract. In some cases In-Process records themselves replace Articles in Press.

### Aboriginal and Torres Strait Islander peoples

The review of evidence relating to the effectiveness of homeopathy did not specifically search for, or limit, the retrieval of articles to studies that included Aboriginal and Torres Strait Islander peoples. However, the evidence reviewers did not identify any papers that addressed these populations for specific consideration by the HWC.

The evidence reviewer notes that no relevant socioeconomic literature pertaining to Aboriginal and Torres Strait Islander peoples was identified in the literature searches for the systematic evidence review.

## 3.3 Study eligibility

The inclusion of studies identified through the literature search for the primary clinical research question was based on whether or not the pre-specified elements of the PICO criteria were met. All citations identified in the literature searches described in Table 3 were assessed by one reviewer based on information in the publication title and, where available, the abstract. Relevant publications were retrieved and reviewed in full text before a final decision was made on their inclusion or exclusion for the systematic review.

Consistent with the PICO criteria for the systematic review (Table 1), the following *a priori* exclusion criteria were applied to the citations retrieved through the literature search:

- Duplicate citation
- *Wrong publication type.* Studies that were not systematic reviews or meta-analyses were excluded. Editorials, comments, book chapters, animal studies, correspondence, and news items were excluded. Studies were also excluded if they were not reported in full (e.g. research or systematic review protocols, conference proceedings, articles published in abstract form)
- *Wrong intervention*. Studies that did not investigate the effect of homeopathy were excluded
- *Wrong outcomes*. Studies that did not include outcomes relevant to the primary research question were excluded
- Study not published in the English language

## 3.4 Data extraction

Standardised data extraction forms and evidence summary tables were used to capture information relevant to the systematic review of the effectiveness of homeopathy in accordance with NHMRC standards (NHMRC, 2007). Extracted information included:

- General study details (citation, study design, evidence level, country and setting)
- Affiliations/sources of funds for each of the included studies
- Internal and external validity considerations
- Participant details, including key demographic characteristics
- Primary, secondary and other study outcome results

The data were extracted by a single reviewer and checked by a second reviewer. Data extraction was completed only for systematic reviews that received a 'yes' rating for questions 3 and 7 of the AMSTAR measurement tool (Shea et al, 2007). Systematic reviews that received a 'yes' rating in question 3 but did not identify any included studies and therefore could not have answered yes to question 7 were also included. Data extraction forms for all included studies are presented in Appendix A.

## 3.5 Critical appraisal

Systematic reviews identified for inclusion from the literature search were critically appraised and evaluated based on the quality assessment questions included in the AMSTAR measurement tool kit, see Appendix B (Shea et al, 2007). The quality assessment was performed by a single reviewer and checked by a second reviewer. The quality assessment forms for the included reviews are presented in Appendix A.

The systematic reviews were assigned scores (maximum of 11/11) based on the AMSTAR measurement toolkit. When one or more of the AMSTAR items were not applicable to a particular systematic review, the denominator was reduced to reflect the number of relevant criteria. For example, if the systematic review did not conduct a meta-analysis the item pertaining to the

appropriate pooling of results was not applicable and the systematic review was given a score out of 10. Similarly, if a systematic review did not identify any primary studies for the clinical condition of interest the systematic review was given a score out of 5. For the purposes of the evidence statements, those reviews that identified primary studies were also assigned a quality rating (poor, medium, good) based on the AMSTAR score. There are no established thresholds for assigning descriptive quality ratings; however, for the purposes of this Overview Report, a score of 5 or less was considered 'poor', 6-8 'medium' and 9+ was considered a 'good' quality systematic review. The same thresholds were applied regardless of whether the denominator was 10 or 11.

## 3.6 Assessment of the body of evidence

### 3.6.1 Evidence summaries

Evidence summaries for each clinical condition included in this overview were developed by the evidence reviewer to provide details of the evidence base and outcomes, a discussion of the strengths and limitations of the included studies, the size of the studies, and a description of the totality of the evidence. Evidence summaries for some clinical conditions feature commentary in italicized text under the heading "Reviewer Comments". This aimed to highlight limitations of the body of evidence as noted by the evidence reviewer. For example, to note discrepancies between the quality score of a primary study as reported in different systematic reviews, to highlight studies that were carried out by the same research group, or to emphasise circumstances where a systematic review drew their overall conclusion based on lower levels of evidence than those considered in the Overview Report.

The following information was extracted from the studies included in each review into an evidence summary table: intervention/comparator treatment regimens, length of follow up, total sample size, outcomes examined, results, the quality of the primary study as reported in the systematic review, and overall conclusion of the authors. Issues that were faced by the evidence reviewer with the systematic reviews sourced include:

- Information on primary outcomes of the primary studies was often not reported in the systematic reviews
- Difficulty in ascertaining if different systematic reviews were reporting on the same outcome of a primary study
- It was unclear from many systematic reviews if the reported sample size of a primary study was the number of people randomised or the number of people who completed the study. Thus, different systematic reviews reported different sample sizes for the same primary study
- Variability in the reported quality of a primary study between systematic reviews.

Consequently, the evidence summary tables are presented according to the included systematic review and not by study outcomes.

Effect sizes and confidence intervals for all primary outcomes were provided in the evidence summary tables where possible. However, this was often not available and thus all reported outcomes are presented in this Overview Report. If the author of the systematic review stated that a statistically significant difference was found between the intervention and comparator, the relevant

box in the 'results as reported in the systematic review' column was shaded. This approach was adopted irrespective of the reporting of a p-value (<0.05). For the purposes of this Overview Report, "effectiveness" was defined as a statistically significant improvement in a clinically relevant outcome. The clinical significance (or the practical importance) of an outcome was not assessed by the evidence reviewer.

The quality of the included studies was also not assessed by the evidence reviewer as the primary studies were not retrieved. The methodological quality of the primary studies that are reported in the Overview Report are based on the scores assigned by the authors of the systematic reviews. The majority of systematic reviewers that assessed the quality of the included studies used the Jadad scoring system to rate quality. Further information about the classification of primary studies is provided in Appendix C.

Ideally, the evidence reviewer would have focused on a 'key' systematic review in each evidence summary. In some therapeutic areas, this approach is possible due to large evidence bases and rigorous meta-analyses. However, it was difficult to adopt that approach in this overview, as the systematic reviews were often of poor methodological quality, or reporting from poorly conducted trials.

### 3.6.2 Development of evidence statements

Evidence statements about the effectiveness of homeopathy as a treatment for each clinical condition were formulated by the evidence reviewer in consultation with the HWC. The evidence statements aim to advise members of the community about the effectiveness of homeopathy, to enable them to make informed decisions about their health care. The final wording of each evidence statement was approved by the HWC.

To ensure a consistent approach across all clinical conditions, a standard format for evidence statements was developed comprising three elements: (i) a description of the body of evidence; (ii) a level of confidence (LOC) rating for the body of evidence; (iii) a concluding statement that described the effectiveness of homeopathy as a treatment for a particular condition, compared with either placebo or other treatment(s). The full criteria for the development of evidence statements are outlined in Appendix C.

The formulation of recommendations was not within the scope of this overview.

## 3.7 Independent methodological review

The first draft of the Overview Report and Appendix A were reviewed by an independent referee (the methodological reviewer) to confirm that an appropriate and rigorous approach had been taken. Specifically, the methodological reviewers examined whether (i) the review followed the approach documented in the research protocol; (ii) the inclusion/exclusion criteria used for the selection of studies were clearly described and applied appropriately; (iii) the critical appraisal process was clearly described and applied appropriately; and (iv) the process by which the draft evidence statements were derived, including how the evidence was synthesised and interpreted, was appropriate and clear.

The methodological reviewer provided five key points and numerous specific recommendations that were intended to improve the transparency of the methods and the interpretation of the findings.

The findings of the methodological review were discussed at a meeting of the HWC on 11 July 2013. The Overview Report and Appendix A were modified in response to the recommendations of the methodological reviewer and additional appendixes, Appendix B and Appendix C, were added to the Overview Report. The evidence statements were also refined to reflect suggestions in the methodological review.

The methodological reviewer was provided with an updated version of the Overview Report and a response to their initial comments and concerns. The methodological reviewer then examined the changes and provided final comments and suggestions that were incorporated into the Overview Report on 9 September 2013.

## 3.8 Changes from the research protocol

During the evaluation of the evidence, several changes from the research protocol approved by NHMRC in December 2012 were made as follows:

- The literature search was conducted on 3 January 2013, and not December 2012 as reported in the research protocol. Consequently, articles published or otherwise made available after 3 January 2013 were not included in the evaluation of the evidence.
- Studies that were identified during the systematic review of Level I evidence were not assessed according to the NHMRC dimensions of evidence as planned in the research protocol. These dimensions were originally developed for use in assessing primary studies. It became apparent during the evidence review that they would not be appropriate for overviews, as study-level data was often incompletely reported in the systematic reviews (e.g. primary outcomes were often not specified, effect estimates and confidence intervals were rarely reported).
- Appendix A in the protocol (Table 1 in the Overview Report) has been updated. The research question now reflects the fact that data pertaining to adverse events were included in the overview if such information was found in a systematic review that also considered effectiveness. The other changes to the table were not significant in terms of content; the changes were made in order to facilitate a clearer understanding of the research question for the reader.
- The research protocol stated that “for each condition and outcome a summary of the identified evidence will be presented. This will include an evidence table with the details of the evidence and a discussion of the strengths and limitations of the included studies, the powering of the studies and a description of the totality of the evidence”. Additionally, the research protocol stated that the results will be presented by outcome.

  However, the included systematic reviews presented a wide array of outcomes which were often reported differently between systematic reviews. This made it difficult to ascertain whether outcomes that were reported differently between two or more systematic reviews were, in fact, referring to the same results. Consequently, the evidence summary tables have been presented according to systematic review and not by outcome. Each primary study that was identified by each systematic review is listed with the study details, meaning that some trials are listed numerous times within one evidence table. This change was necessitated due to incomplete reporting; it was very rare that one systematic review

reported all of the outcomes, results, and patient characteristics of an included study. Thus, all primary trial data is presented as it was reported in the systematic reviews.

- The research protocol stated that "the full quality checklist developed for this project, including a key to the three quality ratings (good, moderate, poor) is shown in Appendix C (of the research protocol)". This key was not provided in Appendix C of the protocol but is described in Section 3.6.2 of this Overview Report.
- The research protocol described a standard sentence format for the development of evidence statements. However, a different, new framework was developed by the evidence reviewer in conjunction with the HWC due to the incomplete reporting of the systematic reviews and the difficulty in ascertaining which results were the primary outcomes. Details of the new framework are provided in Section 3.6.2 of this Overview Report.
- The research protocol stated that a 'Process Report' would accompany the Overview Report and comprise most of the methodology. It was later decided by NHMRC that this information should be read in conjunction with the evidence evaluation and was thus integrated into the Overview Report.
- In Appendix A of the research protocol, footnote 'a' to the table states that "preference will be given to patient-relevant over surrogate outcomes". This was subsequently deleted as it was not applicable to this evidence evaluation.

# 4 Results of the overview

## 4.1 Results of the literature searches, data extraction and quality appraisal

A total of 1367 citations were identified by the evidence reviewer using the search strategy described in Section 3.2. An assessment of the 1367 titles and abstracts resulted in 183 potentially relevant studies that were published in English and assessed the effectiveness of homeopathy for the treatment of patients with a specific clinical condition, compared with no homeopathy/other treatments. Ten studies were brought to the attention of the HWC as they were not published in the English language. These studies were noted by the HWC and excluded. The full citation details for those publications are provided in Section 7.1.3. The application of the exclusion criteria, outlined in Section 3.3, to citations identified through the systematic literature searches is shown in Table 4.

Of the 183 studies that were reviewed in full text, 121 were excluded and are documented, with their reason for exclusion, in Section 7.1.2. Consequently, 60 systematic reviews were identified that fulfilled the initial inclusion criteria (Table 4).

**Table 4 Summary of citations retrieved**

| Literature search for systematic reviews | Total number of citations |
|---|---|
| Total number of citations identified | 1367 |
| Citations excluded after title/abstract review:<br>Duplicate citation<br>Wrong study type<br>Wrong intervention<br>Wrong outcomes<br>Not in English | <br>374<br>729<br>39<br>32<br>10 |
| Number of studies reviewed in full text | 183 |
| Studies excluded after full text review[a]<br>Wrong study type<br>Wrong intervention<br>Wrong outcomes<br>Superseded publication | <br>71<br>30<br>10<br>12 |
| Final number of eligible reviews | 60 |

[a] Studies excluded after full text review are documented, with their reasons for exclusion in Section 7.1.2

The quality of each of these 60 systematic reviews was assessed using the AMSTAR measurement toolkit (Appendix A). Three studies were subsequently excluded as they did not assess the quality of the included studies (question 7 of the AMSTAR measurement tool) and are listed in Table 5. This resulted in a final total of 57 systematic reviews that were appraised in this Overview Report, with full citation details presented in Section 7.1.1. Sources of funding and the declared interests of the authors in each included review are detailed in the corresponding data extraction form for the study (Appendix A).

**Table 5 Citation details for excluded studies that failed to meet 'essential' quality criteria[a]**

| |
|---|
| Jorm AF, Christensen H, Griffiths KM, Parslow RA, Rodgers B, Blewitt KA (2004) Effectiveness of complementary and self-help treatments for anxiety disorders. *Med J Aust* 181(7 SUPPL.):S29-S46. |
| Mathie RT (2003) The research evidence base for homeopathy: a fresh assessment of the literature. *Homeopathy* 92:84-91. |
| Seidl MM, Stewart DE (1998) Alternative treatments for menopausal symptoms. Systematic review of scientific and lay literature. *Can Fam Physician* 44:1299-308. |

[a] Studies that were excluded as they received a 'no' rating for questions 3 or 7 of the AMSTAR measurement tool

A total of 68 specific clinical conditions were assessed in the systematic reviews included in this overview and for the purposes of this report, were grouped into 15 broad therapeutic areas as shown in Table 6.

**Table 6 List of clinical conditions covered by the included systematic reviews**

| Therapeutic area | Clinical conditions | Number of systematic reviews | Number of unique studies | Number of participants |
|---|---|---|---|---|
| **Eye, ear and labyrinth disorders** | Children with otitis media | 3 | 4 | 365 |
| | Glaucoma | 1 | 0 | 0 |
| **Gastrointestinal disorders** | Children with constipation | 2 | 0 | 0 |
| | Children with diarrhoea | 4 | 4 | 544 |
| | Irritable bowel syndrome | 2 | 1 | 23 |
| | Postoperative ileus | 3 | 5 | 1095 |
| | Proctocolitis | 1 | 1 | 20 |
| **Genitourinary disorders** | Nocturnal enuresis | 1 | 0 | 0 |
| | Men with lower urinary tract symptoms | 1 | 0 | 0 |
| **Infections and infestations** | Amebiasis and giardiasis | 1 | 1 | 34 |
| | Cholera | 1 | 1 | 44 |
| | Human immunodeficiency virus (HIV) | 1 | 2 | 112 |
| | Influenza-like illness | 3 | 4 | 1259 |
| | Malaria | 1 | 1 | 74 |
| | Recurrent vulvovaginal candidiasis | 1 | 1 | 150 |
| **Injury, trauma and postoperative disorders** | Acute ankle sprains | 1 | 1 | 69 |
| | Acute trauma | 1 | 1 | 20 |
| | Mild traumatic brain injury | 2 | 1 | 61 |

| Therapeutic area | Clinical conditions | Number of systematic reviews | Number of unique studies | Number of participants |
|---|---|---|---|---|
| | Postoperative pain-agitation syndrome | 2 | 1 | 50 |
| **Musculoskeletal and connective tissue disorders** | Ankylosing spondylitis | 1 | 1 | 104 |
| | Chronic polyarthritis | 1 | 1 | 111 |
| | Delayed-onset muscle soreness | 2 | 8 | 315 |
| | Fibromyalgia | 7 | 4 | 163 |
| | Knee joint haematoma | 1 | 1 | 80 |
| | Osteoarthritis | 3 | 5 | 998 |
| | Rheumatoid arthritis | 3 | 5 | 573 |
| **Neurological** | Broca's aphasia in people who have had a stroke | 1 | 1 | 36 |
| | Stroke | 1 | 1 | 40 |
| | Migraine and headache | 4 | 4 | 295 |
| **Pregnancy and childbirth** | Dystocia | 1 | 1 | 34 |
| | Induction of labour or reducing duration of labour | 1 | 2 | 133 |
| **Psychiatric and behavioural disorders** | Children with attention deficit/hyperactivity disorder | 4 | 4 | 170 |
| | Anxiety or stress-related conditions | 2 | 11 | 581 |
| | Personality disorder | 1 | 0 | 0 |
| | Dementia | 1 | 0 | 0 |
| | Depression | 1 | 2 | 34 |
| | Heroin addiction | 1 | 1 | 60 |
| **Reproductive system and breast disorders** | Premenstrual syndrome | 3 | 5 | 103 |
| | Lactation in postpartum women who elect not to breastfeed | 1 | 1 | 71 |
| **Respiratory and allergic** | Adenoid vegetation in children | 1 | 2 | 137 |
| | Allergic rhinitis | 5 | 16 | 1831 |
| | Asthma | 6 | 8 | 675 |
| | Bronchitis | 1 | 1 | 258 |

| Therapeutic area | Clinical conditions | Number of systematic reviews | Number of unique studies | Number of participants |
|---|---|---|---|---|
| | Cough | 1 | 1 | 60 |
| | Oral lichen planus | 1 | 1 | 30 |
| | Non-allergic rhinitis | 1 | 4 | 1359 |
| | Sinusitis | 2 | 3 | 420 |
| | Upper respiratory tract infection | 3 | 7 | 3192 |
| **Skin and subcutaneous tissue disorders** | Acne vulgaris | 1 | 1 | 30 |
| | Boils and pyoderma | 1 | 1 | 46 |
| | Bruising | 1 | 2 | 23 |
| | Second and third degree burns | 1 | 1 | 103 |
| | Eczema | 2 | 1 | 277 |
| | Seborrhoeic dermatitis | 1 | 1 | 41 |
| | Ulcers | 2 | 2 | 123 |
| | Uraemic pruritis | 1 | 1 | 28 |
| | Warts | 4 | 3 | 277 |
| **Sleep disorders and fatigue** | Chronic fatigue syndrome | 6 | 3 | 197 |
| | Sleep or circadian rhythm disturbances | 4 | 8 | 330 |
| **Adverse effects of cancer treatments** | Adverse effects of venous cannulation | 1 | 1 | 29 |
| | Chemotherapy-associated nausea/vomiting | 1 | 1 | 65 |
| | Chemotherapy-induced stomatitis | 3 | 2 | 59 |
| | Hot flushes in women with a history of breast cancer | 3 | 2 | 136 |
| | Radiodermatitis in patients undergoing radiotherapy | 3 | 1 | 66 |
| **Pain** | Chronic facial pain | 1 | 0 | 0 |
| | Lower back pain | 1 | 1 | 161 |
| | Pain in dental practice | 2 | 6 | 364 |
| | Pain following orthopaedic surgery | 1 | 3 | 181 |

## 4.2 Summary of systematic reviews that broadly examined the effectiveness of homeopathy across a range of clinical conditions

Forty nine of the included systematic reviews examined the effectiveness of homeopathy for a specific clinical condition. The remaining eight systematic reviews broadly examined the effectiveness of homeopathy across a range of different clinical conditions and therapeutic areas. Whilst these broad reviews do not aim to inform clinical decision making on the effectiveness of homeopathy for a specific clinical condition, they provide useful, high level evidence on the general effectiveness of homeopathy in comparison to placebo. In this Overview Report, these broad systematic reviews have been split according to the clinical conditions reported in the review (i.e. the results of specific clinical conditions have been extracted from the systematic review and reported under the relevant clinical conditions in this report). However, the overall aims and results of these broad systematic reviews are summarised in Sections 4.2.1 to 4.2.8 below.

### 4.2.1 Bellavite et al (2011)

The systematic review by Bellavite et al (2011) aimed "to evaluate the effectiveness of homeopathy for the treatment of respiratory allergies, common upper respiratory tract infections, otorhinolaryngologic complaints and rheumatic diseases". The review included a total of 83 primary studies that comprised Level II and Level III-2 studies, in addition to non-randomised, uncontrolled studies. Only the 50 Level II and 12 Level III-2 studies that examined 16 clinical conditions were considered in this Overview Report. Bellavite et al (2011) provided a descriptive individual assessment of the body of evidence on homeopathy for these specific clinical conditions, based on whether there was good, unclear or conflicting, or negative scientific evidence. However, the authors noted that "a large 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".

### 4.2.2 Davidson et al (2011)

The systematic review by Davidson et al (2011) aimed "to systematically review placebo-controlled randomised trials of homeopathy for psychiatric conditions". The review included 25 Level II studies that examined seven clinical conditions (mild traumatic brain injury, fibromyalgia, children with attention deficit/hyperactivity disorder (ADHD), anxiety or stress-related conditions, premenstrual syndrome, chronic fatigue syndrome (CFS), and sleep or circadian rhythm disturbances). Davidson et al (2011) provided a general descriptive assessment of the body of evidence on homeopathy for these psychiatric conditions. The authors noted that "sample sizes were generally small, and overall confidence in the results was graded as moderate or low, suggesting that further research could well change the estimate of effect". Overall, Davidson et al (2011) concluded that the "results do not preclude the possibility of some benefit (of homeopathy) – efficacy was found for the functional somatic syndromes group (fibromyalgia and chronic fatigue syndrome), but not for anxiety or stress. For other disorders, homeopathy produced mixed effects".

### 4.2.3 Simonart et al (2011)

The systematic review by Simonart et al (2011) aimed to "assess the evidence for the efficacy of homeopathic treatments in dermatology". The review included eight Level II studies and four Level III-2 studies that examined six clinical conditions (recurrent vulvovaginal candidiasis, eczema,

seborrhoeic dermatitis, ulcers, uraemic pruritis, and radiodermatitis in breast cancer patients undergoing radiotherapy). Simonart et al (2011) provided a general descriptive assessment of the body of evidence on homeopathy for dermatology. Overall, the authors concluded that "the hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence. The evidence in our overall analysis would be more compelling if there were independently replicated, large-scale rigorous homeopathic trials. Until more compelling results are available, homeopathy cannot be viewed as an evidence-based form of therapy in dermatology".

### 4.2.4 Altunc et al (2007)

The systematic review by Altunc et al (2007) aimed "to assess the evidence of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments". The review included 16 Level II studies that descriptively examined nine clinical conditions in children and adolescents (adenoid vegetation, children with ADHD, asthma, acute otitis media, conjunctivitis, diarrhoea, postoperative pain-agitation syndrome, upper respiratory tract infection (URTI), and warts). The authors noted that with the exception of ADHD and diarrhoea (three primary studies each), no condition was assessed in more than two double-blind Level II studies. Altunc et al (2007) concluded that "the evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition".

### 4.2.5 Cucherat et al (2000)

Cucherat et al (2000) performed a systematic review and meta-analysis to determine "whether there is any evidence from randomised controlled trials of the efficacy of homeopathic treatment in patients with any disease". The review included 16 Level II studies that examined 15 clinical conditions. The authors synthesised the evidence by combining the significance levels (p-values) for the primary outcomes from the individual trials. The results showed that the combined p-value for homeopathy was highly significant (p=0.000036). However, sensitivity analysis showed that the p-value tended towards a non-significant value (p=0.08) as trials were excluded in a stepwise manner based on their level of quality. Overall, Cucherat et al (2000) concluded that "there is some evidence that homeopathic treatments are more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies".

### 4.2.6 Ernst and Pittler (1998)

The systematic review by Ernst and Pittler (1998) aimed to "systematically review the clinical efficacy of homeopathic *Arnica*". The review included four Level II studies and four Level III-2 studies that examined four clinical conditions (acute trauma, delayed-onset muscle soreness (DOMS), stroke, and bruising). Ernst and Pittler (1998) provided a general descriptive assessment of the body of evidence on homeopathy for these conditions. The authors noted that they did not perform a meta-analysis as "the conclusions that can be drawn from such meta-analysis are limited and several caveats have been identified. There could be indefinable bias and the pooling of trials of vastly different remedies for vastly different conditions is of debatable legitimacy". The authors also commented that the included primary studies were methodologically weak, and "generally speaking, the more rigorous studies tended to be the ones that yielded negative findings". Overall, Ernst and Pittler (1998)

concluded that "the hypothesis claiming that homeopathic *Arnica* is clinically effective beyond a placebo effect is not based on methodologically sound placebo-controlled trials".

### 4.2.7 Linde and Melchart (1998)

Linde and Melchart (1998) performed a systematic review and meta-analysis to "summarise the actual state of clinical efficacy research on individualised homeopathy". The review included 31 Level II or Level III-1 studies that examined 19 clinical conditions. A meta-analysis of the 17 trials that presented sufficient data for meta-analysis showed an overall trend in favour of homeopathy (Risk Ratio (RR) 1.62; 95% confidence interval (CI) 1.17 to 2.23). The pooled risk ratio of the six studies that were likely to have good methodological quality as subjectively assessed by Linde and Melchart (1998) was smaller and not statistically significant (RR 1.12; 95% CI 0.87 to 1.44). The authors noted, however, that "the results of the quantitative meta-analysis should only be seen as a crude indicator of the trend of the results in the single trials. However, the fact that the more rigorous trials had less positive results is an indicator that in the less rigorous trials, bias may have led to an overestimation of eventual differences between treatment and placebo". Overall, Linde and Melchart (1998) concluded that "the results of the available randomised trials suggest that individualised homeopathy has an effect over placebo. The evidence, however, is not convincing because of methodological shortcomings and inconsistencies".

### 4.2.8 Linde et al (1997)

Linde et al (1997) performed a systematic review and meta-analysis to "assess whether the clinical effect reported in randomised controlled trials of homeopathic remedies is equivalent to that reported in placebo". The review included 89 controlled trials that examined the effectiveness of homeopathy across multiple clinical conditions. All 89 studies were pooled together in a meta-analysis, where the result of a single outcome for each study was presented as a forest plot of odds ratios. However, the numerical odds ratio was not presented for each individual study and the input data to calculate the odds ratios were not provided. The pooled meta-analysis also comprised multiple different clinical conditions, homeopathic interventions, and outcomes. Nevertheless, the results of the meta-analysis reported a significant effect in favour of homeopathy (Odds Ratio (OR) 2.27; 95% CI 1.62 to 3.18) (Erratum in Linde, 1998). For the purposes of this Overview Report, only the clinical conditions with numerical results data were extracted and included in this evidence review (two clinical conditions; post-operative ileus and allergic rhinitis). Overall, Linde et al (1997) concluded that "the results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition".

# 4.4 Eye, ear and labyrinth disorders

## 4.4.1 Children with otitis media

The effectiveness of homeopathy for the treatment of children with otitis media was assessed in three systematic reviews as summarised in Table 7 and Table 8. In total, two Level II studies and two Level III-2 studies were included in the assessment of otitis media (Table 7). None of the systematic reviews performed a meta-analysis of the data.

**Table 7 Matrix indicating the studies that were included in the systematic reviews of children with otitis media**

| | | Study ID | | | |
|---|---|---|---|---|---|
| | | Jacobs et al (2001) [Level II] | Harrison (1999) [Level II] | Kruse (1998) [Level III-2] | Friese et al (1997) [Level III-2] |
| Systematic review | NCC-WCH (2008) [Level I] | | ✓ | | |
| | Altunc e al (2007) [Level I] | ✓ | | | |
| | Bellavite et al (2011) [Level I/III] | ✓ | | ✓ | ✓ |

The National Collaborating Centre for Women's and Children's Health (2008) (hereafter referred to as NCC-WCH, 2008) (AMSTAR score 6/10) performed a systematic review of the effectiveness of non-surgical interventions in children with otitis media with effusion. The results of this review formed the basis of a National Institute for Health and Care Excellence (NICE) clinical practice guideline. The homeopathy search yielded one relevant Level II study that was given a rating of -1 (i.e. poor quality), using the Scottish Intercollegiate Guidelines Network (SIGN) assessment tool. Harrison (1999) was a pilot Level II study to determine if homeopathic treatment of children with otitis media with effusion was more effective than standard care (i.e. "watchful waiting" with autoinflation and in some cases, a course of low-dose antibiotics). After 12 months of follow up, there was no significant difference in audiometric improvement between the two groups, but there was a significant difference in favour of homeopathy for improvement in tympanograms. The systematic review noted, however, that this Level II study was limited by the small sample size and no blinding of the participants. Importantly, there was a significant difference in the level of initial hearing loss at baseline between children in the treatment and placebo groups. NCC-WCH (2008) concluded that due to the lack of a published evidence base, "homeopathy is not recommended for the management of otitis media with effusion".

The systematic review by Altunc et al (2007) (AMSTAR score 6/10) assessed the evidence for homeopathy (and other therapeutic or preventive interventions) for childhood and adolescent ailments. For the otitis media indication, one Level II study (with a Jadad score of 5) was included; Jacobs et al (2001) investigated the effect of individualised homeopathic treatments in children with acute otitis media compared with placebo. The study reported no significant difference in treatment failures or the presence of middle ear effusion between the two groups. There was, however, a significant decrease in symptom scores as recorded by parent diaries in the homeopathy group compared with placebo. Altunc et al (2007) noted that these data require independent replication

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

Bellavite et al (2011) (AMSTAR score 5/10) aimed to evaluate the effectiveness of homeopathy for the treatment of a range of diseases including infections of the upper airways and ear-nose-throat ailments. One Level II study and two Level III-2 studies were included in the review for otitis media. Bellavite et al (2011) reported that the Level II study by Jacobs et al (2001) found a non-significant trend towards less treatment failure and a significant decrease in symptoms ($p<0.05$) in the homeopathy group compared with placebo in children with acute otitis media. Both of the Level III-2 studies (Friese et al, 1997; Kruse, 1998) assessed the effect of individualised homeopathy in children with otitis media. Kruse (1998) reported "equivalent efficacy" in homeopathy and conventional therapies based on the duration of pain and therapy, and Friese et al (1997) found no significant difference between individualised homeopathy and conventional therapy (antibiotics, mucolytics and antipyretics) in mean duration of pain. Overall, Bellavite et al (2011) concluded there was "good positive evidence" for individualised homeopathy in otitis media.

*Reviewer comments*

*In addition to the trials described above, Bellavite et al (2011) took results from additional non-controlled studies into account when they drew their conclusion of "good positive evidence" for individualised homeopathy in otitis media. Those studies were not within the scope of this overview and have therefore not been considered.*

*The quality of the studies included in the systematic review by Bellavite et al (2011) was also not assessed by the authors. Based on the quality rating given by Altunc et al (2007), the evidence reviewer assumes that Jacobs et al (2001) was a good-quality trial; however, the quality of the two Level III-2 studies that were only reported by Bellavite et al (2011) is unknown.*

*Evidence statement*

Two systematic reviews of poor and medium quality identified one small randomised controlled trial (good quality; 75 participants) that compared homeopathy with placebo for the treatment of children with acute otitis media. LOC: Low.

Based on only one small study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of children with acute otitis media.

Two systematic reviews of poor and medium quality identified one very small randomised controlled trial (poor quality; 33 participants) and two prospectively designed, non-randomised controlled studies (quality not reported; 126 and 131 participants) that compared homeopathy with other therapies (antibiotics, mucolytics, secretolytics, antipyretics and nasal sprays) or watchful waiting for the treatment of children with acute otitis media or otitis media with effusion.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Very low - low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is as effective as the other therapies for the treatment of children with acute otitis media or otitis media with effusion.

**Table 8 Evidence summary table: the effectiveness of homeopathy for the treatment of children with otitis media**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| NCC-WCH (2008)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of CAM for acute otitis media | Harrison (1999)<br>[Level II]<br>SIGN EL 1-[d]<br>N=33 | Children aged 18 months to 8 years with a diagnosis of otitis media with effusion by the patient's general practitioner, hearing loss >20 dB and an abnormal tympanogram | Homeopathy | Standard care ("watchful waiting" with autoinflation or a course of low-dose antibiotics) | Audiometric improvement (hearing loss <20 dB) | No significant difference | "Homeopathy is not recommended for the management of otitis media with effusion." |
| | | | | | Improvement in tympanograms | Significant difference in favour of homeopathy (p=0.01) (76.4% versus 31.3%) | |
| Altunc et al (2007)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Jacobs et al (2001)<br>[Level II]<br>Jadad score 5[e]<br>N=75 | Children with acute otitis media<br>• Intervention group: mean age 3.5 years<br>• Control group: mean age 3.1 years<br>• 41% male<br>• Concomitant treatment: analgesics (10 in placebo group and 5 in homeopathy group) | Individualised homeopathy, non-material potencies, 5 days or until improvement<br>• 8 different remedies in C30 potency; 4 most commonly used were P*ulsatilla nigrans, Chamomilla, sulphur, Calcarea carbonica*; 3-5 pellets 3 times daily | Placebo | Symptom scores (as recorded by parent diaries) | Significant difference in favour of homeopathy (p<0.05) | "The evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to children with otitis media) |
| | | | | | Treatment failures | No significant difference | |
| | | | | | Presence of middle ear effusion | No significant difference | |
| | | | | | Adverse events | None | |
| Bellavite et al (2011)<br>[Level I/III]<br>AMSTAR: 5/10<br><br>SR of | Jacobs et al (2001)<br>[Level II]<br>Quality not specified<br>N=75 | Children with acute otitis media | Individualised homeopathy | Placebo | Treatment failure (5 days, 2 weeks, 6 weeks) | Less failure in homeopathy group, non-significant | Good positive evidence for individualised homeopathy in otitis |
| | | | | | Symptom scores (as | Significant decrease in | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| homeopathy for multiple conditions | | | | | recorded by parent diaries) | symptoms in homeopathy group compared to placebo ($p<0.05$) at 24 and 64 hours after treatment | |
| | Kruse (1998)<br>[Level III-2]<br>Quality not specified<br>N=126 | Children with otitis media | Individualised homeopathy | Conventional therapies (antibiotics, secretolytics, antipyretics and nasal sprays) | Duration of pain and therapy | "Equivalent efficacy" (3 days in the homeopathy group; 4 days in the conventional therapy group) | |
| | | | | | Recurrence | No significant difference (70.7% in the homeopathy group; 64% in the conventional therapy group) | |
| | Friese et al (1997)<br>[Level III-2]<br>Quality not specified<br>N=131 | Children with otitis media | Individualised homeopathy | Conventional therapies (antibiotics, mucolytics, antipyretics) | Mean duration of pain | No significant difference | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicine; C, centesimal; dB, decibels; EL, evidence level; NCC-WCH, National Collaborating Centre for Women's and Children's Health; SIGN, Scottish Intercollegiate Guidelines Network, SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] SIGN evidence level assesses the quality of the evidence based on study design and risk of bias. The range of possible scores is 4 (low) to $1^{++}$ (high). Studies with a level of evidence '–' should not be used as a basis for making a recommendation due to high risk of bias.

[e] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.4.2 Glaucoma

The effectiveness of homeopathy for the treatment of patients with glaucoma was assessed in one systematic review that formed the basis of a NICE clinical practice guideline on the diagnosis and management of chronic open angle glaucoma and ocular hypertension (National Collaborating Centre for Acute Care, 2009; AMSTAR score 3/5). The results of a literature search conducted in August 2008 identified no studies that met the inclusion criteria.

*Evidence statement*

One systematic review (2008) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy in people with glaucoma.

## 4.5 Gastrointestinal disorders

### 4.5.1 Children with constipation

The effectiveness of homeopathy for the treatment of children with constipation was assessed in two systematic reviews (National Collaborating Centre for Mental Health, 2010; Tabbers et al, 2011). No relevant published evidence was found in the literature search conducted by the National Collaborating Centre for Mental Health (2010) (AMSTAR score 3/5) in July 2009. A literature search in January 2010 by Tabbers et al (2011) (AMSTAR score 4/5) also failed to identify any prospectively designed and controlled studies on the effects of homeopathy for children with constipation.

*Evidence statement*

Two systematic reviews (2010, 2011) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy in children with constipation.

### 4.5.2 Children with diarrhoea

The effectiveness of homeopathy for the treatment of children with diarrhoea was assessed in four systematic reviews as summarised in Table 9 and Table 10. In total, the systematic reviews included four Level II studies that were all conducted by the same research group (Table 9).

**Table 9 Matrix indicating the studies that were included in the systematic reviews of diarrhoea**

| | | Study ID | | | |
|---|---|---|---|---|---|
| | | **Jacobs (2006) [Level II]** | **Jacobs (1997/2000)[a] [Level II]** | **Jacobs (1994) [Level II]** | **Jacobs (1993) [Level II]** |
| **Systematic review** | **NCC-WCH (2009) [Level I]** | ✓ | ✓ | ✓ | ✓ |
| | **Altunc et al (2007) [Level I]** | | ✓ | ✓ | ✓ |
| | **Cucherat et al (2000) [Level I]** | | | ✓ | |
| | **Linde and Melchart (1998) [Level I]** | | ✓ | ✓ | ✓ |

[a] Jacobs (1997) and Jacobs (2000) were the same study. The study was referred to as Jacobs (1997) in Linde and Melchart (1998) and Jacobs (2000) in NCC-WCH (2009) and Altunc et al (2007).

The National Collaborating Centre for Women's and Children's Health (2009) (hereafter referred to as NCC-WCH, 2009; AMSTAR score of 5/10) performed a systematic review of alternative or complementary therapies in the treatment of gastroenteritis. The results of this review formed the basis of a NICE clinical practice guideline on diarrhoea and vomiting caused by gastroenteritis. One review and one good-quality Level II study were included. Jacobs (2006) was a Level II study that investigated the effect of homeopathic combination therapy tablets in children aged between 5 months and 6 years who had acute diarrhoea. The study found no significant difference between homeopathy and placebo for the duration of diarrhoea, mean rate of unformed stool passage per day, or total number of unformed stools during follow-up. NCC-WCH (2009) also considered the results of a review[1] and meta-analysis (Jacobs et al, 2003) that included the Level II studies by Jacobs (1993), Jacobs (1994) and Jacobs (2000). Overall, NCC-WCH (2009) concluded "the clinical trials assessing homeopathy had significant methodological limitations. Moreover, there was a lack of consistency in the evidence. Therefore, no recommendation was made for the use of homeopathy".

The systematic review by Altunc et al (2007) (AMSTAR score of 6/10) assessed the evidence of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescent ailments. Three Level II studies (each assigned a Jadad score of 5 by Altunc et al) were identified for the treatment of children with diarrhoea (Jacobs, 2000; Jacobs, 1994; Jacobs, 1993). All three Level II studies were similar in design and tested individualised homeopathy in acute childhood diarrhoea. Two Level II studies (Jacobs, 2000; Jacobs, 1994) reported significant effects in favour of homeopathy

[1] This review was excluded for the purposes of the current overview as the included studies were not identified by systematic means.

for the duration of diarrhoea and the number of unformed stools. The third Level II study (Jacobs, 1993) found no significant differences between homeopathy and placebo for either of these outcomes. Altunc et al (2007) concluded that "the evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition".

Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". One Level II study (Jacobs, 1994) was identified for the childhood diarrhoea indication. Similar to the other systematic reviews, Cucherat et al (2000) also reported that there was a significant effect of homeopathy (p=0.048) in the duration of diarrhoea. The quality of Jacobs (1994) was not formally assessed by Cucherat et al (2000); however, a general comment was made about all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". Cucherat et al (2000) also noted that the studies of high methodological quality were more likely to provide negative results for homeopathy compared to the lower quality studies. Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

In addition, Cucherat et al (2000) conducted several meta-analyses with different combinations of studies (based on attributes such as blinding, attrition and type of homeopathic preparation). However, the authors acknowledge that "the meta-analysis method used does not allow any conclusion on what homeopathic treatment is effective in which diagnosis or against which symptoms". For that reason, the results of the meta-analyses will not be discussed in detail in the remainder of this report.

Linde and Melchart (1998) (AMSTAR score of 8/11) examined the state of clinical efficacy research on individualised homeopathy and identified three Level II studies (Jacobs, 1993; Jacobs, 1994; Jacobs, 1997) for the childhood diarrhoea indication. Consistent with all of the above systematic reviews, Linde and Melchart (1998) reported a significant effect of homeopathy in all of the primary outcomes measured in Jacobs (1994). The authors of the systematic review also noted that there were "positive trends, but no significant inter-group differences" between homeopathy and placebo in Jacobs (1993). Jacobs (1997), reported elsewhere as Jacobs (2000), was a Level II study that tested the effect of individualised homeopathy in children with diarrhoea. The study found no significant difference between the homeopathy and placebo groups.

A meta-analysis of all included studies for all clinical conditions (not specific to children with diarrhoea) conducted by Linde and Melchart (1998) found an overall trend in favour of homeopathy (RR 1.62; 95% CI 1.17, 2.23). However, the pooled rate ratio of the "methodologically best" studies (which included Jacobs, 1994) was clearly smaller and no longer statistically significant (RR 1.12; 95% CI 0.87, 1.44). The pooled findings are unlikely to be of value due to the highly heterogeneous group of studies and conditions that were included in the meta-analyses. As such, the results of the meta-analyses conducted by Linde and Melchart (1998) will not be discussed in detail in the remainder of this report. Overall, Linde and Melchart (1998) concluded that any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

*Reviewer comments*

*The current evidence base for homeopathy for the treatment of children with diarrhoea is limited by the fact that all of the identified studies were carried out by the same research group.*

*Evidence statement*

Four systematic reviews of poor to good quality identified four randomised controlled trials (medium to good quality; total of 544 participants, range: 34-292), all conducted by the same research group, that compared homeopathy with placebo for the treatment of children with diarrhoea.

The one medium-sized, good-quality trial (292 participants) did not detect a difference between combined homeopathy and placebo in the treatment of children with diarrhoea.

The studies of individualised homeopathy are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low - moderate.

Based on the body of evidence evaluated in this review combined homeopathy is not more effective than placebo for the treatment of children with diarrhoea and there is no reliable evidence that individualised homeopathy is more effective than placebo for the treatment of children with diarrhoea.

**Table 10 Evidence summary table: the effectiveness of homeopathy for the treatment of children with diarrhoea**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| NCC-WCH (2009)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of CAM for childhood diarrhoea | Jacobs (2006)<br>[Level II]<br>SIGN EL 1+[d]<br>N=292 | Children aged between 5 months and 6 years who had acute diarrhoea (defined as the passage of three or more unformed stools in the previous 24 hours) that was confirmed visually by study staff | Homeopathic combination therapy tablets (Arsenicum album, Calcarea carbonica, chamomilla, podophyllum and *sulphur* – in a liquid homeopathic dilution in the 30C potency) | Placebo | Duration of diarrhoea | No significant difference | "The Guidelines Development Group considered that the clinical trials assessing homeopathy had significant methodological limitations. Moreover, there was a lack of consistency in the evidence. Therefore, no recommendation was made for the use of homeopathy." |
| | | | | | Mean rate of unformed stool passage per day during follow up | No significant difference | |
| | | | | | Total number of unformed stools during follow up | No significant difference | |
| Altunc et al (2007)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Jacobs (2000)[e]<br>[Level II]<br>Jadad score 5[f]<br>N=126 | Children with diarrhoea<br>• Intervention: mean age 1.7 years<br>• Control: mean age 1.4 years<br>• 67.5% male<br>• Concomitant treatment: oral rehydration therapy, normal feeding; standard antiparasitic medication at end of intervention if needed | 19 different remedies in 30C potency, one dose after every unformed stool for 5 days; 5 most common: *Podophyllum, sulphur, Arsenicum album, Calcarea carbonica, Chamomilla* | Placebo | Number of days with diarrhoea | Significant effect in favour of homeopathy (p=0.04) | "The evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition."<br><br>(Note: this conclusion refers to all clinical conditions and is |
| | | | | | Number of daily stools | Significant effect in favour of homeopathy (p=0.02) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Jacobs (1994)<br>[Level II]<br>Jadad score 5[f]<br>N=92 | Children with diarrhoea<br>• Intervention: mean age 1.6 yr<br>• Control: mean age 1.5 yr<br>• Concomitant treatment: oral rehydration therapy, normal feeding; standard antiparasitic medication at the end of intervention if needed; 11 children were given antidiarrheal medication by their parents (6 in placebo group; 5 in homeopathy group) | 18 different remedies in 30C potency, one dose after every unformed stool for 5 days: *Podophyllum, Chamomilla, Arsenicum album, Calcarea carbonica, sulphur, Mercurius vivus, Pulsatilla, phosphorus, China, Gambogia, Aethusia, aloe, belladonna, Bryonia, Colchicum, Croton tiglium, Dulcamara, Nux vomica* | Placebo | Number of days with diarrhoea | Significant effect in favour of homeopathy (p=0.048) | not specific to childhood diarrhoea) |
| | | | | | Number of daily stools | Significant effect in favour of homeopathy difference (p<0.05) | |
| | | | | | Adverse events | No adverse events | |
| | Jacobs (1993)<br>[Level II]<br>Jadad score 5[f]<br>N=34 | Children aged between 6 months to 5 years with diarrhoea<br>• Concomitant treatment: oral rehydration therapy, normal feeding; standard antiparasitic medication at the end of intervention if needed | Various remedies in 30C potency (no details reported), 2 pills daily for 3 days or until improvement | Placebo | Number of days with diarrhoea | No significant difference | |
| | | | | | Number of daily stools | No significant difference | |
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple | Jacobs (1994)<br>[Level II]<br>Quality not specified<br>N=92 (81 evaluated) | Children with acute childhood diarrhoea | Individualised homeopathy | Placebo | Number of days with diarrhoea | Significant difference in favour of homeopathy (p=0.048) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| conditions | | | | | | | not specific to childhood diarrhoea) |
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Jacobs (1997)[e]<br>[Level II]<br>Quality not specified<br>N=126 | Children with diarrhoea | Fully individualised, computer-assisted (RADAR) choice of remedy, taken as C30 after each unformed stool | Placebo | Number of days with diarrhoea | No significant difference | Conclusion of the systematic review:<br>A meta-analysis found an overall trend in favour of homeopathy.<br>1. The rate ratio was 1.62 (95% CI 1.17 to 2.23) and the odds ratio was 2.62<br>2. The pooled rate ratio of the methodologically best studies was clearly smaller and not statistically significant (1.12, 95% CI 0.87, 1.44). This meta-analysis included Jacobs (1994).<br>3. The rate ratio of the six studies published in MEDLINE-listed journals was not significantly different from placebo (1.22, 95% CI 0.94, 1.56). This meta-analysis included Jacobs (1994)<br><br>(Note: results of meta-analysis refer to all clinical conditions and are not specific to diarrhoea) |
| | Jacobs (1994)<br>[Level II]<br>Quality: 5,5[g]<br>N=92 | Children with diarrhoea | Fully individualised, computer-assisted (RADAR) choice of remedy, taken as C30 after each unformed stool | Placebo | Number of days with diarrhoea | Significant difference between groups (p<0.05)<br>• Intervention: 3.0 days<br>• Control: 3.8 days | |
| | | | | | Days to first formed stool | "Homeopathy significantly better" (p-value not reported) | |
| | | | | | Diarrhoea score | "Homeopathy significantly better" (p-value not reported) | |
| | Jacobs (1993)<br>[Level II]<br>Quality: 3,3[g]<br>N=34 | Children with diarrhoea | Fully individualised computer-assisted (RADAR) choice of remedy, taken as C30 twice daily for 3 days | Placebo | Number of days with diarrhoea | Positive trends, but no significant inter-group differences (p=0.28)<br>• Intervention: 2.4 days | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | • Control: 3.0 days | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CAM, complementary and alternative medicines; EL, Evidence level; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] SIGN evidence level assesses the quality of the evidence based on study design and risk of bias. The range of possible scores is 4 (low) to $1^{++}$ (high). Studies with a level of evidence '–' should not be used as a basis for making a recommendation due to high risk of bias.

[e] Jacobs (1997) and Jacobs (2000) were the same study. The study was referred to as Jacobs (1997) in Linde and Melchart (1998) and Jacobs (2000) in NCC-WCH (2009) and Altunc et al (2007).

[f] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

[g] Quality was assessed using (i) Jadad score, out of five; (ii) internal validity score, out of six.

### 4.5.3 Irritable bowel syndrome

The effectiveness of homeopathy for the treatment of patients with irritable bowel syndrome was assessed in two systematic reviews (Linde and Melchart, 1998; National Collaborating Centre for Nursing and Supportive Care, 2008) as summarised in Table 11. The review conducted by the National Collaborating Centre for Nursing and Supportive Care (AMSTAR score 3/5) formed the basis of the NICE clinical practice guideline on the diagnosis and management of irritable bowel syndrome in primary care. Based on a literature search conducted in June 2007, the review authors did not find any studies that met their inclusion criteria.

The systematic review by Linde and Melchart (1998) (AMSTAR score 8/11) examined the efficacy of individualised homeopathy on a range of clinical conditions. The authors identified one Level II study (Lecoyte et al, 1993; Jadad score 1) that assessed the effectiveness of individualised homeopathic simillimum compared to conventional remedies (dicyclomine hydrochloride, faecal bulking agents, diet advice) for the treatment of irritable bowel syndrome. No studies were identified that compared homeopathy to placebo for the treatment of irritable bowel syndrome. Lecoyte et al (1993) reported "similar improvements in both groups"; however, the measure used to assess improvements was not clear. Linde and Melchart (1998) did not provide an overall conclusion regarding the efficacy of homeopathy in patients with irritable bowel syndrome. However, they stated that the trial was of poor quality, with an insufficient sample size and no blinding.

*Evidence statement*

Two systematic reviews (1998, 2008) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy compared with placebo for the treatment of people with irritable bowel syndrome.

One systematic review of medium quality identified one very small randomised controlled trial (poor quality; 23 participants) that compared homeopathy (Simillimum) with other therapies (dicyclomine hydrochloride, faecal bulking agents and diet advice) for the treatment of people with irritable bowel syndrome. LOC: Very low.

Based on only one very small poor quality study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to the other therapies for the treatment of people with irritable bowel syndrome.

**Table 11 Evidence summary table: the effectiveness of homeopathy for the treatment of irritable bowel syndrome**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Lecoyte et al (1993)<br>[Level II]<br>Quality: 1, 1.5[d]<br>N=23 | Patients with irritable bowel syndrome (all female; 20-69 years of age) | Individualised simillimum | Dicyclomine hydrochloride, faecal bulking agents, diet advice | Unclear | "Similar improvements in both groups" | No specific conclusions were provided regarding the efficacy of homeopathy for irritable bowel syndrome.<br><br>The trial was of poor quality due to an insufficient sample size and no blinding. |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality was assessed using (i) Jadad score, out of five; (ii) internal validity score, out of six.

### 4.5.4 Postoperative ileus

The effectiveness of homeopathy for the treatment of patients with postoperative ileus was assessed in three systematic reviews as summarised in Table 12 and Table 13. In total, the systematic reviews included five Level II studies and two Level III-2 studies (Table 12). Two of the systematic reviews (Barnes et al, 1997; Linde et al, 1997) performed a meta-analysis of the data.

**Table 12 Matrix indicating the studies that were included in the systematic reviews of postoperative ileus**

| | | Systematic review | | |
|---|---|---|---|---|
| | | Cucherat et al (2000) [Level I] | Barnes et al (1997) [Level I] | Linde et al (1997) [Level I] |
| Study ID | GRECHO (1987/1989) [Level II] | ✓ | ✓ | ✓ |
| | Aulagnier (1985) [Level II] | | ✓ | ✓ |
| | Chevrel (1984) [Level II] | | ✓ | ✓ |
| | Estrangin (1983) [Level II] | | | ✓ |
| | Valero (1981) [Level II] | | ✓ | ✓ |
| | Dorfman (1992) [Level III-2] | | ✓ | ✓ |
| | Castelin (1979) [Level III-2] | | ✓ | |

Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The review included the results of GRECHO (Groupe de Rechereche et d'Essais Cliniques en Homeopathie) (1989), which was a three-armed Level II study that examined the effect of homeopathic *Opium* or homeopathic *Raphanus* and *Opium* compared with placebo in patients with postoperative ileus. The study found no significant difference in the delay to first stool between homeopathy and placebo groups, in either intervention arm. Cucherat et al (2000) concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

Barnes et al (1997) (AMSTAR score of 6/11) performed a systematic review and meta-analysis of controlled trials "to determine if homeopathic treatment has any greater effect than placebo treatment in the restoration of intestinal peristalsis in patients after abdominal or gynaecologic surgery". Six prospectively designed and controlled studies were included in the analysis (Aulagnier, 1985; Castelin, 1979; Chevrel, 1984; Dorfman 1992; GRECHO, 1989; Valero, 1981), however the evidence reviewer notes that this includes a mix of Level II and Level III-2 studies. A seventh study (Estrangin, 1983) was excluded as the data were expressed in an inappropriate form for meta-analysis. Quantitative results of the time to first flatus and time to first faeces were presented for all of the included studies where applicable; however, any statistical significance of the data was not

specified. Rather, Barnes et al (1997) descriptively noted that all of the studies (with the exclusion of GRECHO, 1989) reported a "positive" effect for homeopathy, compared with placebo, on the time to first flatus. The Level II study by GRECHO (1989) found "no effect" for homeopathy in this respect. Two of the four studies that also measured time to first faeces reported a positive effect for homeopathy (Castelin, 1979; Aulagnier, 1985), one reported a "statistically non-significant" mean reduction in time to first faeces in patients who received homeopathy (Chevrel, 1984) and one Level II study reported no difference between homeopathy and placebo (GRECHO, 1989).

A meta-analysis of all six included studies revealed a statistically significant effect in favour of homeopathy for time to first flatus (weighted mean difference (WMD) -7.4; 95% CI -4.0 to -10.8; $p<0.05$). This effect remained even with the exclusion of the two low quality studies (Castelin, 1979; Dorfman, 1992) (WMD -6.11; 95% CI -2.31 to -9.91; $p<0.005$). A significant effect in favour of homeopathy was also found for time to first flatus when a homeopathic remedy of less than 12C potency was used (4 studies; WMD -6.6; 95% CI -2.6 to -10.5; $p<0.05$). However, there was no significant difference in time to first flatus with homeopathic remedies greater than 12C potency (3 studies; WMD -3.1; 95% CI -7.5 to 1.3). Barnes et al (1997) warned that the results of the meta-analysis "must be interpreted with caution" as the included studies had a number of limitations. Notably, two of the studies were non peer-reviewed theses (Castelin, 1979; Valero, 1981) and heterogeneity was evident in the included studies. Overall, Barnes et al (1997) concluded that "there is some evidence to support the administration of a homeopathic remedy immediately after surgery to reduce the duration of ileus. However, there is no evidence to support the use of a particular homeopathic remedy or for a combination of remedies".

Linde et al (1997) (AMSTAR score 9/11) conducted a systematic review and meta-analysis that aimed to “assess whether the effect seen with homeopathic remedies is equivalent to that seen with placebo”. Six prospectively designed and controlled studies were included in the analysis for postoperative ileus (Aulagnier, 1985; Chevrel, 1984; Dorfman 1992; Estrangin, 1983; GRECHO, 1987; Valero, 1981). The result of a single outcome for each study was presented as a forest plot of odds ratios. The numerical odds ratio was not presented and the input data to calculate the odds ratios were not provided. A graphical interpretation of the forest plot suggested a positive effect of homeopathy for the primary outcome of three included studies (Aulagnier, 1985; Chevrel, 1984; Dorfman, 1992). There appeared to be no difference between homeopathy and placebo in the remaining three studies (Estrangin, 1983; GRECHO, 1987; Valero, 1981).

A meta-analysis of all included studies (excluding Estrangin, 1983) also found a statistically significant difference in time to first flatulence (Cohen's *d* -0.22; 95% CI -0.36 to -0.09). Similarly, there was a significant difference in time to first stool (Cohen's *d* -0.18; 95% CI -0.33 to -0.03).The overall conclusion by Linde et al (1997) was that there was “insufficient evidence” that homeopathy is “clearly efficacious for any single clinical condition”.

*Evidence statement*

Three systematic reviews of medium to good quality identified five randomised controlled trials (poor to good quality; total of 1095 participants, range: 96-600) and two prospectively designed, non-randomised controlled studies (poor to medium quality; 20 and 80 participants) that compared homeopathy with placebo for the treatment of people with postoperative ileus.

Two of the systematic reviews conducted meta-analyses that found a significant difference in favour of homeopathy, but both meta-analyses included a number of poor quality studies with a high risk of bias. The one large, good-quality trial (600 participants) did not detect a difference between homeopathy and placebo in the treatment of postoperative ileus. LOC: Moderate.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with postoperative ileus.

**Table 13 Evidence summary table: the effectiveness of homeopathy for the treatment of postoperative ileus**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | GRECHO (1989)<br>[Level II]<br>Quality not specified<br>N=450[d] | Patients with post-surgery ileus | *Opium* 15 °C | Placebo[e] | Time to first faeces (hr) | No significant difference (p=0.699) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective"<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to postoperative ileus) |
| | | Patients with post-surgery ileus | *Raphanus* 15 °C and *Opium* 15 °C | Placebo[e] | Time to first faeces (hr) | No significant difference (p=0.358) | |
| Barnes et al (1997)<br>[Level I]<br>AMSTAR: 6/11<br><br>SR of homeopathy for postoperative ileus | GRECHO (1989)<br>[Level II]<br>Quality: 90/100[g]<br>N=600[f] | Patients with postoperative ileus after abdominal or gynaecologic surgery | *Opium* 15C | Placebo | Time to first flatus (hr) | Mean (SD)<br>• Intervention group: 54.2 (24.7)<br>• Control group: 52.3 (26.8)<br>Significance NR | Interpretation of the included Level II studies:<br>"Our analyses suggest that homeopathic treatment administered immediately after abdominal surgery may reduce the time to first flatus when compared with placebo administration. They do not provide evidence for the use of a particular homeopathic remedy or for a combination of remedies for postoperative ileus."<br><br>Conclusion of the systematic review:<br>A meta-analysis of the results found:<br>• A significant effect in favour of homeopathy for time to first flatus when all studies were included (WMD -7.4; 95% CI -4.0, -10.8; p<0.05). |
| | | | | | Time to first faeces (hr) | Mean (SD)<br>• Intervention group: 96.2 (39.8)<br>• Control group: 94.4 (40.7)<br>Significance NR | |
| | | | *Opium* 15C + *Raphanus sativus* 5C | No treatment | Time to first flatus (hr) | Mean (SD)<br>• Intervention group: 54.8 (26.1)<br>• Control group: 56.6 (26.3)<br>Significance NR | |
| | | | | | Time to first faeces (hr) | Mean (SD)<br>• Intervention group: 98.8 (42)<br>• Control group: 95.4 (23.7)<br>Significance NR | |
| | Aulagnier (1985)<br>[Level II] | Patients with postoperative ileus after abdominal or | *Opium* 9C + *Arnica Montana* 9C + *Raphanus* | Placebo (unmedicated granules) | Time to first flatus (hr) | Mean (SD)<br>• Intervention group: 59.28 (21.36)<br>• Control group: 76.08 (30) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Quality: 75/100[g]<br>N=200 | gynaecologic surgery | *sativus* 9C | | | Significance NR | • A significant effect in favour of homeopathy for time to first flatus when 2 low quality studies were excluded<br>(WMD -6.11; 95% CI -2.31, -9.91; p<0.05)<br>• A significant effect in favour of homeopathy for time to first flatus with homeopathic remedy of <12C potency<br>(WMD -6.6; 95% CI -2.6, -10.5; p<0.05)<br>• No significant difference in time to first flatus with homeopathic remedy of ≥12C potency<br>(WMD -3.1; 95% CI -7.5, 1.3) |
| | | | | | Time to first faeces (hr) | Mean (SD)<br>• Intervention group: 96.96 (34.08)<br>• Control group: 117.12 (38.4)<br>Significance NR | |
| | Chevrel (1984)<br>[Level II]<br>Quality: 58/100[g]<br>N=96 | Patients with postoperative ileus after abdominal or gynaecologic surgery | *Opium* 15C | Placebo (unmedicated granules) | Time to first flatus (hr) | Mean (SD)<br>• Intervention group: 42.7 (21.9)<br>• Control group: 52.0 (22.0)<br>Significance NR | |
| | | | | | Time to first faeces (hr) | No significant difference.<br>Mean (SD)<br>• Intervention group: 78.2 (30.5)<br>• Control group: 99.9 (37.9) | |
| | Valero (1981)<br>[Level II]<br>Quality: 80/100[g]<br>N=80 | Patients with postoperative ileus after abdominal or gynaecologic surgery | *Raphanus sativus* 7C | Placebo (unmedicated granules) | Time to first flatus (hr) | Mean (SD)<br>• Intervention group: 53.3 (25.02)<br>• Control group: 58.6 (22.27)<br>Significance not reported | |
| | Dorfman (1992)<br>[Level III-2]<br>Quality: 50/100[g]<br>N=80 | Patients with postoperative ileus after abdominal or gynaecologic surgery | *China regia* 5C + *Arnica montana* 9C + *Raphanus sativus* 5C | Placebo (drops – alcohol diluted in water) | Time to first flatus (hr) | Mean (SD)<br>• Intervention group: 46.5 (23.5)<br>• Control group: 62 (28)<br>Significance NR | |
| | Castelin (1979)<br>[Level III-2]<br>Quality: 20/100[g] | Patients with postoperative ileus after abdominal or | *Opium* 15C | Placebo (unmedicated granules) | Time to first flatus (hr) | Mean (SD)<br>• Intervention group: 24.9 (8.6)<br>• Control group: 34.8 (14.2)<br>Significance NR | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | N=20 | gynaecologic surgery | | | Time to first faeces (hr) | Mean (SD)<br>• Intervention group: 83.7 (21.6)<br>• Control group: 110.8 (37.1)<br>Significance NR | |
| Linde et al (1997)<br>[Level I]<br>AMSTAR: 9/11<br><br>SR of homeopathy for multiple conditions | GRECHO (1987)<br>[Level II]<br>Quality: 80/86[h]<br>N=450 | Patients with postoperative ileus | *Opium* C15 (+C15, *Raph* C5 | Placebo | Time to first flatus <2 days | Odds ratio showed no difference between homeopathy and placebo | Conclusion of the systematic review:<br>A meta-analysis of all included studies (excluding Estrangin, 1983) found:<br>• A significant difference between homeopathy and placebo in time to first flatulence (Cohen's *d* -0.22; 95% CI -0.36, -0.09)[k]<br>• A significant difference between homeopathy and placebo in time to first stool (Cohen's d -0.18; 95% CI -0.33, -0.03)[k] |
| | Aulagnier (1985)<br>[Level II]<br>Quality: 40/64[h]<br>N=200 | Patients with postoperative ileus | *Opium* C9, *Raph*. C9, *Arnica* C9 | Placebo | Global assessment, patient | Odds ratio favoured homeopathy | |
| | Chevrel (1984)<br>[Level II]<br>Quality: 40/71[h]<br>N=96 | Patients with postoperative ileus | *Opium* C15 | Placebo | Time to first faeces | Odds ratio favoured homeopathy | |
| | Estrangin (1983)<br>[Level II]<br>Quality: 40/43[h]<br>N=97 | Patients with postoperative ileus | *Arnica* C7, *China* C7, *Pyrog* C5 | Placebo | Time to flatus <2 days | Odds ratio showed no difference between homeopathy and placebo | |
| | Valero (1981)<br>[Level II]<br>Quality: 80/64[h]<br>N=102 | Patients with postoperative ileus | *Raphanus* C7 | Placebo | Time to first faeces[i] | Odds ratio showed no difference between homeopathy and placebo | |
| | Dorfman (1992)<br>[Level III-2] | Patients with postoperative ileus | Complex[j] | Placebo | Patients without pain | Odds ratio favoured homeopathy | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Quality: 40/36[h]<br>N=80 | | | | | | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CI, confidence interval; NR, not reported; SD, standard deviation; SR, systematic review; WMD, weighted mean difference.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] According to Cucherat et al (2000) the same control group was used for comparisons with both active arms.

[e] Identically prepared globules (without active constituent)

[f] According to Barnes et al (1997) the trial included four arms with 150 patients in each arm.

[g] Quality scoring system described by Kleijnen et al (1991). A score of ≥55 indicates a study of higher quality.

[h] Jadad score / IV score, where the scores are expressed as a percentage of the maxium possible score. Note: the maximum possible Jadad score is 5; the maximum possible internal validity score is 7.

[i] Trials with continuous outcomes (converted to odds ratios).

[j] No further information about this homeopathic remedy was provided.

[k] The publication by Linde et al (1997) contained a discrepancy in the reporting of this result. The confidence interval reported in Table 5 of the publication suggested a non-significant difference (e.g. 95% confidence interval: -0.36, 0.09), whereas the confidence interval reported in the text suggested a significant difference (e.g. 95% confidence interval: -0.36, -0.09) between the treatment groups. An effort was made to contact the authors to clarify the discrepancy; however, no response was received. In the absence of a response from the authors it was assumed that the results in the text of the systematic review were correct.

### 4.5.5 Proctocolitis

The effectiveness of homeopathy for the treatment of patients with procotocolitis was assessed in one systematic review (Linde and Melchart, 1998; AMSTAR score 8/11) as summarised in Table 14. The authors conducted a broad review of the efficacy of individualised homeopathy across a range of clinical areas. One Level II study was identified that assessed the efficacy of individualised homeopathic simillimum (C30, C100 or C200) compared with placebo or salazopyrine and aminosalicylic acid (ASA) for the treatment of proctocolitis (Janssen et al, 1992). The outcome measure used to assess efficacy was not clear to the authors of the systematic review; however, they suggested that "conventional therapy seemed most effective". Linde and Melchart (1998) stated that the study was "totally uninterpretable" and also flawed due to very poor recruitment. Overall, the authors of the systematic review concluded that, across all clinical conditions, any evidence suggesting that homeopathy has an effect is "not convincing because of methodological shortcomings and inconsistencies".

*Evidence statement*

One systematic review of medium quality identified one very small randomised controlled trial (medium quality; 20 participants) that compared homeopathy (*Simillimum*) with placebo and other therapies (salazopyrine and aminosalicylic acid) for the treatment of people with proctocolitis. LOC: Very low.

Based on only one very small study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo or the other therapies for the treatment of people with proctocolitis.

**Table 14 Evidence summary table: the effectiveness of homeopathy for the treatment of proctocolitis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Janssen et al (1992)<br>[Level II]<br>Quality: 4,3.5[d]<br>N=20 | Patients with proctocolitis (55% female; age 19 to 69 years) | Individual simillimum once in C30, C200 or C100 | Salazopyrine + ASA, or placebo | Unclear | "Hard to interpret – but conventional therapy seemed most effective." | "Well-planned trial; recruitment failed completely – totally uninterpretable." |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; ASA, aminosalicylic acid; C, centesimal; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality assessed using (i) Jadad score (out of 5); (ii) internal validity score (out of 6).

## 4.6 Genitourinary disorders

### 4.6.1 Nocturnal enuresis

The effectiveness of homeopathy for the treatment of nocturnal enuresis in children was assessed in one systematic review (Huang et al, 2011; AMSTAR score 5/5). This Cochrane review aimed to determine the effects of complementary and miscellaneous treatments (including homeopathy) in children with nocturnal enuresis. The results identified no prospectively designed and controlled studies that had addressed the effect of homeopathy versus no treatment or placebo or another treatment in a literature search that was conducted in June 2010.

*Evidence statement*

One systematic review (2010) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy in children with nocturnal enuresis.

### 4.6.2 Men with lower urinary tract symptoms

The effectiveness of homeopathy for the treatment of men with lower urinary tract symptoms was assessed in one systematic review that formed the basis of a NICE clinical practice guideline on the management of lower urinary tract symptoms in men (National Clinical Guideline Centre, 2010; AMSTAR score 3/5). The results of a literature search conducted in June 2009 identified no studies that met the inclusion criteria.

*Evidence statement*

One systematic review (2009) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy in men with lower urinary tract symptoms.

# 4.7 Infections and infestations

## 4.7.1 Amebiasis and giardiasis

The effectiveness of homeopathy for the treatment of amebiasis and giardiasis was assessed in one systematic review (Linde and Melchart, 1998; AMSTAR score 8/11) as summarised in Table 15. Linde and Melchart (1998) examined the efficacy of homeopathy in a number of chronic conditions and infectious diseases, and identified one Level II study that specifically examined homeopathy as a treatment for amebiasis and giardiasis (Solanki and Gandhi, 1995). Solanki and Gandhi (1995) investigated the number of patients that were cured using individualised homeopathic simillimum compared with a placebo group. The Level II study reported a better response in the homeopathy group (58%) compared to placebo (13%), and the systematic review authors calculated a rate ratio of 4.34 (95% CI 1.13, 16.7).

Linde and Melchart (1998) reported that the methodological quality of Solanki and Gandhi (1995) was "not assessable" and it was thought to have "major flaws". It was suggested by the systematic review authors that insufficient reporting, particularly the absence of any description of how outcomes were defined/measured, may explain the "extremely positive results". Overall, Linde and Melchart (1998) concluded that, across all clinical conditions, any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

*Reviewer comments*

*The evidence reviewer notes that the trial by Solanki and Gandhi (1995) was included in the meta-analysis by Linde and Melchart (1998); however, the meta-analysis has not been discussed in detail in this summary. The relevance of the pooled results to the treatment of amebiasis and giardiasis is limited due to the fact that the trial was only one of 19 studies included in the meta-analysis, all of which examined different clinical conditions and a variety of homeopathic remedies.*

*Evidence statement*

One systematic review of medium quality identified one very small randomised controlled trial (medium quality; 34 participants) that compared homeopathy (*Simillimum*) with placebo for the treatment of people with amebiasis and giardiasis. LOC: Very low.

Based on only one very small study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with amebiasis and giardiasis.

**Table 15 Evidence summary table: the effectiveness of homeopathy for the treatment of amebiasis and giardiasis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Solanki and Gandhi (1995)<br>[Level II]<br>Jadad score 3[d]<br>N=34 | Patients with amebiasis and giardiasis (all female; age range 4 to 35 years) | Individual simillimum | Placebo | Number cured (physician assessed) | Better response in homeopathy group:<br>• Intervention group: 11/19 (58%)<br>• Control group: 2/15 (13%)<br>• Rate ratio (95% CI): 4.34 (1.13, 16.7) | Comments regarding the included Level II study:<br>"Insufficient report; completely unclear how response/cure was established/defined; extremely positive results."<br><br>Conclusion of the systematic review:<br>A meta-analysis found an overall trend in favour of homeopathy.<br>• The rate ratio was 1.62 (95% CI 1.17 to 2.23) and the odds ratio was 2.62<br>• The pooled rate ratio of the methodologically best studies was clearly smaller and not statistically significant (1.12, 95% CI 0.87, 1.44)<br>• The rate ratio of the six studies published in MEDLINE-listed journals was not significantly different from placebo (1.22, 95% CI 0.94, 1.56)<br><br>(Note: Results of meta-analysis refer to all clinical conditions and are not specific to amebiasis and giardiasis) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.7.2 Cholera

The effectiveness of homeopathy for the treatment of cholera was assessed in one systematic review (Linde and Melchart, 1998; AMSTAR score 8/11) as summarised in Table 16. Linde and Melchart (1998) examined the efficacy of homeopathy in a number of chronic conditions and infectious diseases. The systematic review identified one Level II study (with a Jadad score of 2) that specifically examined homeopathic remedies (one of eight pre-selected options) as a treatment for cholera, compared with placebo (Gaucher et al, 1994). Linde and Melchart (1998) reported that "no significant differences" were observed; however the primary outcome examined in the study was not reported in the systematic review, so the result provides no meaningful evidence for the treatment of cholera with homeopathy.

Linde and Melchart (1998) indicated that the Level II study by Gaucher et al (1994) was a poor-quality trial, was poorly-reported, and contained a very limited amount of useful data. As such, they excluded the trial from their meta-analysis. Overall, Linde and Melchart (1998) concluded that, across all clinical conditions, any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

*Reviewer comments*

*The most informative finding presented by Linde and Melchart (1998) was that there were "no significant differences"; however, it was unclear to the evidence reviewer whether the null result alluded to differences within the homeopathy arm (from baseline to follow-up) or differences between treatment arms (homeopathy versus placebo). The evidence reviewer made the assumption that the results referred to an absence of significant differences between the homeopathy and placebo treatment arms.*

*Evidence statement*

One systematic review of medium quality identified one very small randomised controlled trial (poor quality; 44 participants) that compared homeopathy with placebo for the treatment of people with cholera. LOC: Very low.

Based on only one very small poor quality study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with cholera.

**Table 16 Evidence summary table: the effectiveness of homeopathy for the treatment of cholera**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998) [Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Gaucher et al (1994) [Level II]<br>Jadad score 2[d]<br>N=44[e] | Patients with cholera | Most indicated homeopathic remedy chosen from 8 preselected options | Placebo | Not reported | No significant differences | Interpretation of the included Level II study:<br>Due to insufficient reporting, a reliable and valid assessment of this trial was not possible<br><br>Conclusion of the systematic review:<br>A meta-analysis found an overall trend in favour of homeopathy.<br>• The rate ratio was 1.62 (95% CI 1.17 to 2.23) and the odds ratio was 2.62<br>• The pooled rate ratio of the methodologically best studies was clearly smaller and not statistically significant (1.12, 95% CI 0.87, 1.44)<br>• The rate ratio of the six studies published in MEDLINE-listed journals was not significantly different from placebo (1.22, 95% CI 0.94, 1.56)<br><br>(Note: results of meta-analysis refer to all clinical conditions and are not specific to cholera) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

[e] Number included not clear; 44 is the number of participants analysed.

### 4.7.3 Human immunodeficiency virus (HIV)

The effectiveness of homeopathy for the treatment of patients with HIV was assessed in one systematic review (Mills et al, 2005; AMSTAR score 8/10) as summarised in Table 17. This systematic review aimed to assess the effectiveness of complementary therapies, including homeopathy, for HIV and HIV-related symptoms. Two poor-quality Level II studies were included in the review that used homeopathic regimens as the intervention. Rastogi (1999) examined the effect of an unspecified homeopathic treatment on CD4 cell count in HIV-positive patients. It was reported that "in the persistent generalised lymphadenopathy group, there is a significant difference in CD4 cell count before and after the treatment. There was no change in placebo group and asymptomatic HIV infection". Mills et al (2005) noted that there were concerns about the conduct of this Level II study and that there were potential fatal flaws related to ethical concerns. Struwe (1993) investigated the effect of homeopathic dronabinol on the weight, body fat, and distress of HIV-positive patients. The study found a significant increase in body fat (p=0.04) and a significant decrease in symptom stress (p=0.04) in the treatment group compared with placebo. However, the systematic review noted that Stuwe (1993) was limited by a small study size with large dropouts in both groups; a total of seven patients (58% of participants) dropped out of the trial. Mills et al (2005) thus concluded that there is no good-quality evidence to support the use of homeopathy as a treatment for HIV.

*Evidence statement*

One systematic review of medium quality identified two randomised controlled trials (poor quality; 12 and 100 participants) that compared homeopathy with placebo for the treatment of people with human immunodeficiency virus.

These studies are of insufficient quality and size to warrant further consideration of their findings. LOC: Very low - low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with human immunodeficiency virus.

**Table 17 Evidence summary table: the effectiveness of homeopathy for the treatment of HIV**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Mills et al (2005)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of CAM for HIV | Rastogi (1999)<br>[Level II]<br>Poor quality<br>N=100 | HIV-positive patients, including 71 men and 29 women. Age range 18-50 years | Homeopathy – not specific | Placebo | CD4 cell count | Significant difference in cell count before and after treatment in the PGL group. No change in placebo and asymptomatic HIV group | There is no good-quality evidence to support the use of homeopathy in the HIV community. |
| | Struwe (1993)<br>[Level II]<br>Poor quality<br>N=12 | HIV-positive patients, mean age 38.0 (SD=7.3) | Dronabinol (delta-9-tetrahydrocannabinol) | Placebo | Body fat | Significantly increase body fat (1%, p=0.04) in the treatment group compared with the control group | |
| | | | | | Symptom distress | Significantly decreased symptom stress (p=0.04) in the treatment group compared with the control group | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; HIV, human immunodeficiency virus; PGL, persistent generalised lymphadenopathy; SD, standard deviation; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.7.4 Influenza-like illness

The effectiveness of homeopathy for the treatment of influenza-like illness was assessed in three systematic reviews (Bellavite et al, 2011; Cucherat et al, 2000; Mathie et al, 2012) as summarised in Table 18 and Table 19. In total, the systematic reviews included four Level II studies (Table 18).

**Table 18 Matrix indicating the studies that were included in the systematic reviews of influenza or influenza-like illness**

| | | Systematic reviews | | |
|---|---|---|---|---|
| | | **Mathie et al (2012) [Level I]** | **Bellavite et al (2011) [Level I]** | **Cucherat et al (2000) [Level I]** |
| **Study IDs** | **Papp et al (1998) [Level II]** | ✓ | ✓ | ✓ |
| | **Ferley et al (1989) [Level II]** | ✓ | ✓ | ✓ |
| | **Casanova and Gerard (1988) [Level II]** | ✓ | ✓ | |
| | **Casanova et al (1984) [Level II]** | ✓ | | |

Mathie et al (2012) (AMSTAR score 9/11) undertook a Cochrane review of homeopathic *Anas barbariae* 200k (Oscillococcinum®) for influenza-like illness. The review provided an update of earlier work completed by Vickers and Smith (2006). Four Level II studies (Casanova and Gerard, 1988; Casanova et al, 1984; Ferley et al, 1989; Papp et al, 1998) were identified and included in the review, all of which treated patients with various regimens of homeopathic *Anas barbariae* or placebo. The studies reported efficacy based on a wide array of outcomes, including the presence of fever, cough, spinal pain, muscle pain, headache, and fitness for work at various time points. Mathie et al (2012) reported differences between the treatment arms using relative risks or mean differences, where appropriate. In the study reported by Papp et al (1998), the relative risk significantly favoured homeopathy according to "no spinal pain at 48 hours" (p=0.030); "no muscle pain at 48 hours" (p=0.010); "no articular pain at 48 hours" (p=0.0090); and "use of concomitant medication during the trial" (p=0.020). Significant inter-group differences were not reported for any other outcomes (measures of headache, backache, physician-assessed symptoms and fitness for work).

An earlier study by Ferley et al (1989) also examined the efficacy of homeopathic *Anas barbariae* compared to placebo. No significant inter-group differences were found for medications used for cough or coryza and the prevalence of antibiotic use; however, the relative risk estimates significantly favoured homeopathy based on "absence of symptoms at 48 hours", stratified by patient age (RR 1.98; 95% confidence interval (CI) 1.14, 3.43) and symptom severity (RR 1.65; 95% CI 1.02, 2.65). Similarly, the relative risk estimate significantly favoured homeopathy in terms of medication used for pain or fever (p=0.048).

Mathie et al (2012) only reported one outcome from the Level II study conducted by Casanova and Gerard (1988). The mean difference between the homeopathic *Anas barbariae* and placebo groups on that outcome (temperature at 48 hours) significantly favoured homeopathy (p<0.00001). Similarly, the majority of results reported in the study by Casanova et al (1984) significantly favoured homeopathic *Anas barbariae:* "no fever at 48 hours" (p=0.00061), "no general aches at 48 hours"

(p=0.0072), and "no day cough at 48 hours" (p=0.0076). No significant difference was found between the treatment groups based on night cough at 48 hours.

Mathie et al (2012) conducted a meta-analysis in which the results of the individual trials were pooled (Table 20). Pooled estimates that included data from at least two Level II studies were provided for five outcomes: patient-assessed absence of symptoms at 48 hours; no chills at 48 hours; patient-assessed absence of symptoms at 3 days; patient-assessed absence of symptoms at 4 days; and patient-assessed absence of symptoms at 5 days. Significant differences between homeopathic *Anas barbariae* and placebo were found on three of the outcomes, two of which had no significant heterogeneity between the included trials (patient-assessed absence of symptoms at 48 hours, p=0.0014; patient-assessed absence of symptoms at 3 days, p=0.020). Based on the individual study results and the results of the meta-analyses, Mathie et al (2012) concluded that there is "insufficient good evidence to enable robust conclusions" about the efficacy of homeopathic *Anas barbariae* in the treatment of influenza and influenza-like illness. In addition, the authors stated that the results do not preclude the possibility of a clinical effect; however, they concluded that the evidence for the efficacy of homeopathic *Anas barbariae* is not compelling, based on the low quality of the included studies.

Bellavite et al (2011) (AMSTAR score 5/10) conducted a broad review of recent advances in homeopathy and immunology across a range of clinical areas. Three studies (all discussed above) were identified and included in the review: Casanova and Gerard (1988), Ferley et al (1989) and Papp et al (1998). The authors of the systematic review did not provide results that were specific to each of the outcomes assessed in the trials (as presented by Mathie et al, 2012) and did not provide p-values to support claims of significance. However, the overall conclusion made by Bellavite et al (2011) was that there was "good positive evidence" from three Level II studies for the use of *Anas barbariae* 200K in the treatment of patients with influenza-like symptoms.

Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The review included two Level II studies (Papp et al, 1998; Ferley et al, 1989), and reported "significant differences" between the treatment arms in favour of the homeopathy groups over placebo in both trials. Cucherat et al (2000) only reported one outcome for the study by Papp et al (1998) which was a single variable of "rate of patients affected and duration of disease"; however, as the way in which those outcomes were combined into one measure was not clear, the validity of the results are questionable. Although the authors of the systematic review did not provide a conclusion that was specific to homeopathy in influenza patients, they did conclude that overall, across the clinical conditions, there is "insufficient evidence to conclude that homeopathy is clinically effective" due to the low methodological quality of the included trials.

*Reviewer comments*

*The systematic review by Mathie et al (2012) did not provide overall quality assessment scores for the included studies, yet measures of internal validity were assessed and documented. Two of the included studies (Casanova et al 1984; Casanova and Gerard 1988) had an "unclear risk of bias" due to the fact that details relating to allocation concealment, random sequence generation, and blinding*

*of participants and outcome assessors were not reported. In addition, the reporting of outcome data was not complete in either of the studies.*

*Similarly, Ferley et al (1989) did not provide any details about random sequence generation, allocation concealment or blinding. Papp et al (1998) did provide information regarding randomisation, allocation concealment and blinding of participants and was deemed to have a low risk of bias on those measures. However, the risk of bias was unclear for the blinding of outcome assessment and the reporting of outcome data was incomplete.*

*As a result, the evidence reviewer supports the conclusion by Mathie et al (2012) that the evidence for the efficacy of homeopathic Anas barbariae is not compelling based on the low quality of the included studies.*

*Evidence statement*

Three systematic reviews of poor to good quality identified four randomised controlled trials (quality not reported; total of 1259 participants, range: 100-487) that compared homeopathy (*Anas barbariae*) with placebo for the treatment of people with influenza-like illness.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with influenza-like illness.

**Table 19 Evidence summary table: the effectiveness of homeopathy for the treatment of influenza-like illness**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Mathie et al (2012)<br>[Level I]<br>AMSTAR: 9/11<br><br>SR of homeopathy for influenza | Papp et al (1998)<br>[Level II]<br>Quality score not reported<br>N=372 | Patients in primary care with influenza-like symptoms<br>• mean age 35 years | Oscillococcinum®<br>3 times a day for 3 days | Placebo | Fitness for work at 2 days | No significant difference (RR 1.80; 95% CI 0.99-3.26) | "There is insufficient good evidence to enable robust conclusions to be made about Oscillococcinum in the treatment of influenza and influenza-like illness. Our findings do not rule out the possibility that Oscillococcinum could have a clinically useful treatment effect but, given the low quality of the eligible studies, the evidence is not compelling. There was no evidence of clinically important harms due to Oscillococcinum." |
| | | | | | Fitness for work at 4 days | No significant difference (RR 1.04; 95% CI 0.83-1.30) | |
| | | | | | No headache at 48 hours | No significant difference (RR 1.20; 95% CI 0.88-1.63) | |
| | | | | | No backache at 48 hours | No significant difference (RR 1.27; 95% CI 1.00-1.61; p=0.05) | |
| | | | | | No spinal pain at 48 hours | Favours homeopathy (RR 1.27; 95% CI 1.02-1.58; p=0.030) | |
| | | | | | No muscle pain at 48 hours | Favours homeopathy (RR 1.47; 95% CI 1.10-1.97; p=0.010) | |
| | | | | | No articular pain at 48 hours | Favours homeopathy (RR 1.40; 95% CI 1.09-1.80; p=0.0090) | |
| | | | | | Improvement in symptoms at 48 hours – physician assessment | No significant difference (RR 1.07; 95% CI 0.98-1.18) | |
| | | | | | Absence of symptoms at 48 hours – physician assessment | No significant difference (RR 1.28; 95% CI 0.79-2.06) | |
| | | | | | Increased use of concomitant medication during trial | Favours homeopathy (RR 0.61; 95% CI 0.40-0.92; p=0.020) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | Ferley et al (1989)<br>[Level II]<br>Quality score not reported<br>N=487 | Participants in primary care with a complaint of influenza-like illness<br>• aged 12 years or older (mean age approx. 34 years)<br>• rectal temperature above 38°C | Oscillococcinum® twice a day for 5 days | Placebo | Absence of symptoms at 48 hours – patient assessment by age (12-29 yr; 30+ yr) | Favours homeopathy (RR 1.98; 95% CI 1.14-3.43; p-value not reported) | |
| | | | | | Absence of symptoms at 48 hours – patient assessment by severity of symptoms (severe; mod to severe) | Favours homeopathy (RR 1.65; 95% CI 1.02-2.65; p-value not reported) | |
| | | | | | Medication used for pain or fever | Favours homeopathy (RR 0.82; 95% CI 0.67-1.00; p=0.048) | |
| | | | | | Medication used for cough or coryza | No significant difference (RR 0.96; 95% CI 0.76-1.21) | |
| | | | | | Antibiotics used | No significant difference (RR 0.87; 95% CI 0.47-1.62) | |
| | Casanova and Gerard (1988)<br>[Level II]<br>Quality score not reported<br>N=300 | Patients complaining of influenza<br>• average age 44 years in intervention group; 38 years placebo | Oscillococcinum® twice a day for 3 to 4 days | Placebo | Temperature at 48 hours | Favours homeopathy (MD -0.50; 95% CI -0.67, -0.33; p<0.00001) | |
| | Casanova et al (1984)<br>[Level II] | Patients with influenza-like illness | Oscillococcinum®, 4 doses in over 2 days at 6-hour | Placebo | No fever at 48 hours | Favours homeopathy (RR 1.98; 95% CI 1.34-2.92; p=0.00061) | |
| | | | | | No rhinitis at 48 hours | No significant difference | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Quality score not reported<br>N=100 | • onset <48 hours previously<br>• average age approx. 42 years | intervals | | | (RR 1.33; 95% CI 0.66-2.70) | |
| | | | | | No general aches at 48 hours | Favours homeopathy (RR 1.73; 95% CI 1.16-2.59; p=0.0072) | |
| | | | | | No night cough at 48 hours | No significant difference (RR 1.44; 95% CI 0.73-2.84) | |
| | | | | | No day cough at 48 hours | Favours homeopathy (RR 2.00; 95% CI 1.20-3.31; p=0.0076) | |
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Papp et al (1998)<br>[Level II]<br>Quality score not reported<br>N=372 | Patients with influenza-like symptoms | Oscillococcinum (*Anas barbariae* 200k) 1 dose, 3 times per day for 3 days | NR | Evaluation of symptoms after treatment | Statistically significant reduction of symptoms after 48 hours in the homeopathy group | There is "good positive evidence" from three Level II studies for the use of *Anas barbariae* 200K in the treatment of influenza-like symptoms |
| | Ferley et al (1989)<br>[Level II]<br>Quality score not reported<br>N=487 | Patients with influenza-like symptoms | Oscillococcinum (*Anas barbariae* 200k) 5 doses, one every 12 hours | NR | Healing rate at 48 hours after diagnosis based on rectal temperature and two of the following: headache, stiffness, lumbar pain, articular ache, shivering | Clinical healing after 48 hours and rate of temperature reduction better in the homeopathy group | |
| | Casanova and Gerard (1988)<br>[Level II]<br>Quality score not reported<br>N=300 | Patients with influenza-like symptoms | Oscillococcinum (*Anas barbariae* 200K), one dose morning and evening for 3-4 days | NR | Temperature, shivering and myalgia | In the homeopathy group: faster temperature reduction, significantly less shivering and less myalgia after 4 days | |
| Cucherat et al (2000) | Papp et al (1998)<br>[Level II] | Patients with influenza-like | Oscillococcinum | Placebo | Multiple endpoint: rate of patients affected and duration | Significant difference in favour of homeopathy (p=0.0257) | "There is some evidence that homeopathic treatments are more |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| [Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Quality score not reported[d]<br>N=372 | syndromes | | | of disease | | effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies. Further high quality studies are needed to confirm these results."<br><br>"It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to influenza-like illness) |
| | Ferley et al (1989)<br>[Level II]<br>Quality score not reported[d]<br>N=487 | Patients with influenza-like syndromes | Fixed, Oscillococcinum | Placebo | Recovery rate within 48 hours of treatment | Significant difference in favour of homeopathy (p=0.032) | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; MD, mean difference; NR, not reported; RR, relative risk; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality of included studies was not formally assessed by the authors. The authors noted that "the only criterion for quality used for selection was adequate concealment of treatment allocation (by a suitable randomisation method)".

[e] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

**Table 20 Pooled results presented in Mathie et al (2012)**

| Outcome | Intervention group n/N (%) | Control group n/N (%) | RR (95% CI) | p-value Heterogeneity[a] |
|---|---|---|---|---|
| Treatment: *Anas barbariae* versus placebo | | | | |
| Absence of symptoms at 48 hours – patient assessment<br>(2 Level II studies; N=796)<br>Ferley 1989<br>Papp 1998 | 66/395 (16.7) | 36/401 (9.0) | 1.86 (1.27-2.73) | Favours homeopathy (p=0.0014)<br>No significant heterogeneity<br>(p=0.46; $I^2$=0%) |
| No chills at 48 hours<br>(2 Level II studies; N=418)<br>Casanova 1984<br>Papp 1998 | 136/209 (65.1) | 108/209 (51.7) | 1.30 (1.04-1.63) | Favours homeopathy (p=0.020)<br>Moderate heterogeneity<br>(p=0.19; $I^2$=42%) |
| Absence of symptoms at 3 days (patient's assessment)<br>(2 Level II studies; N=796)<br>Ferley 1989<br>Papp 1998 | 136/395 (34.4) | 109/401 (27.2) | 1.27 (1.03-1.56) | Favours homeopathy (p=0.020)<br>No significant heterogeneity<br>(p=0.94; $I^2$=0%) |
| Absence of symptoms at 4 days (patient's assessment)<br>(2 Level II studies; N=796)<br>Ferley 1989<br>Papp 1988 | 223/395 (56.5) | 203/401 (50.6) | 1.11 (0.98-1.27) | No significant difference (p=0.10)<br>No significant heterogeneity<br>(p=0.88; $I^2$=0%) |
| Absence of symptoms at 5 days (patient's assessment)<br>(2 Level II studies; N=796)<br>Ferley 1989<br>Papp 1988 | 277/395 (70.1) | 266/401 (66.3) | 1.06 (0.96-1.16) | No significant difference (p=0.25)<br>No significant heterogeneity<br>(p=0.94; $I^2$=0%) |

Abbreviations: CI, confidence interval; RR, relative risk.

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

### 4.7.5 Malaria

The effectiveness of homeopathy for the treatment of malaria was assessed in one systematic review (Linde and Melchart, 1998) (AMSTAR score 8/11) as summarised in Table 21. Linde and Melchart (1998) examined the efficacy of homeopathy in a number of chronic conditions and infectious diseases, and identified one Level II study (Jadad score of 2) that specifically examined homeopathy as a treatment for malaria (van Erp and Brands, 1996). Van Erp and Brands (1996) compared the number of patients assessed as "globally improved" between those treated with chloroquine and those treated with individualised homeopathic simillimum. No Level II, Level III-1 or Level III-2 studies were identified that compared homeopathy to placebo for the treatment of malaria. In Van Erp and Brands (1996), a similar improvement was reported in the homeopathy and chloroquine groups (83% and 72% of patients, respectively); the statistical significance of the result was not reported. Linde and Melchart (1998) concluded that the result "seemed promising"; however the study was excluded from their meta-analysis due to methodological flaws, including "insufficient description of outcome measurement".

*Evidence statement*

One systematic review (1998) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy compared with placebo for the treatment of people with malaria.

One systematic review of medium quality identified one small randomised controlled trial (poor quality; 74 participants) that compared homeopathy (*Simillimum*) with chloroquine for the treatment of people with malaria. LOC: Very low.

Based on only one small poor quality study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to chloroquine for the treatment of people with malaria.

**Table 21 Evidence summary table: the effectiveness of homeopathy for the treatment of malaria**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | van Erp and Brands (1996)<br>[Level II]<br>Jadad score 2[d]<br>N=74 | Patients with malaria attack (57% female) | Individual simillimum | Chloroquine | Number of patients assessed globally as improved | Similar response in both groups. Intervention group: 25/30 (83%); Control group: 18/25 (72%).<br><br>Significance of inter-group differences not reported | Comments about the included Level II study:<br>"The trial of van Erp and Brands (1996) on malaria seems promising, but the reporting in the study is inadequate."<br><br>Conclusions of the systematic review:<br>A meta-analysis found an overall trend in favour of homeopathy.<br>• The rate ratio was 1.62 (95% CI 1.17 to 2.23) and the odds ratio was 2.62<br>• The pooled rate ratio of the methodologically best studies was clearly smaller and not statistically significant (1.12, 95% CI 0.87, 1.44)<br>• The rate ratio of the six studies published in MEDLINE-listed journals was not significantly different from placebo (1.22, 95% CI 0.94, 1.56)<br><br>(Note: results of meta-analysis refer to all clinical conditions and are not specific to malaria) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.7.6 Recurrent vulvovaginal candidiasis

The effectiveness of homeopathy for the treatment of patients with recurrent vulvovaginal candidiasis was assessed in one systematic review (Simonart et al, 2011; AMSTAR score 8/10) as summarised in Table 22. This systematic review aimed to assess the evidence for the efficacy of homeopathic treatments in dermatology. For the recurrent vulvovaginal candidiasis indication, one relevant Level II study was identified. Witt et al (2009) investigated the effect of individually selected homeopathic remedies compared with conventional therapy (itraconazole) in women with recurrent vulvovaginal candidiasis. No Level II, Level III-1 or Level III-2 studies were identified that compared homeopathy to placebo. In Witt et al (2009) all of the measured outcomes found statistically significant differences in favour of conventional treatment; women treated by the conventional therapy had a significantly lower level of discomfort ($p<0.001$), were significantly more satisfied ($p<0.0001$) and reached a culture-free status earlier than women treated by homeopathy ($p<0.0001$). Simonart et al (2011) noted, however, that the study had some limitations including a high dropout rate (53% of participants) and blinding was uncertain. Overall, the authors concluded that "the hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".

*Evidence statement*

One systematic review (2011) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy compared with placebo for the treatment of women with recurrent vulvovaginal candidiasis.

One systematic review of medium quality identified one medium-sized randomised controlled trial (quality not reported; 150 participants) that compared homeopathy with itraconazole for the treatment of women with recurrent vulvovaginal candidiasis. LOC: Low.

Based on only one study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to itraconazole for the treatment of women with recurrent vulvovaginal candidiasis.

**Table 22 Evidence summary table: the effectiveness of homeopathy for the treatment of recurrent vulvovaginal candidiasis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Simonart et al, 2011<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Witt et al, 2009<br>[Level II]<br>Quality not specified<br>N=150 | Women with recurrent vulvovaginal candidiasis | Individually selected homeopathic remedies for 12 months | Conventional therapy (itraconazole) | Culture-free status | Conventional therapy group reached a culture-free status significantly earlier than homeopathy group (p<0.0001)<br>• 9/23 in homeopathy group and 18/23 in conventional therapy group | "The hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to recurrent vulvovaginal candidiasis) |
| | | | | | Level of discomfort | Significantly lower level of discomfort in conventional therapy group (p<0.001)<br>• VAS score 36.8 in homeopathy group and 25.1 in conventional therapy group | |
| | | | | | Level of satisfaction | Conventional therapy group were significantly more satisfied than homeopathy group (p<0.0001) | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

## 4.8 Injury, trauma and postoperative disorders

### 4.8.1 Acute ankle sprains

The effectiveness of homeopathy for the treatment of patients with acute ankle sprains was assessed in one systematic review (Cucherat et al, 2000; AMSTAR score 10/11) as summarised in Table 23.

Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The systematic review included one Level II study (Zell, 1988) that investigated the effect of homeopathic *Traumeel* ointment in patients with acute ankle sprains. The systematic review reported that the Level II study found a significant difference (p=0.028) in composite criteria of treatment success that favoured homeopathy over placebo. The quality of Zell (1988) was not formally assessed by Cucherat et al (2000); however, a general comment was made about all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Evidence statement*

One systematic review of good quality identified one small randomised controlled trial (quality not reported; 69 participants) that compared homeopathy (*Traumeel*) with placebo for the treatment of people with acute ankle sprains. LOC: Very low.

Based on only one small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with acute ankle sprains.

**Table 23 Evidence summary table: the effectiveness of homeopathy for the treatment of acute ankle sprains**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Zell (1988)<br>[Level II]<br>Quality not specified<br>N=69[d] | Patients with acute ankle sprains | Traumeel ointment | Ointment base without active constituent | Composite criteria of treatment success | Significant difference in favour of homeopathy (p=0.028) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to ankle sprains) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Number of participants refers to the number who were evaluated. The number randomised was not reported.

### 4.8.2 Acute trauma

The effectiveness of homeopathy for the treatment of acute trauma was assessed in one systematic review as summarised in Table 24 (Ernst and Pittler, 1998; AMSTAR score 6/10). The systematic review examined the effect of homeopathic *Arnica* in treating a number of clinical conditions, and included one Level III-2 study (Gibson et al, 1991) (with a Jadad score of 2) that assessed the effect of homeopathic *Arnica* on patients with acute trauma. The quality of Gibson et al (1991) was judged to be relatively poor by Ernst and Pittler (1998). Four outcomes were assessed in the Level III-2 study, namely pulse rate, respiratory rate, blood pressure and subjective symptoms (not specified). No evidence of any statistically significant benefit was found for any of the outcomes. Overall, the authors of the systematic review concluded that there is no evidence from "methodologically sound placebo-controlled trials" to indicate that homeopathic *Arnica* is clinically superior to placebo for any of the clinical conditions examined.

*Reviewer comments*

*A major flaw of the systematic review by Ernst and Pittler (1998) was poor reporting; however, it was unclear whether the authors of the included trial poorly-reported their findings, or whether the results were poorly conveyed by the systematic review authors. For example, Ernst and Pittler (1998) indicated that there were "no significant differences" across the four outcomes, although it was unclear whether the significance was referring to differences between treatment arms (homeopathy versus placebo), or within treatment arms (from baseline to follow-up). Based on the author's overall conclusions it was assumed that the lack of significance referred to a lack of inter-group differences.*

*Interpretation of the results by the evidence reviewer was also limited by the fact that the systematic review authors did not present any numerical data or p-values to support their conclusions about homeopathy and acute trauma. Again, it was unclear to the evidence reviewer whether the numerical values were omitted from the systematic review, or not available in the included studies.*

*Evidence statement*

One systematic review of medium quality identified one very small prospectively designed, non-randomised controlled study (poor quality; 20 participants) that compared homeopathy (*Arnica*) with placebo for the treatment of people with acute trauma. LOC: Very low.

Based on only one very small poor quality study is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with acute trauma.

**Table 24 Evidence summary table: the effectiveness of homeopathy for the treatment of acute trauma**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Ernst and Pittler (1998)<br>[Level I/III]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Gibson et al (1991)<br>[Level III-2]<br>Jadad score 2[d]<br>N=20 | Orthopaedic patients for the treatment of acute trauma | *Arnica* 30. Frequency and dose of medication not stated. | Placebo | Pulse rate | No significant difference | "The hypothesis claiming that homeopathic *Arnica* is clinically effective beyond a placebo effect is not based on methodologically sound placebo-controlled trials."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to acute trauma) |
| | | | | | Blood pressure | No significant difference | |
| | | | | | Respiratory rate | No significant difference | |
| | | | | | Subjective symptoms | No significant difference | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.8.3 Mild traumatic brain injury

The effectiveness of homeopathy for the treatment of patients with mild traumatic brain injury was assessed in two systematic reviews (Davidson et al, 2011; Linde and Melchart, 1998) as summarised in Table 25. Davidson et al (2011) (AMSTAR score 8/10) conducted a systematic review which examined the effectiveness of homeopathy for the treatment of psychiatric conditions. One good-quality Level II study (Chapman et al, 1999) was identified that examined the effect of individualised homeopathy compared with placebo in patients with mild traumatic brain injury. The Level II study reported a significant improvement in functional assessment in favour of homeopathy (p-value not reported) compared with placebo. Davidson et al (2011) concluded that there were "weakly positive results in favour of homeopathy for mild traumatic brain injury".

Linde and Melchart (1998) (AMSTAR score 8/11) performed a systematic review that examined the efficacy of individualised homeopathy on a variety of clinical conditions. The authors identified an earlier publication of the same Level II study (Chapman et al, 1997) that also reported that homeopathy was "significantly superior" to placebo for the treatment of mild traumatic brain injury. As the study was only available as an abstract at the time of the 1998 systematic review, no details regarding the specific outcomes that were used to measure efficacy were provided. In addition, no p-values were reported in order to support the claim of "significance". Overall, Linde and Melchart (1998) concluded that, across all clinical conditions, any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

*Evidence statement*

Two systematic reviews of medium quality identified one small randomised controlled trial (good quality; 61 participants) that compared homeopathy with placebo for the treatment of people with mild traumatic brain injury. LOC: Low.

Based on only one small study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with mild traumatic brain injury.

**Table 25 Evidence summary table: the effectiveness of homeopathy for the treatment of mild traumatic brain injury**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Davidson et al (2011)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Chapman et al (1999)<br>[Level II]<br>Good quality<br>N=61[d] | Patients with mild traumatic brain injury | Individualised homeopathy | Placebo | Multivariate analysis of variance for functional assessment | Significant improvement favouring homeopathy (p=NR) | Weakly positive results in favour of homeopathy for mild traumatic brain injury |
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Chapman et al (1997)[e]<br>[Level II]<br>Quality not assessed[f]<br>N=50 | Patients with mild traumatic brain injury | Best-fitting from 18 predefined homeopathic remedies | Placebo | Unclear | "Homeopathy significantly superior" | No overall conclusions were provided about the efficacy of homeopathy in patients with mild traumatic brain injury |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; NR, not reported; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] 50 participants completed the study.

[e] Chapman et al (1997) is an abstract and refers to the same study that was later reported in Chapman et al (1999) and included in the systematic review by Davidson et al (2011).

[f] The quality of the study was not assessed, as it was available as an abstract only.

### 4.8.4 Postoperative pain-agitation syndrome

The effectiveness of homeopathy for the treatment of patients with postoperative pain-agitation syndrome was assessed in two systematic reviews (Altunc et al, 2007; Cucherat et al, 2000) as summarised in Table 26. Both systematic reviews included the same Level II study (Alibeu and Jobert, 1990).

Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". Altunc et al (2007) (AMSTAR score 6/10) performed a systematic review to assess the efficacy of homeopathy in nine childhood and adolescent conditions, including postoperative pain-agitation syndrome. The Level II study by Alibeu and Jobert (1990) investigated the effect of homeopathic *aconite* in 50 patients with postoperative pain-agitation syndrome. Both systematic reviews reported that the Level II study found a significant difference in sedation of agitation 15 minutes after operation that favoured homeopathy over placebo. Altunc et al (2007) noted that the "beneficial effects" for homeopathy in the treatment of postoperative agitation "require independent replication". The quality of the Level II study was not specified by Cucherat et al (2000). Altunc et al (2007) graded Alibeu and Jobert (1990) a Jadad score of 2. Overall, Altunc et al (2007) concluded that "the evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition". Cucherat et al (2000) concluded "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Evidence statement*

Two systematic reviews of medium to good quality identified one small randomised controlled trial (poor quality; 50 participants) that compared homeopathy (*Aconite*) with placebo for the treatment of people with postoperative pain-agitation syndrome. LOC: Very low.

Based on only one small poor quality study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with postoperative pain-agitation syndrome.

**Table 26 Evidence summary table: the effectiveness of homeopathy for the treatment of postoperative pain-agitation syndrome**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Altunc et al (2007)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Alibeu and Jobert (1990)<br>[Level II]<br>Jadad score 2[d]<br>N=50 | Patients with postoperative pain-agitation syndrome<br>• Mean age 6 months-14 years<br>• 72% male<br>• Concomitant treatment: Halothane (1.5%), nitric oxide, Alimemazine (1 mg/kg), methohexital (25 mg/kg intrarectally) | *Aconite*, dose not reported, administered at least once, to be repeated as many times as necessary | Placebo | Sedation of agitation (within 15 minutes of operation) | Significant difference ($p<0.05$) | "The evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to postoperative pain-agitation syndrome) |
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Alibeu and Jobert (1990)<br>[Level II]<br>Quality not specified<br>N=50 | Patients with postoperative pain-agitation syndrome | *Aconite* 4 °C | Placebo | Sedation of agitation (within 15 minutes of operation) | Significant difference in favour of homeopathy ($p=0.002$) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to postoperative pain-agitation syndrome) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

## 4.9 Musculoskeletal and connective tissue disorders

### 4.9.1 Ankylosing spondylitis

The effectiveness of homeopathy for the treatment of ankylosing spondylitis was assessed in one systematic review (Bellavite et al, 2011; AMSTAR score 5/10) as summarised in Table 27. The authors conducted a broad review of recent advances in homeopathy and immunology across a range of clinical areas. One Level II study was identified that assessed the efficacy of homeopathy compared to placebo in patients with ankylosing spondylitis (Schirmer et al, 2000). The intervention group received intramuscular treatment with a combination of low homeopathic potencies of *Formica rufa* and the patient's own blood. No significant differences were found between the homeopathy and placebo groups, based on a questionnaire on arthritis and a general assessment by a physician. The quality of the study by Schirmer et al (2000) was not formally assessed by the authors of the systematic review. Bellavite et al (2011) concluded that there was "negative scientific evidence" (i.e. a lack of evidence of benefit) for *Formica rufa* 6X in ankylosing spondylitis.

*Evidence statement*

One systematic review of poor quality identified one small randomised controlled trial (quality not reported; 104 participants) that compared homeopathy (*Formica rufa*) with placebo for the treatment of people with ankylosing spondylitis. LOC: Very low.

Based on only one small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with ankylosing spondylitis.

**Table 27 Evidence summary table: the effectiveness of homeopathy for the treatment of ankylosing spondylitis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Schirmer et al (2000)<br>[Level II]<br>Quality result not reported<br>N=104 | Patients with ankylosing spondylitis | Intramuscular treatment with a combination of low homeopathic potencies of *Formica rufa* and the patient's own blood | Placebo (injection of saline) | Questionnaire on arthritis and general physician assessment | No difference compared to placebo | There is "negative scientific evidence" (i.e. lack of evidence of benefit) regarding the efficacy of *Formica rufa* 6X in patients with ankylosing spondylitis |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.9.2 Chronic polyarthritis

The effectiveness of homeopathy for the treatment of chronic polyarthritis was assessed in one systematic review (Bellavite et al, 2011; AMSTAR score 5/10) as summarised in Table 28. The authors conducted a broad review of recent advances in homeopathy and immunology across a range of clinical areas. One Level II study was identified that assessed the efficacy of homeopathy compared to placebo in patients with chronic polyarthritis (Wiesenauer and Gaus, 1991). Efficacy was assessed based on several outcomes: inflammation markers, functional indexes, use of 'standard' drugs, and a general assessment. The Level II study reported remarkable improvement in symptoms in both groups; however, according to Bellavite et al (2011), "the result was a significant efficacy of the homeopathy remedy" when consumption of antirheumatic and analgesic drugs and the assessment of pain by the patient were combined into a single outcome variable. Bellavite et al (2011) concluded that overall there were slightly better outcomes for homeopathy (based on one Level II study of unknown quality).

*Reviewer comments*

*The evidence reviewer cannot comment on the quality of the one included Level II study, as it was not formally assessed by Bellavite et al (2011). It was also unclear to the evidence reviewer how the individual outcomes were combined into a single outcome variable and whether the grouping of outcomes into a single measure was the intention of Wiesenauer and Gaus (1991) at the beginning of the study or whether it was a post-hoc analysis.*

*It was assumed from the results provided by Bellavite et al (2011) that the "significant efficacy" of the combined measure in the homeopathy group referred to a significant difference over the placebo group, rather than a change from baseline; however, this was unclear from the poor wording of the results.*

*Evidence statement*

One systematic review of poor quality identified one small randomised controlled trial (quality not reported; 111 participants) that compared homeopathy (*Rheumaselect*) with placebo for the treatment of people with chronic polyarthritis. LOC: Very low.

Based on only one small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with chronic polyarthritis.

**Table 28 Evidence summary table: the effectiveness of homeopathy for the treatment of chronic polyarthritis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Wiesenauer and Gaus (1991)<br>[Level II]<br>Quality result not reported<br>N=111 | Patients with chronic polyarthritis | Homeopathic preparation Rheumaselect[d] | Placebo | Inflammation markers, functional indexes, use of 'standard' drugs, general assessment | A remarkable improvement in symptoms was reported for both groups. However, when consumption of antirheumatic and analgesic drugs and the assessment of pain by the patient were combined into a single outcome variable, the result was a significant efficacy of the homeopathic remedy. | Overall slightly better outcomes in the homeopathy group |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] A mixture of low potencies of *Rhus toxicodendron, Bryonia, Nux vomica, Berberis, Ledum*

### 4.9.3 Delayed-onset muscle soreness

The effectiveness of homeopathy for the treatment of DOMS was assessed in two systematic reviews (Ernst and Barnes, 1998; Ernst and Pittler, 1998) as summarised in Table 30. In total, the systematic reviews included three Level II studies (Jawara et al, 1997; Tveiten et al, 1991; Vickers et al, 1997) and a series of five Level III-2 trials by the same authors (Hildebrandt and Eltze 1983a; Hildebrandt and Eltze 1983b; Hildebrandt and Eltze 1983c; Hildebrandt and Eltze 1983d; Hildebrandt and Eltze, 1984) (Table 29). Both of the systematic reviews were of reasonable quality, although neither performed a meta-analysis of the data.

**Table 29 Matrix indicating the studies that were included in the systematic reviews of delayed-onset muscle soreness**

| | | Systematic review | |
|---|---|---|---|
| | | **Ernst and Barnes (1998) [Level I/III]** | **Ernst and Pittler (1998) [Level I/III]** |
| **Study ID** | **Jarawa et al (1997) [Level II]** | ✓ | |
| | **Vickers et al (1997) [Level II]** | ✓ | |
| | **Tveiten et al (1991) [Level II]** | ✓ | ✓ |
| | **Hildebrandt and Eltze (1984) [Level III-2)** | ✓ | ✓ |
| | **Hildebrandt and Eltze (1983a) [Level III-2)** | ✓ | |
| | **Hildebrandt and Eltze (1983b) [Level III-2)** | ✓ | |
| | **Hildebrandt and Eltze (1983c) [Level III-2)** | ✓ | |
| | **Hildebrandt and Eltze (1983d) [Level III-2)** | ✓ | |

Ernst and Barnes (1998) (AMSTAR score 7/10) conducted a systematic review aimed at comparing the efficacy of homeopathy to placebo in DOMS. Three Level II studies were identified that examined DOMS in healthy volunteers (Jawara et al, 1997; Tveiten et al, 1991; Vickers et al, 1997). None of the trials reported a significant difference in soreness intensity or mean muscle soreness after exercise between the homeopathy and placebo groups. In terms of the timing or duration of soreness, Tveiten et al (1991) reported no significant difference in soreness duration between the treatment groups, and Vickers et al (1997) reported no significant inter-group differences based on “symptom free days”, “days to no soreness” and “days of no medication”.

The systematic review also included five Level III-2 studies (Hildebrandt and Eltze 1983a; Hildebrandt and Eltze 1983b; Hildebrandt and Eltze 1983c; Hildebrandt and Eltze 1983d; Hildebrandt and Eltze, 1984) that examined a variety of strengths and dosing regimens of *Rhus toxicodendron* or *Arnica* on DOMS in female participants. All five studies measured DOMS in the participants’ arms and reported a smaller decrease in muscle strength in at least one of the homeopathic regimens compared to

placebo; however the statistical significance of the findings were not reported. One study reported a shorter duration of arm soreness (Hildebrandt and Eltze, 1984) and another reported less intense soreness (Hildebrandt and Eltze 1983d) in at least one active treatment group, and in at least one arm of the participant, compared with placebo. Again, the significance of the findings is not clear due to the fact that p-values were not provided. As it is likely that any statistically significant findings would have been clearly identified, it is assumed that no statistically significant inter-group differences were achieved.

Overall, Ernst and Barnes (1998) reported that the "partly positive findings" in favour of homeopathy were all from Level III-2 studies that had a high risk of bias. They concluded that there was "no convincing evidence that the homeopathic remedies tested are more than placebos".

Ernst and Pittler (1998) (AMSTAR score 6/10) performed a broad review of homeopathic *Arnica* and included the DOMS studies by Tveiten et al (1991; Level II) and Hildebrandt and Eltze (1984; Level III-2). No additional results were reported, and the systematic review authors concluded overall that there is no evidence based on "methodologically sound placebo-controlled trials" that *Arnica* has any clinical effect beyond that of placebo.

*Reviewer comments*

*A major limitation of the evidence base for DOMS was low recruitment/small studies. For example, Jawara et al (1997) calculated that a sample size of 170 would be needed to have 80% power at a 5% level of significance; however, the study only included 36 participants.*

*A meta-analysis is often conducted as a means of overcoming small sample sizes and underpowered studies; however it would have been inappropriate in this instance given the highly heterogeneous trials. In particular, a wide variety of homeopathic remedies were used and there were also significant differences between the trials in terms of the type and extent of exercise used to induce DOMS (for example, bilateral upper arm muscle flexion and extension; bench-stepping exercise; or running a marathon).*

*Evidence statement*

Two systematic reviews of medium quality identified three randomised controlled trials (medium to good quality; total of 143 participants, range: 36-57) and five prospectively designed, non-randomised controlled studies (poor quality; total of 172 participants, range: 24-44) that compared homeopathy with placebo for the treatment of people with delayed onset muscle soreness. The five non-randomised controlled studies were conducted by the same research group. LOC: Low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with delayed-onset muscle soreness.

**Table 30 Evidence summary table: the effectiveness of homeopathy for the treatment of delayed-onset muscle soreness**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Ernst and Barnes (1998)<br>[Level I/III]<br>AMSTAR: 7/10<br><br>SR of homeopathy for delayed-onset muscle soreness | Jawara et al (1997)<br>[Level II]<br>Quality score 85[d]<br>N=36 | Oslo Marathon participants with delayed-onset muscle soreness | *Arnica Montana* D30, 5 pills twice daily for 5 days starting 1 day prior to the Oslo Marathon | Placebo | Soreness intensity (VAS) | No significant inter-group differences, but a trend for less soreness in homeopathy compared with placebo group | "The partly positive findings in favour of homeopathy… are based on trials that were non-randomised and thus are open to bias, and which involve small numbers of patients."<br><br>"The results of all eight clinical trials of homeopathy for delayed-onset muscle soreness do not provide convincing evidence that the homeopathic remedies tested are more than placebos." |
| | | | | | Serum CK concentrations | No significant inter-group differences, but a trend for lower serum CK in homeopathy compared with placebo group | |
| | Vickers et al (1997)<br>[Level II]<br>Quality score 85[d]<br>N=57 | Healthy volunteers with delayed-onset muscle soreness | *Arnica Montana* 30C + *Rhus toxicodendron* 30C + sarcolactic acid 30C, one tablet three times daily, one day prior to exercise until cessation of soreness | Placebo | Mean muscle soreness (during the 5 post-exercise days) | No significant inter-group differences, but a trend for less soreness in placebo compared with the homeopathy group | |
| | | | | | Symptom free days | No significant inter-group differences | |
| | | | | | Maximum soreness score | No significant inter-group differences | |
| | | | | | Days to no soreness | No significant inter-group differences | |
| | | | | | Days of no medication | No significant inter-group differences | |
| | Tveiten et al (1991)<br>[Level II]<br>Quality score 60[d]<br>N=50 | Healthy volunteers with delayed-onset muscle soreness | *Arnica montana* 30C + *Rhus toxicodendron* 30C one tablet three times daily one day prior to exercise continuing until cessation of soreness | Placebo | Soreness intensity (VAS) | Intergroup differences did not approach statistical significance (p>0.2), but trend favoured homeopathy | |
| | | | | | Soreness duration | Intergroup differences did not approach statistical significance (p>0.2), but trend favoured homeopathy | |
| | Hildebrandt and Eltze (1984)<br>[Level III-2]<br>Quality score 38[d] | Healthy women with delayed-onset muscle | *Arnica* (a) D2 (b) D3 (c) D4 (d) D5 (e) D6 (f) D8, 3x16 drops daily for 6 days post | Placebo | Soreness intensity | No significant inter-group differences | |
| | | | | | Soreness duration | Shorter duration in homeopathic group (b) compared with placebo (both arms) and in group (c) compared with placebo (left arm | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | N=42 | soreness | exercise | | | only); p-values NR | |
| | | | | | Maximal isometric muscle strength | Less decrease in muscle strength in homeopathic group (b) vs placebo (both arms), and in group (c) vs placebo (left arm only); p-values NR | |
| | | | | | Serum CK concentrations | NR | |
| | Hildebrandt and Eltze (1983a)<br>[Level III-2]<br>Quality score 38[d]<br>N=28 | Healthy women with delayed-onset muscle soreness | *Rhus toxicodendron* D4, 5x10 drops daily for 7 days post exercise | Placebo | Soreness intensity | No significant inter-group differences | |
| | | | | | Soreness duration | No significant inter-group differences | |
| | | | | | Maximal isometric muscle strength | Less decrease in muscle strength in homeopathy group vs placebo; p-value NR | |
| | Hildebrandt and Eltze (1983b)<br>[Level III-2]<br>Quality score 38[d]<br>N=34 | Healthy women with delayed-onset muscle soreness | *Rhus toxicodendron* D4 (a) 1x50 drops daily, (b) 3x16 drops daily, (c) 5x10 drops daily, (d) 6x8 drops daily, for 7 days post exercise | Placebo | Soreness intensity | NR | |
| | | | | | Soreness duration | NR | |
| | | | | | Maximal isometric muscle strength | Less decrease in muscle strength in homeopathic groups (a) and (d) vs placebo; p-value NR | |
| | | | | | Serum CK concentrations | NR | |
| | Hildebrandt and Eltze (1983c)<br>[Level III-2]<br>Quality score 38[d]<br>N=24 | Healthy women with delayed-onset muscle soreness | *Rhus toxicodendron* D4 (a) 1x5 drops daily, (b) 3x5 drops daily, (c) 5x10 drops daily, for 7 days post exercise | Placebo | Soreness intensity | No significant inter-group differences | |
| | | | | | Soreness duration | No significant inter-group differences | |
| | | | | | Maximal isometric muscle strength | Less decrease in muscle strength in homeopathic groups (b) and (c) vs placebo (right arm only); p-value NR | |
| | Hildebrandt and Eltze (1983d) | Healthy women with | *Rhus toxicodendron* (a) D2 (b) D3 (c) D4 | Placebo | Soreness intensity | Less soreness in homeopathic group (c) vs placebo (both arms); p-value NR | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | [Level III-2]<br>Quality score 38[d]<br>N=44 | delayed-onset muscle soreness | (d) D5 (e) D6 (f) D8, 3x16 drops daily for 7 days post exercise | | Soreness duration | NR | |
| | | | | | Maximal isometric muscle strength | Less decrease in muscle strength in homeopathic group (a) vs placebo (both arms) and in group (c) compared with placebo (right arm only); p-value NR | |
| | | | | | Serum CK concentrations | Lower serum values in homeopathic group (a) compared with placebo; p-value NR | |
| Ernst and Pittler (1998)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Tveiten et al (1991)<br>[Level II]<br>Jadad score 4[e]<br>N=36 | Participants in the Oslo Marathon (Norway) | *Arnica montana* D30 5 pills twice daily for 5 days starting 1 day prior to race | Placebo pills as per verum schedule | Blood tests, including serum creatine kinase concentrations | "No significant intergroup differences but a trend for serum creatine kinase concentrations to be lower with *Arnica* than placebo" | "The hypothesis claiming that homeopathic *Arnica* is clinically effective beyond a placebo effect is not based on methodologically sound placebo-controlled trials."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to delayed-onset muscle soreness) |
| | | | | | Soreness intensity (VAS) | "No significant intergroup differences but a trend for soreness to be lower with *Arnica* than placebo" | |
| | | | | | Soreness duration | No significant difference | |
| | Hildebrandt and Eltze (1984)<br>[Level III-2]<br>Jadad score 1[e]<br>N=42 | Healthy women for the treatment of delayed-onset muscle soreness | *Arnica* D2, D3, D4, D5, D6, D8 - 16 drops, 3 times a day for 6 days after exercise | Placebo drops as per verum schedule | Maximal isometric muscle strength | "Less decrease in muscle strength in group B vs placebo (both arms)"[e] | |
| | | | | | Soreness intensity | No significant difference | |
| | | | | | Soreness duration | "Shorter duration of soreness in group B (both arms) and C (left arm only) vs placebo"[f,g] | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CK, creatinine kinase; D, decimal; NR, not reported; SR, systematic review; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality was assessed using a "pre-defined list of criteria" (further details not specified) in which a score of ≥55 indicates studies of "higher quality".
[e] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).
[f] What constitutes groups B and C were not defined by the authors.
[g] Lower creatinine kinase concentration on day 6 in group C vs placebo.

### 4.9.4 Fibromyalgia

The effectiveness of homeopathy in the treatment of fibromyalgia was assessed in seven systematic reviews as summarised in Table 31 and Table 32. Overall, the systematic reviews included four Level II studies (Bell et al, 2004; Fisher et al, 1989; Fisher, 1986; Relton et al, 2009). Two of the seven reviews (Bellavite et al, 2011; Perry et al, 2010) reported results from all four Level II studies (see Table 31). Perry et al (2010) provided the most comprehensive details of the individual study results.

**Table 31 Matrix indicating the studies that were included in the systematic reviews of fibromyalgia**

| | | Study ID | | | |
|---|---|---|---|---|---|
| | | Relton et al (2009) [Level II] | Bell et al (2004) [Level II] | Fisher et al (1989) [Level II] | Fisher (1986) [Level II] |
| Systematic review | Bellavite et al (2011) [Level I] | ✓ | ✓ | ✓ | ✓ |
| | Davidson et al (2011) [Level I] | | ✓ | ✓ | ✓ |
| | de Silva et al (2010) [Level I] | | ✓ | ✓ | ✓ |
| | Perry et al (2010) [Level I] | ✓ | ✓ | ✓ | ✓ |
| | Porter et al (2010) [Level I] | | ✓ | ✓ | |
| | Baranowsky et al (2009) [Level I] | | ✓ | | |
| | Holdcraft et al (2003) [Level I] | | | ✓ | |

Perry et al (2010) (AMSTAR score 8/10) conducted a systematic review that specifically examined the efficacy of homeopathy in the treatment of fibromyalgia. Four Level II studies (Bell et al, 2004; Fisher et al, 1989; Fisher, 1986; Relton et al, 2009) were identified, none of which were "without serious flaws" (Perry et al, 2010). The two highest quality studies (Bell et al, 2004; Fisher et al, 1989) received a Jadad score of 4 (Perry et al, 2010), and both reported significantly fewer tender points (or a significantly greater improvement in tender point count) in the homeopathy group, compared to placebo. In addition, Bell et al (2004) reported statistically significant differences in favour of homeopathy in the following outcomes: number of patients with at least a 25% improvement in tender point pain on palpation; Fibromyalgia Score; and Global Health Rating. Fisher et al (1989) (a cross-over study) also reported that a significantly greater number of patients experienced improved pain and sleep in the homeopathy group (*Rhus toxicodendron*) compared with placebo (p=0.0052). However, Perry et al (2010) noted that a re-analysis of the data performed by Colquhoun (1990) "suggested that there was no evidence for the efficacy of homeopathy treatment when distribution-free-randomisation tests were employed".

An earlier Level II study by Fisher (1986; Jadad score 3) examined the efficacy of three homeopathic remedies compared to placebo. The main criticisms of the trial cited by Perry et al (2010) were that the authors did not describe the randomisation process, presented very little demographic information on the patients, conducted the trial over a short duration, and recruited very few patients (≤5 patients in each of the three homeopathic treatment arms). No significant differences were reported between the three homeopathy groups and the placebo group in terms of pain and sleep; however, the results of both outcomes significantly favoured homeopathy when the authors re-grouped patients into those who received "poorly-indicated" homeopathic remedies and those that received "well-indicated" treatments.

Finally, Perry et al (2010) identified a poor-quality Level II study (Jadad score 2) by Relton et al (2009) for inclusion in their systematic review. Relton et al (2009) adopted an individually tailored homeopathic approach (i.e. where remedy choice and potency could be altered throughout the study). The results indicated that those in the homeopathy group achieved a significantly greater reduction in the total Fibromyalgia Impact Questionnaire score, compared to the "usual care" group ($p<0.01$) which included patients treated with one or more of physiotherapy, aerobic exercise, anti-inflammatory drugs, or anti-depressants. However, on all other outcomes (tender point count, European Quality of Life Scale, Hospital Anxiety and Depression Scale, Measure Yourself Medical Outcome Profile, and Fibromyalgia Impact Questionnaire – pain score), the study found no significant inter-group differences. Perry et al (2010) highlighted the major limitations of the Level II study by Relton et al (2009), including the utilisation of a study design that did not control for placebo effects and a very small sample size due to a high dropout rate in the "usual care" treatment arm. Overall, Perry et al (2010) concluded that the "effectiveness of homeopathy as a symptomatic treatment for fibromyalgia remains unproven", largely due to the limited number of Level II studies and the relatively poor scientific quality of the existing trials.

The systematic review by Bellavite et al (2011) (AMSTAR score 5/10) aimed to evaluate the effectiveness of homeopathy for the treatment of upper airways and ear-nose-throat ailments, respiratory allergies, arthrorheumatic diseases and osteoarthritis. Based on the findings of three of the included Level II studies (Bell et al, 2004; Fisher et al, 1989; Relton et al, 2009), Bellavite et al (2011) concluded that there was "good positive evidence" for the effective treatment of fibromyalgia with individualised homeopathy. Based on Fisher (1996), Bellavite et al (2011) concluded that there was "negative scientific evidence" (i.e. lack of evidence of benefit) for homeopathic *Arnica, Rhus toxicodendron* and *Bryonia* 6C for the treatment of fibromyalgia. Bellavite et al (2011) did not provide a quality assessment of these studies.

The findings of Bellavite et al (2011) were limited by poor reporting. In many instances it was unclear whether the positive findings were statistically significant, as p-values were rarely reported. Instead, general statements were provided, such as "there was a better reduction of symptoms in patients treated with homeopathy". The one exception was the reporting of results from the study by Bell et al (2004) as finding "significantly better outcomes" in the homeopathy patients compared to placebo, although the exact p-values were still not clear and the specific outcomes that achieved statistical significance were not identified.

Davidson et al (2011) (AMSTAR score 8/10) examined the evidence for the efficacy of homeopathy across a variety of chronic conditions, including fibromyalgia. Davidson et al (2011) identified three of the same Level II studies as the systematic reviews by Perry et al (2010) and Bellavite et al (2011)

(Bell et al, 2004; Fisher 1986; Fisher et al, 1989). Bell et al (2004) was the methodologically strongest study, scoring well in terms of methodology on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and SIGN quality assessment measures. Fisher (1986) and Fisher et al (1989) were both given low ratings. Bell et al (2004) reported statistically significant differences favouring homeopathy over placebo on four of the five measures presented in Davidson et al (2011). One of those measures was the McGill Affective Pain score and was reported as $p<0.01$; however this conflicts with reporting of that measure in the systematic review by Perry et al (2010), which reported a positive but non-significant trend favouring homeopathy and a p-value of $p<0.1$.

Davidson et al (2011) noted that poor reporting, particularly in Fisher et al (1989) made some results "impossible to interpret". Beyond poor reporting, the authors of the systematic review made a general statement that the current evidence base for homeopathy and fibromyalgia is neither "sufficiently rigorous nor sufficiently plentiful" to warrant any definite answers. However, Davidson et al (2011) concluded that the "results do not preclude the possibility of some benefit".

The remaining four systematic reviews (Baranowsky et al, 2009; de Silva et al, 2010; Holdcraft et al, 2003; Porter et al, 2010), assessed the efficacy of various complementary and alternative medicines (including homeopathy) in the treatment of fibromyalgia. Due to the broad focus of the reviews, the information pertaining specifically to the efficacy of homeopathy was limited, and no additional outcomes or results were provided that have not been discussed above. Two of the reviews had particularly poor reporting: Baranowsky et al (2009) (AMSTAR score 5/10) did not provide any p-values to support claims of significance; and Porter et al (2010) (AMSTAR score 6/10) made a broad statement that a "positive effect" was found for homeopathy, without reporting results according to separate outcome measures.

Baranowsky et al (2009) only included one of the Level II studies (Bell et al, 2004) that was identified by the other systematic reviews. Overall, Baranowsky et al (2009) concluded that homeopathy is a "promising option in the treatment of fibromyalgia" and recommended further studies to confirm the existing findings.

Porter et al (2010) included two of the Level II studies (Bell et al, 2004; Fisher et al, 1989) that were identified by the other systematic reviews. Similarly to Baranowsky et al (2009), Porter et al (2010) concluded that homeopathic treatment was associated with a positive effect on "diagnostic symptoms" of fibromyalgia. However, Porter et al (2010) noted that the homeopathic treatment regimens adopted in many of the trials did not reflect the "clinical approach used by most practitioners" of homeopathy, which involves individually tailored treatments.

Holdcraft et al (2003) (AMSTAR score 5/10) only identified one of the studies (Fisher et al, 1989) for inclusion in their review and was critical of the cross-over design, particularly the absence of a wash-out period between the active and placebo interventions. Holdcraft et al (2003) also questioned the validity of assessing the sleep and pain scores as a combined measure. Overall, Holdcraft et al (2003) stated that there is "limited evidence" to support the use of homeopathy in fibromyalgia due to the low quality evidence.

The review by de Silva et al (2010) (AMSTAR score 7/10) identified three of the relevant Level II studies discussed above (Bell et al, 2004; Fisher et al, 1989; Fisher 1986) and reported that they all found that homeopathy was associated with an improvement in pain, but were small in size. Similarly to Holdcraft et al (2003), de Silva et al (2010) questioned the results of Fisher et al (1989), citing an independent re-analysis that found "no firm support for the efficacy of homeopathic treatment" over

placebo (Colquhoun, 1989). De Silva et al (2010) concluded that independent replication is necessary due to the fact that each of the three trials used different homeopathic remedies. They also stated that publication bias is a "major concern" that needs to be considered alongside the positive results.

*Reviewer comments*

*The general consensus across the seven systematic reviews was that Bell et al (2004) was the most methodologically sound trial of homeopathy and fibromyalgia. The majority of the review authors highlighted the significant methodological flaws in Fisher et al (1989). In particular, the use of a cross-over design with no wash-out period between active and placebo treatments was noted as a major flaw (Holdcraft et al, 2003; Perry et al, 2010). The evidence reviewer concurs that there is a possibility that carry-over treatment effects may have confounded results in Fisher et al (1989).*

*In addition, two of the systematic reviews (de Silva et al, 2010; Perry et al, 2010) made reference to an independent re-analysis of Fisher et al (1989) by Colquhoun (1990) that found "no evidence for the efficacy of homeopathic treatment when distribution-free randomisation tests were employed".*

*Evidence statement*

Seven systematic reviews of poor to medium quality identified three randomised controlled trials (poor to good quality; total of 116 participants, range: 24-62) that compared homeopathy with placebo for the treatment of people with fibromyalgia.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with fibromyalgia.

Two systematic reviews of poor and medium quality identified one very small randomised controlled trial (poor quality; 47 participants) that compared homeopathy with other therapies (physiotherapy, aerobic exercise, anti-inflammatory drugs and anti-depressant medications) for the treatment of people with fibromyalgia. LOC: Very low.

Based on only one very small study of poor quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to the other therapies for the treatment of people with fibromyalgia.

**Table 32 Evidence summary table: the effectiveness of homeopathy for the treatment of fibromyalgia**

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011) [Level I] AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Relton et al (2009) [Level II] Quality not specified N=47 | Fibromyalgia patients | Individualised homeopathic prescription | Conventional treatment | FIQ | Better reduction of symptoms in patients treated with homeopathy compared to control; no adverse effects | The review concluded that there was "good positive evidence" (statistically significant evidence of benefit from 1-2 properly randomised trials) for individualised homeopathy in fibromyalgia.<br><br>• Positive evidence was obtained from Level II studies by Fisher et al (1989), Bell et al (2004), and Relton et al (2009). Bellavite et al (2011) also cited two reviews: one with "positive evidence" for individualised homeopathy and fibromyalgia (Baranowsky et al 2009) and one with "positive but insufficient evidence" (Perry et al 2010).<br><br>The review also concluded that there was "negative scientific evidence" (statistically significant negative evidence (i.e. lack of evidence of benefit) from 1 or more Level II studies) for *Arnica, Rhus toxicodendron and Bryonia* 6C for the treatment of fibromyalgia<br><br>• Fisher 1986 found no |
| | Bell et al (2004) [Level II] Quality not specified N=62 | Fibromyalgia patients | Individualised homeopathic prescription | Placebo | Pain, motion tenderness, quality of life | Significantly better outcomes of the homeopathy group compared to placebo | |
| | Fisher et al (1989) [Level II] Quality not specified N=30[d] | Fibromyalgia patients | *Rhus tox* (individualised) | Placebo | Pain symptoms | Slightly positive therapeutic effect in most patients in the homeopathy group versus placebo | |
| | Fisher (1986) [Level II] Quality not specified N=24 | Fibromyalgia patients | *Arnica, Rhus tox, Bryonia* 6c | Placebo | Pain symptoms | Trend to better improvement in the homeopathic group, not statistically significant | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | | evidence of an effect |
| Davidson et al (2011)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Bell et al (2004)<br>[Level II]<br>SIGN: "good"<br>N=62 | Fibromyalgia patients | Individualised homeopathy | Placebo | 25% improvement in tender point pain on palpation | Statistically significant difference between groups, favouring homeopathy. Homeopathy group: 50%; Placebo: 15%; p<0.01 | Results do not preclude the possibility of some benefit – efficacy was found for the functional somatic syndromes group (fibromyalgia and chronic fatigue syndrome).<br><br>"Results suggest possible utility for homeopathy." |
| | | | | | TPC | Significant improvement compared to placebo (p<0.05) | |
| | | | | | McGill Affective Pain score | Significant improvement compared to placebo (p<0.01) | |
| | | | | | Appraisal of Fibromyalgia | Significant improvement compared to placebo (p<0.05) | |
| | | | | | MSP | No significant difference between treatment arms | |
| | Fisher et al (1989)<br>[Level II]<br>SIGN: "poor"<br>N=30[d] | Fibromyalgia patients | *Rhus toxicodendron* 6C | Placebo | Unclear | Positive results for homeopathy, especially on tender points | |
| | Fisher (1986)<br>[Level II]<br>SIGN: "poor"<br>N=24 | Fibromyalgia patients | *Rhus toxicodendron, Bryonia alba* or *Arnica montana* | Placebo | Pain (VAS) | Analysis gave significant differences on pain for indicated remedy | |
| | | | | | Sleep (VAS) | Analysis gave significant differences on sleep for indicated remedy | |
| de Silva et al (2010)<br>[Level I] | Bell et al (2004)<br>[Level II]<br>Jadad score 5[f] | Patients with fibromyalgia | Individually selected homeopathic | Placebo | Tenderness | NR | "There was some evidence from three small studies regarding three different |
| | | | | | Tender point pain | Significant improvement in favour of homeopathy; p-value NR | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| AMSTAR: 7/10<br><br>SR of CAM for fibromyalgia | N=62 | | remedy | | Tender point count | Significant improvement in favour of homeopathy; p-value NR | homeopathic approaches. Each demonstrated an improvement in pain in those receiving the standardised or individualised homeopathic remedy (compared with placebo) and two studies demonstrated improvement in sleep. While one of these trials received the lowest of all Jadad scores (Fisher, 1986), another received the maximum score (Bell et al, 2004). The third study has been independently re-analysed and no firm support for the efficacy of homeopathic treatment as found." |
| | | | | | Quality of life | Significant improvement in favour of homeopathy; p-value NR | |
| | | | | | Global health | Significant improvement in favour of homeopathy; p-value NR | |
| | | | | | Depression | Significant improvement in favour of homeopathy; p-value NR | |
| | Fisher et al (1989)<br>[Level II]<br>Jadad score 3[f]<br>N=30[d] | Patients with fibromyalgia<br>• Only patients in whom *R. toxicodendron* was positively indicated after a homeopathic consultation were included | *R. toxicodendron* (6c potency) put up on 125 mg lactose taken 3 times per day. This was a cross-over study with treatment phases of 1 month each in random sequence | Placebo | Tenderness | "Homeopathic treatments significantly improved tenderness as assessed by VAS" (p<0.005) | |
| | | | | | Pain (VAS) | "Homeopathic treatments significantly improved pain as assessed by VAS" (p<0.005) | |
| | | | | | Sleep (VAS) | "Homeopathic treatments significantly improved sleep disturbance as assessed by VAS" (p<0.005) | |
| | Fisher (1986)<br>[Level II]<br>Jadad score 1[f]<br>N=24 | Patients with fibromyalgia | One remedy from *Arnica montana*, *Bryonia alba* and *R. toxicodendron* (all of 6c potency). All the patients received the same | Placebo | Pain | Homeopathic treatments significantly improved pain compared with placebo as assessed by VAS (p<0.05) | |
| | | | | | Sleep | Homeopathic treatments significantly improved sleep compared with placebo as assessed by VAS (p<0.05) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | treatment throughout a 3 month period | | | | |
| Perry et al (2010)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for fibromyalgia | Relton et al (2009)<br>[Level II]<br>Jadad score 2[f]<br>N=47 | Patients with fibromyalgia | Individually tailored homeopathic remedies (one 1 hour baseline interview with homeopath followed by four 30 minute follow up interviews where remedy choice and potency can be assessed and changed | Usual care with one or more of the following: physiotherapy, aerobic exercise, anti-inflammatory drugs, anti-depressants | TPC | No significant inter-group differences | The effectiveness of homeopathy as a symptomatic treatment for fibromyalgia remains unproven (mainly due to the limited number of Level II studies and the relatively poor scientific quality of the existing trials).<br><br>The authors acknowledged that the four included trials were all seriously flawed. In particular, the re-analysis of Fisher et al (1989) by Colquhoun suggested there was no evidence for the efficacy of homeopathic treatment when distribution-free randomisation tests were employed. He criticised Fisher for combining pain and sleep scores thus invalidating the results. Relton (2004) used a design that did not control for placebo effects and was also insufficiently powered due to a high drop-out rate in the |
| | | | | | EuroQol | No significant inter-group differences | |
| | | | | | MYMOPS | No significant inter-group differences | |
| | | | | | HADS | No significant inter-group differences | |
| | | | | | FIQ pain scores | No significant inter-group differences | |
| | | | | | FIQ total score | Significantly greater reduction in total score in the homeopathic group compared to the usual care group (p<0.01) | |
| | Bell et al (2004)<br>[Level II]<br>Jadad score 4[f]<br>N=62 | Patients with fibromyalgia | 41 remedies used, given as LM potencies. Remedy and dosing regimen could be altered at any time after consultation with a homeopath | Placebo | Improvement in TPC | Significantly greater improvement in TPC in intervention group compared to placebo (p<0.05) | |
| | | | | | Number of patients with at least a 25% improvement in TPP on palpation | Significantly more patients experienced a 25% improvement in the intervention group (n=13/26) compared to placebo (n=4/27); p=0.008 (Fisher's exact test, two-tailed) | |
| | | | | | Fibromyalgia scores | Significantly greater improvement in homeopathy compared to placebo group (p<0.05) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | Global health rating (adjusted for anger and depression) | Significantly greater improvement in homeopathy compared to placebo group (p<0.05). At 6 months, those who stayed in the experimental group had a greater gain in global health than the placebo-switch group | usual care group. |
| | | | | | McGill Pain Questionnaire | Greater improvement in homeopathy group compared to placebo (p<0.10) | |
| | | | | | POMS | Greater improvement in homeopathy group compared to placebo (p<0.10) | |
| | Fisher et al (1989)<br>[Level II]<br>Jadad score 4[f]<br>N=30[d] | Patients with fibromyalgia | *Rhus toxicodendron* 6c, two tablets three times daily | Placebo – two tablets three times daily | Number of patients with improved pain and sleep (pain and sleep VAS – combined measure) | Significantly more patients improved in the intervention group (n=53) compared to placebo (n=27); p=0.0052 | |
| | | | | | TPC | Intervention group had significantly fewer tender points (10.6) compared to placebo (14.1); p<0.005[e] | |
| | Fisher (1986)<br>[Level II]<br>Jadad score 3[f]<br>N=24 | Patients with fibromyalgia | One of three homeopathic remedies (*Rhus toxicodendron, Arnica Montana*, or *Bryonia*) in 6c potency twice a day | Placebo – twice a day | Pain | No significant difference between intervention groups and placebo (p=0.19) | |
| | | | | | Pain – subgroup analysis | Significant difference between intervention and placebo groups at 2 and 3 months when those with "poorly indicated" homeopathic remedies were removed, leaving only | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | those with "optimal fit" (p<0.05) | |
| | | | | | Sleep | No significant difference between intervention groups and placebo (p=0.078) | |
| | | | | | Sleep – subgroup analysis | Significant difference between intervention and placebo groups at 2 and 3 months when those with "poorly indicated" homeopathic remedies were removed, leaving only those with "optimal fit" (p<0.05) | |
| Porter et al (2010)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of CAM for multiple conditions | Bell et al (2004)<br>[Level II]<br>Jadad score 5[f]<br>N=62 | Patients with fibromyalgia | Homeopathy – details not specified | Placebo | Physical and psychological outcomes | Positive effect reported for homeopathy – outcomes not reported separately | Both fibromyalgia studies reported that homeopathic treatment had a positive effect on diagnostic symptoms of fibromyalgia.<br><br>However, the treatments used in the review do to necessarily reflect the "clinical approach used by most practitioners to treat these illnesses, which include a mix of natural and unconventionally used |
| | Fisher et al (1989)<br>[Level II]<br>Jadad score 3[f]<br>N=30[d] | Patients with fibromyalgia | *Rhus toxicodendron* | Placebo | Physical outcomes, QoL | Positive effect reported for homeopathy – outcomes not reported separately | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | | medications and natural hormones tailored to each individual case". |
| Baranowsky et al (2009)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of CAM for fibromyalgia | Bell et al (2004)<br>[Level II]<br>Quality score according to 16 formal criteria: 57.5/100<br>N=62 | Patients with fibromyalgia | Individually prescribed homeopathic remedies of daily oral liquid, flexibly dosed LM potencies | Placebo (oral daily liquid) | TPC | Significant improvement in active group compared to placebo; p-value NR | Significant improvement in active group in TPC and TP pain on palpation, appraisal of fibromyalgia scores, global health ratings and helpfulness of treatment as compared to placebo group.<br><br>Homeopathy is a promising option in the treatment of fibromyalgia, although further studies are needed to confirm the findings. |
| | | | | | TPP on palpation | Significant improvement in active group compared to placebo; p-value NR | |
| | | | | | McGill Pain Questionnaire | NR | |
| | | | | | Fibromyalgia quality of life scores | Significant improvement in active group compared to placebo; p-value NR | |
| | | | | | POMS | NR | |
| | | | | | Global health rating (adjusted for anger and depression) | Significant improvement in active group compared to placebo; p-value NR | |
| | | | | | Treatment helpfulness rating | Significant improvement in active group compared to placebo; p-value NR | |
| Holdcraft et al (2003)<br>[Level I]<br>AMSTAR: 5/10 | Fisher et al (1989)<br>[Level II]<br>CONSORT score: 10<br>N=30[d] | Patients with fibromyalgia | *Rhus toxicodendron* (poison ivy) | Placebo | TPC | Mean number of tender points was reduced by 25% in active group. Significant improvement compared to placebo ($p<0.05$) | There is limited evidence to support the use of homeopathy for fibromyalgia due to the low quality of the Level II study. |
| | | | | | Number of | Significant improvement in active | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| SR of CAM for fibromyalgia | | | | | patients with improved pain and sleep (pain and sleep VAS – combined measure) | compared to placebo group (p<0.05) | Results limited by the fact that sleep and pain scores were not reported separately and also by the fact that there was no wash-out period between the active and placebo interventions. |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; CONSORT, Consolidated Standards of Reporting Trials; FIQ, Fibromyalgia Impact Questionnaire; MSP, McGill Sensory Pain; NR, not reported; POMS, Profile of Mood States scale; SIGN, Scottish Intercollegiate Guidelines Network quality analysis; SR, systematic review; TP, tender point; TPC, tender point count; TPP, tender point pain; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit

[c] Study quality as reported in the systematic review

[d] Refers to the number of participants that completed the cross-over periods

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

[f] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.9.5 Knee joint haematoma

The effectiveness of homeopathy for the treatment of knee joint haematoma was assessed in one systematic review (Cucherat et al, 2000; AMSTAR score 10/11) as summarised in Table 33. Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The systematic review identified one Level II study (Thiel, 1991) that investigated the effect of intraarticular injections of homeopathic Traumeel R in patients with knee joint haematoma, compared with intraarticular injections of sodium chloride. Cucherat et al (2000) reported a significant difference in joint mobility (p=0.026) in this Level II study in favour of the homeopathy group. The quality of Thiel (1991) was not formally assessed by Cucherat et al (2000); however, a general comment was made about all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Evidence statement*

One systematic review of good quality identified one small randomised controlled trial (quality not reported; 80 participants) that compared homeopathy (*Traumeel R*) with placebo for the treatment of people with knee joint haematoma. LOC: Very low.

Based on only one small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with knee joint haematoma.

**Table 33 Evidence summary table: the effectiveness of homeopathy for the treatment of knee joint haematoma**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Thiel (1991)<br>[Level II]<br>Quality not specified<br>N=80[d] | Patients with knee joint haematoma | Intraarticular Traumeel R | Intraarticular injections of sodium chloride | Joint mobility | Significant difference in favour of homeopathy (p=0.026) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to knee joint haematoma) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] 73 patients were evaluated.

### 4.9.6 Osteoarthritis

The effectiveness of homeopathy in osteoarthritis was assessed in three systematic reviews as summarised in Table 34 and Table 35. Overall, the systematic reviews included four Level II studies (Nahler et al, 1998; Shealy et al, 1998; Shipley et al, 1983; van Haselen and Fisher, 2000) and one Level III-2 study (Birnesser et al, 2003) (Table 34). The AMSTAR quality ratings of the five systematic reviews ranged from 5/10 (Bellavite et al, 2011) to 6/10 (De Silva et al, 2011; Long and Ernst, 2001).

**Table 34 Matrix indicating the studies that were included in the systematic reviews of osteoarthritis**

| | | Study ID | | | | |
|---|---|---|---|---|---|---|
| | | Van Haselen and Fisher (2000) [Level II] | Nahler et al (1998) [Level II] | Shealy et al (1998) [Level II] | Shipley et al (1983) [Level II] | Birnesser et al (2003) [Level III-2] |
| Systematic review | De Silva et al (2011) [Level I] | ✓ | | ✓ | ✓ | |
| | Long and Ernst (2001) [Level I] | ✓ | ✓ | ✓ | ✓ | |
| | Bellavite et al (2011) [Level I/III] | ✓ | ✓ | ✓ | ✓ | ✓ |

De Silva et al (2011) (AMSTAR score 6/10) provided a broad review of the efficacy of a range of complementary and alternative medicines in the management of osteoarthritis. Three Level II studies were identified that were specific to homeopathy and osteoarthritis (Shealy et al, 1998; Shipley et al, 1983; van Haselen and Fisher, 2000; median Jadad score of 3). One Level II study with three parallel treatment arms reported that homeopathy and placebo were both less effective than fenoprofen in terms of pain on movement and pain at rest in hip or knee osteoarthritis (Shipley et al, 1983). It is assumed that the results were statistically significant; however, no numerical evidence was provided in order to confirm that assumption. The authors concluded that the evidence base was "insufficiently large" to provide conclusive evidence for or against homeopathy in osteoarthritis.

Long and Ernst (2001) (AMSTAR score 6/10) identified four Level II studies for inclusion in their systematic review of homeopathy for the treatment of osteoarthritis (Nahler et al, 1998; Shealy et al, 1998; Shipley et al, 1983; van Haselen and Fisher, 2000). The Level II studies were of reasonable to good quality with three scoring a Jadad score of 3 and one scoring 4. Long and Ernst (2001) confirmed the assumption made above, that fenoprofen produced "highly statistically significant" pain relief compared to homeopathy and placebo in Shipley et al (1983). In contrast, homeopathy was found to be "at least as effective" as a conventional NSAID gel in van Haselen and Fisher (2000), according to Long and Ernst (2001), and not significantly different to conventional medications (hyaluronic acid and paracetamol) in the remaining two Level II studies (Nahler et al, 1998; Shealy et al, 1998).

Long and Ernst (2001) reported that homeopathy was inferior to conventional medication in one trial and not significantly different in three others. As such, they concluded that there is a "positive trend towards the effectiveness of combination homeopathic preparations". However, they acknowledge

that the limited evidence base precludes them from drawing "firm conclusions as to the effectiveness of combination homeopathic remedies" for osteoarthritis.

Bellavite et al (2011) (AMSTAR score 5/10) conducted a systematic review of homeopathy and immunology in three broad clinical areas, one of which was "Arthrorheumatic diseases and osteoarthritis". The Level II and Level III-2 osteoarthritis studies included in this systematic review included four previously discussed Level II studies (Nahler et al, 1998; Shealy et al, 1998; Shipley et al, 1983; van Haselen and Fisher, 2000) and one large (N=592) Level III-2 study (Birnesser et al, 2003) of patients with knee osteoarthritis. In addition to the findings discussed above, Bellavite et al (2011) reported that the complex homeopathic formulation used in Shealy et al (1999) was associated with better pain relief than acetaminophen, but not to a statistically significant extent. The Level III-2 study by Birnesser et al (2003) compared symptom scores between patients who received a homeopathic treatment (*Zeel compositum-N*) and those who received COX-2 inhibitors, and reported that the homeopathic regimen was equivalent to the COX-2 inhibitors.

Overall, Bellavite et al (2011) concluded that there is "good positive evidence" for *Zeel compositum-N* in the treatment of osteoarthritis based on the findings of Nahler et al (1998) and Birnesser et al (2003); and "negative scientific evidence" (i.e. lack of evidence of benefit) for *Rhus toxicodendron* 6X in the treatment of osteoarthritis based on the findings of Shipley et al (1983). The authors of the systematic review suggest that the negative result of the trial by Shipley et al (1983) could be a result of the non-individualised homeopathic remedy used in that trial. They state that it appears that "the tested remedy cannot be effective if prescribed based only upon a diagnosis of disease, but without individualisation of the therapy".

Furthermore, Bellavite et al (2011) suggest that the reported finding of equivalence between a homeopathic gel and piroxicam gel found in van Haselen and Fisher (2000) is important due to the fact that the benefit of piroxicam gel over placebo has been previously established in several double-blind Level II studies (including Norris and Guttadauria, 1987). The authors therefore suggest that there is "indirect proof of the effectiveness of the tested homeopathic remedy" compared to placebo.

*Reviewer comments*

*Several of the systematic reviews reported that the homeopathic interventions were not significantly different to conventional medications, including piroxicam gel, hyaluronic acid, paracetamol and COX-2 inhibitors (based on Level II and III-2 evidence). However, the Level II study by Shipley et al (1983) (identified by all four systematic reviews) reported that homeopathy was significantly inferior to fenoprofen for the treatment of osteoarthritic pain.*

*The authors of the systematic reviews acknowledged that there were some serious methodological flaws in the included studies. Importantly, the cross-over Level II study by Shipley et al (1983) had no wash-out period between treatments. The relatively short duration of the trials (4 to 6 weeks) was also noted as a potential limitation.*

*The evidence reviewer notes that Bellavite et al (2011) may have over-interpreted their results by claiming that the "equivalence" of a homeopathic gel and piroxicam gel provides "indirect proof" of the effectiveness of homeopathy over placebo. In addition, the same review suggested that the negative outcome of Rhus toxicodendon* 6X *compared to fenoprofen was possibly due to the fact that*

*an individualised homeopathic regimen was not used, without any scientific evidence to support the claim.*

*A major limitation across all of the systematic reviews was a lack of information regarding patient characteristics (age, gender, duration of osteoarthritis), and reporting of primary outcomes and results that were often difficult to interpret. It was unclear whether the gaps in reporting were due to poor-quality reporting in the included trials or the systematic reviews themselves.*

*Evidence statement*

Three systematic reviews of poor to medium quality identified one very small randomised controlled trial (medium quality; 36 participants) that compared homeopathy (*Rhus toxicodendron*) with placebo for the treatment of people with osteoarthritis. LOC: Very low.

Based on only one very small study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with osteoarthritis.

Three systematic reviews of poor to medium quality identified four randomised controlled trials (medium quality; total of 406 participants, range: 36 to 184) and one large prospectively designed, non-randomised controlled study (quality not reported; 592 participants) that compared homeopathy with other therapies (fenoprofen, piroxicam gel, hyaluronic acid, paracetamol and COX-2 inhibitors) for the treatment of people with osteoarthritis.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is as effective as the other therapies for the treatment of people with osteoarthritis.

**Table 35 Evidence summary table: the effectiveness of homeopathy for the treatment of osteoarthritis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| De Silva et al (2011)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of CAM for osteoarthritis | van Haselen and Fisher (2000)<br>[Level II]<br>Quality not specified[d]<br>N=184 | Patients with osteoarthritis | Local application of 1g Spiroflor gel three times daily for 4 weeks | 1g piroxicam gel (0.5%) applied three times daily for 4 weeks | Mean pain reduction (VAS) | No difference between the two treatment groups | "Although there was some promising evidence, the evidence base was either insufficiently large or the evidence base was inconsistent", limiting the ability to draw any conclusions about the efficacy of homeopathy in osteoarthritis. |
| | Shealy et al (1998)<br>[Level II]<br>Quality not specified[d]<br>N=65 | Patients with knee osteoarthritis | A homeopathic preparation including *Rhus toxicodendron* 12x, *Causticum* 12x and *Lac Vaccinum* 12x) | Paracetamol 2.6g/day | Reduction in knee pain | No difference between homeopathic preparation and paracetamol | |
| | Shipley et al (1983)<br>[Level II]<br>Quality not specified[d]<br>N=36 | Patients with hip or knee osteoarthritis | *Rhus toxicodendron* 6x | Placebo or fenoprofen 600mg three times daily | Pain on movement (measured by both 10cm VAS and four point pain scores) | Homeopathy less effective than fenoprofen; no difference compared to placebo | |
| | | | | | Pain at rest (measured by both 10cm VAS and four point pain scores) | Homeopathy less effective than fenoprofen; no difference compared to placebo | |
| Long and Ernst (2001)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for | van Haselen and Fisher (2000)<br>[Level II]<br>Jadad score 3[e]<br>N=184 | Patients with knee osteoarthritis | Topical application of 1g SRL® gel to the knee three times daily | Topical application of 1g 0.05% piroxicam gel to the knee three times daily | Mean pain reduction (VAS) | 16.5mm (SD 24.6) VAS in the intervention group (n=86); 8.1mm (SD 25.7) in the comparator group. Difference between treatment groups was 8.4mm (95% CI 0.8, 15.9), adjusted for pain at baseline was 6.8mm (95% | Two of the four included trials present "positive evidence for the effectiveness of combination homeopathic preparations in comparison to conventional medications".<br><br>A third concluded that "*Rhus* |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| osteoarthritis | | | | | | CI -0.3, -13.8) | *toxicodendron* was significantly inferior to conventional medication", while the fourth reported that homeopathic gel was "at least as effective as a conventional NSAID gel".<br><br>Overall, there appears to be a positive trend towards the effectiveness of combination homeopathic preparations; however, the authors acknowledged the small number of Level II studies from which their conclusions are drawn. |
| | | | | | Joint tenderness (measured by the single-joint Ritchie index) | No significant difference between treatment groups (p=0.78) | |
| | Nahler et al (1998)<br>[Level II]<br>Jadad score 3[e]<br>N=121 | Patients with knee osteoarthritis | Two 2mL intra-articular Zeel® injections per week | One 2mL intra-articular Hyalart® (hyaluronic acid) injection per week | Pain during the night | No significant difference between treatment groups (p=0.3077) | |
| | | | | | Duration of morning stiffness | No significant difference between treatment groups (p=0.9211) | |
| | | | | | Final assessment by physician and patient | No significant difference between treatment groups (p-value NR) | |
| | | | | | Tolerance (measured by VAS) | No significant difference between treatment groups (p-value NR) | |
| | | | | | Subjective reduction in arthritic pain during active movement, measured by standardised VAS | No significant differences between the two treatments (p=0.4298) | |
| | | | | | Number of patients with undesirable adverse effects | Significance of inter-group differences not reported (intervention group: n=6; control group: n=13) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Shealy et al (1998)<br>[Level II]<br>Jadad score 3[e]<br>N=65 | Patients with knee osteoarthritis | Oral administration of 10 drops of a homeopathic preparation (*Rhus toxicodendron, Causticum* and *Lac Vaccinum*) and placebo capsules four times daily | Paracetamol capsules four times daily (daily dose of 2600mg) and liquid placebo | Percentage of patients achieving clinically useful pain reduction (40% or greater), measured daily by VAS | Non-significant difference between treatment groups (55% of patients receiving homeopathy and 38% of those receiving paracetamol) | |
| | Shipley et al (1983)<br>[Level II]<br>Jadad score 4[e]<br>N=36 | Patients with hip or knee osteoarthritis | Five drops of *Rhus toxicodendron* (6x:1/1000000 dilution) three times daily and placebo capsules | Oral administration of two fenoprofen capsules (each 300mg) three times daily and placebo drops; or placebo drops and placebo capsules | Pain at rest (measured by both 10cm VAS and four point pain scores) | No significant difference between homeopathy and placebo; fenoprofen produced highly significant pain relief compared with homeopathy and placebo | |
| | | | | | Pain on movement (measured by both 10cm VAS and four point pain scores) | No significant difference between homeopathy and placebo; fenoprofen produced highly significant pain relief compared with homeopathy and placebo | |
| | | | | | Night pain (measured by both 10cm VAS and four point pain scores) | No significant difference between homeopathy and placebo; fenoprofen produced highly significant pain relief compared with homeopathy and placebo | |
| Bellavite et al (2011) | van Haselen and Fisher (2000) | Patients with knee | Local application of a homeopathic gel | Piroxicam gel | Mean pain reduction (VAS) | No significant inter-group differences. Homeopathy | There is “good positive evidence” for *Zeel* |

| **Study ID**<br>**Level of evidence[a]**<br>**Quality[b]** | **Included study**<br>**Level of evidence[a]**<br>**Quality[c]**<br>**Sample size** | **Patient population** | **Intervention** | **Comparator** | **Outcome** | **Results as reported in the systematic review** | **Systematic review interpretation** |
|---|---|---|---|---|---|---|---|
| [Level I/III]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | [Level II]<br>Quality not reported<br>N=172 | osteoarthritis | | | | group: 16.5mm; Control group: 8.1mm | *compositum-N* in the treatment of osteoarthritis (Nahler et al 1998; Birnesser et al 2003).<br><br>There is "negative scientific evidence" (i.e. lack of evidence of benefit) for *Rhus toxicodendron* 6X in the treatment of osteoarthritis. The negative result of the trial by Shipley et al (1983) suggests that "the tested remedy cannot be effective if prescribed based only upon a diagnosis of disease, but without individualisation of the therapy".<br><br>With regards to the findings of van Haselen and Fisher (2000) the authors of the systematic review state that "since double-blind clinical trials involving patients with osteoarthritis of the knee showed the piroxicam topical gel to the significantly more effective than placebo (Norris and Guttadauria, 1987), this equivalence may be considered as indirect proof of the effectiveness of the tested |
| | Nahler et al (1998)<br>[Level II]<br>Quality not specified<br>N=114 | Patients with knee osteoarthritis | *Zeel compositum*-N | Hyaluronic acid, intrarticular injection | Pain during motion (subjective scores), tolerability | Equivalence of the homeopathic complex and hyaluronic acid | |
| | Shealy et al (1998)<br>[Level II]<br>Quality not specified<br>N=65 | Patients with knee osteoarthritis | Complex homeopathic formulation – *Rhus toxicodendron, Causticum,* and *Lac vaccinum* | Acetaminophen | Motion tenderness (VAS) | Equivalence of homeopathic formulation and acetaminophen | |
| | | | | | Pain relief | Better pain relief in the homeopathy group (55% compared to 38% with acetaminophen), but not statistically significant | |
| | Shipley et al (1983)<br>[Level II]<br>Quality not specified<br>N=36 | Patients with hip and knee osteoarthritis | *Rhus toxicodendron* 6x | Placebo or fenoprofen | Symptoms | No effect of homeopathy versus placebo; fenoprofen better than homeopathy and placebo | |
| | Birnesser et al (2003)<br>[Level III-2]<br>Quality not specified<br>N=592 | Patients with knee osteoarthritis | *Zeel compositum*-N | COX-2 inhibitors | Symptoms scores | Equivalence of homeopathic complex and COX-2 inhibitors | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | | homeopathy remedy". |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; SD, standard deviation; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The systematic review reported that the median Jadad score was 3.

[e] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.9.7 Rheumatoid arthritis

The effectiveness of homeopathy for the treatment of patients with rheumatoid arthritis was assessed in three systematic reviews as summarised in Table 36 and Table 37. In total, the systematic reviews included four Level II studies and one Level III-2 study (see Table 36).

**Table 36 Matrix indicating the studies that were included in the systematic reviews of rheumatoid arthritis**

| | | Study ID | | | | |
|---|---|---|---|---|---|---|
| | | Fisher (2001) [Level II] | Gaus (1993) [Level II] | Andrade (1991) [Level II] | Gibson (1980) [Level II] | Gibson (1978) [Level III-2] |
| Systematic review | Macfarlane et al (2011) [Level I] | ✓ | | ✓ | | |
| | Cucherat et al (2000) [Level I] | | ✓ | | | |
| | Bellavite et al (2011) [Level I/III] | ✓ | | ✓ | ✓ | ✓ |

The systematic review by Macfarlane et al (2011) (AMSTAR score of 8/10) aimed to critically evaluate the evidence regarding complementary and alternative medicine taken orally or applied topically (excluding fish oil) in the treatment of rheumatoid arthritis. For the homeopathy intervention, two Level II studies were identified that both received a Jadad score of 3 (Fisher, 2001; Andrade, 1991). Both Level II studies assessed the effect of homeopathy in patients with rheumatoid arthritis compared with placebo. Neither study reported a significant difference between homeopathy and placebo for any of the primary outcomes. The only exception was in Fisher (2001), where significantly lower pain scores were detected after placebo therapy. Macfarlane et al (2011) thus concluded that "the available evidence does not currently support the use of homeopathy in the management of rheumatoid arthritis".

Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The systematic review included one Level II study (Gaus, 1993) that investigated the effect of homeopathic Rheumaselect in patients with rheumatoid arthritis. Cucherat et al (2000) reported a significant difference (p=0.018) in favour of homeopathy, based on a composite criteria of treatment success in this Level II study. The quality of Gaus (1993) was not formally assessed by Cucherat et al (2000); however, a general comment was made about all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

Bellavite et al (2011) (AMSTAR score 5/10) conducted a systematic review of homeopathy and immunology in three broad clinical areas, one of which was "Arthrorheumatic diseases and osteoarthritis". Three Level II studies and one Level III-2 study were identified for the rheumatoid arthritis indication. The Level II studies included Fisher (2001), which was also included in the systematic review by Macfarlane et al (2011). A different interpretation of the results was given,

however, in that Bellavite et al (2011) reported that there was no effect of homeopathy over placebo in the pain and articular index outcome. Similar to the other systematic reviews, Bellavite et al (2011) concurred that there were "slight but not significant" differences in the homeopathy group over placebo in the Level II study by Andrade (1991).

Gibson (1980) was a Level II study that assessed the effect of individualised homeopathy in patients with rheumatoid arthritis. The study found an improvement in symptoms in 83% of patients in the homeopathy group and 22% of patients in the placebo group. The significance of the results, however, was not reported. Finally, Gibson (1978) was a Level III-2 study of individualised homeopathy in comparison to salicylate or placebo. The study reported better relief in the homeopathic group compared to salicylate or placebo, although the significance of the results was not reported. Bellavite et al (2011) noted that the trial was neither randomised nor double-blind so it was not possible to distinguish between those effects due to the treatment and those due to the difference in practitioner. Overall, Bellavite et al (2011) found that the evidence on rheumatoid arthritis was "unclear or conflicting". It noted "positive evidence from one RCT and one non-randomised controlled trial. No evidence from two RCTs".

*Evidence statement*

Three systematic reviews of poor to good quality identified four randomised controlled trials (unreported or medium quality; total of 378 participants, range: 44-176) and one medium-sized prospectively designed, non-randomised controlled study (quality not reported; 195 participants) that compared homeopathy with placebo for the treatment of people with rheumatoid arthritis.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with rheumatoid arthritis.

One systematic review of poor quality identified one medium-sized prospectively designed, non-randomised controlled study (quality not reported; 195 participants) that compared homeopathy with salicylate for the treatment of people with rheumatoid arthritis. LOC: Low.

Based on only one study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to salicylate for the treatment of people with rheumatoid arthritis.

**Table 37 Evidence summary table: the effectiveness of homeopathy for the treatment of rheumatoid arthritis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Macfarlane et al (2011)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of CAM for rheumatoid arthritis | Fisher (2001)<br>[Level II]<br>Jadad score 3[d]<br>N=112 | Seropositive rheumatoid arthritis patients on stable treatment | Homeopathic medicines in 6cH or 30cH. The most commonly used were *Rhus toxicodendron* and sulphur | Placebo | Pain | Significantly lower pain scores after placebo therapy | "The available evidence does not currently support the use of homeopathy in the management of RA." |
| | | | | | Articular index | No difference between treatment groups | |
| | | | | | ESR | No difference between treatment groups | |
| | | | | | Duration of morning stiffness | No difference between treatment groups | |
| | Andrade (1991)<br>[Level II]<br>Jadad score 3[d]<br>N=44 | Patients with rheumatoid arthritis according to ARA criteria | Individualised homeopathy | Placebo | Morning stiffness | No difference between treatment groups | |
| | | | | | 15-m walking time | No difference between treatment groups | |
| | | | | | Ritchie articular index | No difference between treatment groups | |
| | | | | | Grip strength | No difference between treatment groups | |
| | | | | | Functional class | No difference between treatment groups | |
| | | | | | Other medications | No difference between treatment groups | |
| | | | | | ESR | No difference between treatment groups | |
| | | | | | Seromucoids | No difference between | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | treatment groups | |
| | | | | | Overall improvement (physician assesses) | No difference between treatment groups | |
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Gaus (1993)<br>[Level II]<br>Quality not specified<br>N=176 | Patients with rheumatoid arthritis | Rheumaselect | Placebo | Composite criteria of treatment success | Significant difference in favour of homeopathy<br>(p=0.018) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to rheumatoid arthritis) |
| Bellavite et al (2011)<br>[Level I/III]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Fisher (2001)<br>[Level II]<br>Quality not specified<br>N=112 | Patients with rheumatoid arthritis | NSAIDS + individualised homeopathic prescription | NSAIDS + placebo | Pain and articular index | No effect of homeopathy over the placebo | Unclear of conflicting evidence – positive evidence from one Level II and one Level III-2 study. No evidence from two Level II studies. |
| | Andrade (1991)<br>[Level II]<br>Quality not specified<br>N=44 | Patients with rheumatoid arthritis | Individualised homeopathic prescription | Placebo | Overall improvement (physician assesses) | Slight but not significant differences in the homeopathy group over the placebo<br>• Homeopathy group: 59%<br>• Placebo group: 44% | |
| | Gibson (1980)<br>[Level II]<br>Quality not specified | Patients with rheumatoid arthritis | Individualised homeopathic prescription | Placebo | Improvement in symptoms (spontaneous pain, stiffness in the joint, | Significance of results not reported<br>• Homeopathy group: 83%<br>• Placebo group: 22% | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | N=46 | | | | prensile strength) | | |
| | Gibson (1978)<br>[Level III-2]<br>Quality not specified<br>N=195 | Patients with rheumatoid arthritis | Individualised homeopathic prescription | Salicylate or placebo | Medical assessment | Better relief in the homeopathic group compared to salicylate or placebo (p=NR) | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; ARA, American Rheumatism Association; CAM, complementary and alternative medicines; cH, Hahnemannian centesimal scale; ESR, erythrocyte sedimentation rate; NR, not reported; NSAIDS, non-steroidal anti-inflammatory drugs; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

# 4.10 Neurological

## 4.10.1 Broca's aphasia in people who have had a stroke

The effectiveness of homeopathy for the treatment of Broca's aphasia in people who have had a stroke was assessed in one Level I/III systematic review (Linde and Melchart, 1998; AMSTAR score 8/11) as summarised in Table 38. The authors conducted a broad review of the efficacy of individualised homeopathy across a range of clinical areas. One study was identified that assessed the efficacy of individual homeopathic simillimum compared to placebo for the treatment of Broca's aphasia (Master, 1987). The study was either a Level II or Level III-1 study; however, the method of allocation was not described and it is therefore not clear whether the study was randomised or pseudo-randomised. In the homeopathy group, 92% of patients were assessed as globally improved (physician-rated) compared to 25% in the placebo group. Linde and Melchart (1998) calculated a rate ratio of 3.67 (95% CI 1.37, 9.84), indicating significant inter-group differences. However the authors of the systematic review also stated that the study by Master (1987) was "completely inassessible" due to "totally insufficient reporting" and questioned the reliability of the extremely positive results. Overall, Linde and Melchart (1998) gave the study a Jadad score of 1 and an internal validity rating of 1, suggesting that the trial was of very poor quality.

*Evidence statement*

One systematic review of medium quality identified one very small prospectively designed and controlled study (poor quality; 36 participants) that compared homeopathy (*Simillimum*) with placebo for the treatment of Broca's aphasia in people who have had a stroke. LOC: Very low.

Based on only one very small poor quality study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of Broca's aphasia in people who have had a stroke.

**Table 38 Evidence summary table: the effectiveness of homeopathy for the treatment of Broca's aphasia in people who have had a stroke**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998)<br>[Level I/III]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Master (1987)<br>[Level II or III-1][d]<br>Quality: 1,1[d]<br>N=36 | Stroke patients with Broca's aphasia | Individualised simillimum | Placebo | Number of patients assessed globally as improved (physician-rated) | Significantly favours homeopathy.<br>Intervention group: 22/24 (92%); Control group: 3/12 (25%)<br><br>Rate ratio (95% CI): 3.67 (1.37, 9.84) | "Totally insufficient report – completely inassessible; extremely positive results." |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The study was either randomised or pseudo-randomised; however, the allocation of participants was not described.

[e] Quality assessed using (i) Jadad score (out of 5); (ii) internal validity score (out of 6).

### 4.10.2 Stroke

The effectiveness of homeopathy for the treatment of stroke was assessed in one systematic review as summarised in Table 39 (Ernst and Pittler, 1998; AMSTAR score 6/10). The systematic review performed by Ernst and Pittler (1998) assessed the efficacy of homeopathic *Arnica* for the treatment of various clinical conditions. The systematic review included one Level II study (Livingstone, 1991) that was assessed by the authors of the systematic review to be of reasonable quality (Jadad score of 3). The Level II study recruited patients admitted to hospital within seven days of suffering from a stroke and treated them with homeopathic *Arnica* (in M potency) or placebo. Mortality rates at 3 months were compared between the two groups and no statistically significant difference was found between the intervention and control arms. Ernst and Pittler (1998) did not provide a conclusion that was specific to the effectiveness of homeopathic *Arnica* for the treatment of stroke; however, they concluded that in general the assertion that "homeopathic *Arnica* is clinically effective beyond a placebo effect is not based on methodologically sound placebo-controlled trials".

*Evidence statement*

One systematic review of medium quality identified one very small randomised controlled trial (medium quality; 40 participants) that compared homeopathy (*Arnica*) with placebo for reducing mortality in people who have had a stroke. LOC: Very low.

Based on only one very small study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people who have had a stroke.

**Table 39 Evidence summary table: the effectiveness of homeopathy for the treatment of stroke**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Ernst and Pittler (1998)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Livingston (1991)<br>[Level II]<br>Jadad score 3[d]<br>N=40 | Patients admitted to hospital up to 7 days after acute event for the treatment of stroke | *Arnica* (M potency) | Placebo | 3 month mortality | No significant difference | "The hypothesis claiming that homeopathic *Arnica* is clinically effective beyond a placebo effect is not based on methodologically sound placebo-controlled trials."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to stroke) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.10.3 Migraine and headache

The effectiveness of homeopathy for the treatment of migraine and headache was assessed in four systematic reviews as summarised in Table 40 and Table 41. Overall, the systematic reviews included four unique Level II studies (Brigo and Serpelloni, 1991; Straumsheim et al, 1997; Walach et al, 1997; Whitmarsh et al, 1993/1997) (Table 40).

**Table 40 Matrix indicating the studies that were included in the systematic reviews of migraine and headache**

| | | Study ID | | | |
|---|---|---|---|---|---|
| | | **Straumsheim et al (1997) [Level II]** | **Walach et al (1997) [Level II]** | **Whitmarsh et al (1993/1997)[a] [Level II]** | **Brigo and Serpelloni (1991) [Level II]** |
| **Systematic review** | **Owen and Green (2004) [Level I]** | ✓ | ✓ | ✓ | ✓ |
| | **Cucherat et al (2000) [Level I]** | | | ✓ | |
| | **Vernon et al (1999) [Level I]** | | ✓ | | |
| | **Linde and Melchart (1998) [Level I]** | ✓ | ✓ | ✓ | ✓ |

[a] Whitmarsh et al (1993) and Whitmarsh et al (1997) were the same study. The study was referred to as Whitmarsh et al (1993) in Cucherat et al (2000) and Whitmarsh et al (1997) in Owen and Green (2004) and Linde and Melchart (1998).

The quality of the systematic reviews (as assessed by the AMSTAR tool) varied greatly; from 5/10 (Vernon et al, 1999) to 10/11 (Cucherat et al, 2000). Neither of the two systematic reviews that focused specifically on migraine and chronic headache (Owen and Green, 2004; Vernon et al, 1999) conducted a meta-analysis. The remaining two reviews presented pooled efficacy results across all conditions (including migraine/headache).

The systematic review by Owen and Green (2004) (AMSTAR score 6/10) assessed the efficacy of homeopathy in the treatment of migraine and chronic headache based on all four of the Level II studies identified by the reviews: two low quality Level II studies (Brigo and Serpelloni, 1991; Whitmarsh et al, 1993/1997) and two Level II studies of reasonable quality (Straumsheim et al, 1997; Walach et al, 1997). All four Level II studies reported the frequency, intensity and severity of attacks as well as the level of medication used in the treatment group, compared to the placebo group. In Brigo and Serpelloni (1991), the authors reported that homeopathy was superior to placebo across all four outcomes, although no p-values were provided in the systematic review. The other three Level II studies reported no differences between the homeopathy and placebo groups.

Owen and Green (2004) concluded that there is “insufficient evidence to support or refute the use of homeopathy for tension type, cervicogenic and migraine headache”. The lack of conclusive evidence was partly attributed to the limited number of studies and also to design flaws in the included studies. Importantly, Owen and Green (2004) raised concerns about the short duration of the trials (3-4 months), stating that homeopathy is considered a “gentle” or “soft” therapeutic intervention in which the treatment effects may be small and may not be clinically observable during short periods

of treatment. This was said to be particularly pertinent to patients with chronic illnesses, where therapeutic benefits may not be immediately detectable.

Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". Cucherat et al (2000) included the same Level II study by Whitmarsh et al, 1993/1997 that was included in the review by Owen and Green (2004). Whitmarsh et al (1993/1997) recruited patients that suffer from headaches and compared the efficacy of individualised homeopathy and placebo in terms of mean attack frequency over the course of the trial. No details were provided about the duration of the study. No statistically significant difference was found between the homeopathy and placebo groups in terms of mean attack frequency ($p=0.83$). The quality of Whitmarsh et al (1993/1997) was not formally assessed by Cucherat et al (2000); however, a general comment was made about all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". In addition, Cucherat et al (2000) also noted that the studies of high methodological quality were more likely to provide negative results for homeopathy compared to the lower quality studies. Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

Vernon et al (1999) (AMSTAR score 5/10) conducted a systematic review that assessed a broad range of complementary and alternative medicines in the treatment of tension-type and cervicogenic headache. Vernon et al (1999) included only one of the Level II studies (Walach et al, 1997), which specifically related to homeopathy and headache. Walach et al (1997) reported no significant difference between the placebo and individualised homeopathy groups on "any important clinical variables" over the 12-week study period. The Level II study was assessed by the authors of the systematic review to be of high quality (86% using a quality review protocol modified from van Tulder et al, 1997) and they concluded that the results "might recommend against the use of homeopathy for the treatment of tension-type headache".

Linde and Melchart (1998) (AMSTAR score 8/11) identified all four of the Level II studies identified by the reviews for inclusion in their systematic review of individualised homeopathy in treating a range of clinical conditions. Linde and Melchart (1998) assessed all four included Level II studies to be of reasonable (Brigo and Serpellino, 1991; Straumsheim et al, 1997; Whitmarsh et al, 1993/1997) or good (Walach et al, 1997) quality according to the Jadad scoring system and a separate assessment of internal validity. In Brigo and Serpelloni (1991) there was a significantly greater number of patients assessed as globally improved in the homeopathy group compared to placebo ($p<0.001$). However, all other outcomes across the four included trials were either found to have non-significant differences between treatment groups or the level of significance was not reported. Overall, Linde and Melchart (1998) concluded, across all clinical conditions, that any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

*Evidence statement*

Four systematic reviews of poor to good quality identified four randomised controlled trials (poor to good quality; total of 295 participants, range: 60-98) that compared homeopathy with placebo for the treatment of people with migraine or headache. LOC: Low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with migraine or headache.

**Table 41 Evidence summary table: the effectiveness of homeopathy for the treatment of migraine and headache**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Owen and Green (2004)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for headaches | Walach et al (1997)<br>[Level II]<br>20-item assessment tool: 64.3%<br>N=98 | Patients with chronic headache | Individualised homeopathy | Placebo | Frequency of chronic headache | Reduction in both homeopathic and placebo groups, no significant differences reported between groups | There is insufficient evidence to support or refute the use of homeopathy for managing tension type, cervicogenic, or migraine headache – this is partially due to flaws in design.<br><br>"The present review concurs with earlier studies and indicates that the debate continues whether homeopathy acts as a placebo or an effective intervention." |
| | | | | | Intensity of headache | Reduction in both homeopathic and placebo groups, no significant differences reported between groups | |
| | | | | | Severity of headache | Reduction in both homeopathic and placebo groups, no significant differences reported between groups | |
| | | | | | Level of medication used | Reduction in both homeopathic and placebo groups, no significant differences reported between groups | |
| | Whitmarsh et al (1997)[d]<br>[Level II]<br>20-item assessment tool: 25.0%<br>N=60 | Patients with migraine | Individualised homeopathy | Placebo | Frequency of migraine | "Chance difference. Both groups improved" | |
| | | | | | Intensity of migraine | "Chance difference. Both groups improved" | |
| | | | | | Severity of migraine | "Chance difference. Both groups improved" | |
| | | | | | Level of medication used | "Chance difference. Both groups improved" | |
| | Straumsheim et al (1997)<br>[Level II]<br>20-item assessment tool: 57.1%<br>N=73 | Patients with migraine | Individualised homeopathy | Placebo | Frequency of migraine | Reduction in both homeopathic and placebo groups, no significant differences reported between groups | |
| | | | | | Intensity of migraine | Reduction in both homeopathic and placebo groups, no significant differences reported between groups | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | | | | Severity of migraine | Reduction in both homeopathic and placebo groups, no significant differences reported between groups | |
| | | | | | Level of medication used | Reduction in both homeopathic and placebo groups, no significant differences reported between groups | |
| | Brigo and Serpelloni (1991)<br>[Level II]<br>20-item assessment tool: 38.5%<br>N=60 | Patients with migraine | Single dose 30c/4x in two weeks | Placebo | Frequency of migraine | Homeopathy superior to placebo (p-value NR) | |
| | | | | | Intensity of migraine | Homeopathy superior to placebo (p-value NR) | |
| | | | | | Severity of migraine | Homeopathy superior to placebo (p-value NR) | |
| | | | | | Level of medication used | Homeopathy superior to placebo (p-value NR) | |
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Whitmarsh et al (1993)[d]<br>[Level II]<br>Quality not formally assessed<br>N=64 | Patients with headache | Individualised homeopathy | Placebo | Change in mean attack frequency over the course of the trial | No significant difference (p=0.83) | "From the available evidence, it is likely that among the tested homeopathic treatments tested at least one shows an added effect relative to placebo. The meta-analysis method used does not allow any conclusion on what homeopathic treatment is effective in which diagnosis or against which symptoms."<br><br>"There is some evidence that homeopathic treatments are |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | | more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies. Further high quality studies are needed to confirm these results."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to migraine and headache) |
| Vernon et al (1999)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of CAM for headache | Walach et al (1997)<br>[Level II]<br>Quality: 86% (high quality)<br>N=98 | "About half (of the 98 subjects)" had chronic tension-type headaches | Individualised homeopathic remedy for 12 weeks | Placebo | NR | "No difference between the two groups on any important clinical variables related to headache activity" | "No difference between the two groups on any important clinical variables related to headache activity" |
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy | Straumsheim et al (1997)<br>[Level II]<br>Jadad score; internal validity score: 3[f]; 5[g]<br>N=73 | Patients with migraine | Individual simillimum (if possible constitutional) chosen from 60 available remedies in D30, D200, or 1M and individual dosage | Placebo | Number of patients assessed globally as improved | Intervention group: 8/35 (23%); Control group: 5/33 (15%). Significance of inter-group differences not reported | The meta-analysis found an overall trend in favour of homeopathy.<br>• The rate ratio was 1.62 (95% CI 1.17, 2.23) and the odds ratio was 2.62[e]<br>• The pooled rate ratio of the methodologically best studies was clearly smaller and not statistically significant (1.12, |
| | | | | | Frequency of migraine | Similar decrease in both treatment groups | |
| | | | | | Level of medication used | Similar decrease in both treatment groups | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| for multiple conditions | Walach et al (1997)<br>[Level II]<br>Jadad score; internal validity score: 5[f]; 6[g]<br>N=98 | Patients with chronic headache | Completely free individualised homeopathy treatment | Placebo | Number of patients assessed globally as improved | Trend in favour of placebo. Intervention group: 25/61 (41%); Control group: 19/37 (51%). Significance of inter-group differences not reported | • 95% CI 0.87, 1.44)[e]<br>• Similarly, the poor rate ratio of the six studies published in MEDLINE-listed journals was not significantly different from placebo (1.22, 95% CI 0.94, 1.56)[e]<br><br>(Note: the meta-analysis included all conditions, not just migraine/headache) |
| | | | | | Frequency of chronic headache | Slight decrease in both groups | |
| | | | | | Level of medication used | Slight decrease in both groups | |
| | Whitmarsh et al (1997)[d]<br>[Level II]<br>Jadad score; internal validity score: 4[f]; 4[g]<br>N=63 | Patients with migraine | 11 homeopathic remedies (patients were included provided that the simillimum was among those) in C30, two tablets, twice weekly | Placebo | Number of patients assessed globally as improved | No statistically significant inter-group differences. Intervention group: 11/32 (34%); Control group: 5/31 (16%) | |
| | Brigo and Serpelloni (1991)<br>[Level II]<br>Jadad score; internal validity score: 3[f]; 5[g]<br>N=60 | Patients with migraine | 8 homeopathic remedies (with simillimum among the eight) in C30, four doses in 2-week intervals | Placebo | Number of patients assessed globally as improved | Intervention group: 24/30 (80%); Control group: 4/30 (13%); p<0.001 | |
| | | | | | Intensity of attacks (VAS) | Intervention group: 2.9; Control group: 7.8. Significance of inter-group differences not reported | |
| | | | | | Frequency of attacks/month | Intervention group: 1.8; Control group: 7.9. Significance of inter-group differences not reported | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CAM, complementary and alternative medicines; CI, confidence interval; NR, not reported; SR, systematic review; VAS, visual analogue scale

[a] Level of evidence as assessed by the evidence reviewer.
[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.
[c] Study quality as reported in the systematic review.
[d] Whitmarsh et al (1993) and Whitmarsh et al (1997) were the same study. The study was referred to as Whitmarsh et al (1993) in Cucherat et al (2000) and Whitmarsh et al (1997) in Owen and Green (2004) and Linde and Melchart (1998).
[e] Values >1 indicate results in favour of homeopathy, <1 in favour of placebo. If the 95% confidence interval does not fall below 1 the result is statistically significant.
[f] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).
[g] Internal validity score, maximum 6 points.

# 4.11 Pregnancy and childbirth

## 4.11.1 Dystocia

The effectiveness of homeopathy for the treatment of women with dystocia was assessed in one systematic review (Cucherat et al, 2000; AMSTAR score 10/11) as summarised in Table 42. Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The systematic review included one Level II study (Couldert, 1981) that investigated the effect of homeopathic *Caulophyllum* in women with dystocia. A significant difference was reported for the outcome of "success within 2 hours". The difference was in favour of the homeopathic treatment over placebo (p=0.00055). The quality of Couldert (1981) was not formally assessed by Cucherat et al (2000); however, a general comment was made about all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Evidence statement*

One systematic review of good quality identified one very small randomised controlled trial (quality not reported; 34 participants) that compared homeopathy (*Caulophullum*) with placebo for the treatment of women with dystocia. LOC: Very low.

Based on only one very small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of women with dystocia.

**Table 42 Evidence summary table: the effectiveness of homeopathy for the treatment of dystocia**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Cucherat (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Couldert (1981)<br>[Level II]<br>Quality not specified<br>N=34 | Women with dystocia | *Caulophyllum* 5 °C | Placebo | Success within 2 hours | Significant difference in favour of homeopathy (p=0.00055) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to dystocia) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.11.2 Induction of labour or reducing duration of labour

The effectiveness of homeopathy for the induction of labour or delivery in women was assessed in one systematic review, Smith (2010) (AMSTAR score 8/10), as summarised in Table 43.

Smith (2010) was a Cochrane review that specifically aimed to determine the effects of homeopathy for third trimester cervical ripening or induction of labour. The results of two studies that claimed to be Level II studies were reported (Beer, 1999; Dorfman, 1997). However, upon a quality analysis, Smith (2010) noted that the method of allocation concealment was either not clear or not described in either study. The authors also noted that "the quality of the trials was difficult to assess because of insufficient detail in the research papers, and the small sample sizes provide inadequate power" and "the trials were placebo-controlled and double blind, but the quality was not high".

Beer (1999) examined the effect of homeopathic *Caulophyllum* in women at 38 to 42 weeks' gestation with pre-labour rupture of membranes. The study found no significant difference between homeopathy and placebo for caesarean section, vaginal delivery not achieved within 24 hours, augmentation with oxytocin, or instrumental delivery. Dorfman (1987) compared five homeopathic therapies with placebo in women from 36 weeks' gestation and found a significant difference in favour of placebo for difficult labour (RR 0.28; 95% CI 0.12, 0.66), but no significant difference between homeopathy and placebo for the length of labour (MD -0.40; 95% CI -7.21, 6.41). Overall, Smith (2010) concluded that "there is insufficient evidence to recommend the use of any homeopathic therapies as a method of induction of labour".

*Evidence statement*

One systematic review of medium quality identified two randomised controlled trials (poor quality; 40 and 93 participants) that compared homeopathy to placebo for the induction of labour or reducing the duration of labour. LOC: Very low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the induction of labour or reducing the duration of labour.

**Table 43 Evidence summary table: the effectiveness of homeopathy for the induction of labour or reducing duration of labour in women**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Smith (2010)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for induction of labour | Beer (1999)<br>[Level II]<br>Quality not high[e]<br>N=40 | Women at 38-42 weeks' gestation with prelabour rupture of membranes | *Caulophyllum* D4, doses were repeated hourly for 7 hours or until labour started | Placebo | Caesarean section[e] | No significant difference (p=0.29)<br>• RR 5.00 (95% CI 0.26, 98.00) | "There is insufficient evidence to recommend the use of any homeopathic therapies as a method of induction of labour." |
| | | | | | Vaginal delivery not achieved within 24 hours | No significant difference (p=0.49)<br>• RR 0.33 (95% CI 0.01, 7.72) | |
| | | | | | Augmentation with oxytocin[e] | No significant difference (p=1.0)<br>• RR 1.00 (95% CI 0.50, 1.98) | |
| | | | | | Instrumental delivery[e] | No significant difference (p=1.0)<br>• RR 1.00 (95% CI 0.54, 1.86) | |
| | Dorfman (1987)<br>[Level II]<br>Quality not high[e]<br>N=93 | Women at 36 weeks' gestation. Women were excluded from the study if they had a poor obstetric history, a current history of hypertension, diabetes, previous caesarean section or cephalo-pelvic disproportion | Five homeopathic therapies: *caulophyllum, Arnica, actea racemosa, pulsatilla* and *geranium*, with 3 granules administered morning and evening from 36 weeks' gestation. When labour commenced, the same dosage was | Placebo | Length of labour[e] | No significant difference (p=0.91)<br>• MD -0.40 (95% CI -7.21, 6.41) | |
| | | | | | Difficult labour[e] | Significant difference in favour of placebo<br>• RR 0.28 (95% CI 0.12, 0.66) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | given every 15 minutes and stopped after 2 hours or sooner if the woman was comfortable. No details provided on the precise dosage. | | | | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; D, decimal; MD, mean difference; RR, relative risk; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

[e] A formal quality assessment was not conducted. The author stated that the quality of the trials was “not high” and was difficult to assess because of insufficient detail in the research papers and the small sample sizes provided inadequate power.

# 4.12 Psychiatric and behavioural disorders

## 4.12.1 Children with attention deficit/hyperactivity disorder

The effectiveness of homeopathy for the treatment of children with ADHD was assessed in four systematic reviews (Altunc et al, 2007; Davidson et al, 2011; Heirs and Dean, 2009; Linde and Melchart, 1998) as summarised in Table 44 and Table 45. In total, the reviews included three Level II trials (Frei et al, 2005; Jacobs et al, 2005; Strauss, 2000) and one Level III-1 study (Lamont, 1997).

**Table 44 Matrix indicating the studies that were included in the systematic reviews of ADHD**

| | | Study ID | | | |
|---|---|---|---|---|---|
| | | Frei et al (2005) [Level II] | Jacobs et al (2005) [Level II] | Strauss (2000) [Level II] | Lamont (1997) [Level III-1] |
| Systematic review | Davidson et al (2011) [Level I] | ✓ | ✓ | ✓ | |
| | Heirs and Dean (2009) [Level I/III] | ✓ | ✓ | ✓ | ✓ |
| | Altunc et al (2007) [Level I] | ✓ | ✓ | ✓ | |
| | Linde and Melchart (1998) [Level I/III] | | | | ✓ |

Davidson et al (2011) (AMSTAR score 8/10) was a systematic review of Level II studies that examined the effectiveness of homeopathy for the treatment of psychiatric conditions, including ADHD. The review included three Level II studies (Frei et al, 2005; Jacobs et al, 2005; Strauss, 2000) that examined the effect of individualised homeopathy compared to placebo. All studies were rated by the systematic review authors as "good" using the SIGN quality assessment tool. Frei et al (2005) reported that homeopathy had a statistically significant benefit over placebo in terms of behavioural and cognitive functions ($p<0.05$), using the Conners' Global Index (parent-reported) to measure efficacy. However, Jacobs et al (2005) found no significant difference between treatment groups using the same primary outcome measure. Similarly, Strauss (2000) reported an effect in favour of homeopathy that was "weak at best" based on one parent-reported outcome (Conners' Parent Symptom Questionnaire) and no significant difference compared to placebo based on one child completed test (Children's Checking Task). Overall, Davidson et al (2011) concluded that the mixed results made it difficult to formulate a generalised conclusion for the clinical area as a whole.

Altunc et al (2007) (AMSTAR score 6/10) performed a systematic review to assess the efficacy of homeopathy in nine childhood and adolescent conditions, including ADHD. The review included the three Level II studies discussed above (Frei et al, 2005; Jacobs et al, 2005; Strauss, 2000), and no additional outcomes were presented. The only additional information was that Altunc et al (2007) reported a p-value of $p=0.01$ in favour of homeopathy for the Conners' Parent Symptom

Questionnaire (Strauss, 2000), whereas Davidson et al (2011) had described the effect for this outcome as "weak at best". The actual magnitude of the effect, which is arguably more relevant, was not discussed. The authors of the systematic review assessed the quality of the trials using a Jadad score. Frei at el (2005) and Jacobs et al (2005) received scores of 5 and Strauss (2000) scored a 2. Overall, Altunc et al (2007) concluded that there was "no compelling data" for any homeopathic intervention for the treatment of ADHD due to a mixture of positive and negative results.

Heirs and Dean (2009) (AMSTAR score 11/11) conducted a Cochrane review of homeopathy for ADHD or hyperkinetic disorder. The systematic review included the same three Level II studies that investigated homeopathy in children with ADHD (Frei et al, 2005; Jacobs et al, 2005; Strauss, 2000), plus a pseudo-randomised Level III-1 study (Lamont, 1997). Heirs and Dean (2009) assessed the quality of each of the studies and considered aspects of methodological quality when they assessed heterogeneity; however, no specific quality score was provided for each study. As shown in Table 45, Heirs and Dean (2009) calculated standard mean differences (and 95% confidence intervals) to demonstrate the effect of homeopathy compared to placebo when sufficient data were available. The outcomes measured were stated more explicitly in Heirs and Dean (2009) than the other systematic reviews, and the results of subscales within the overall scores were also provided. For example, the Conners' Parent Rating Scale is presented as a total score and also subscales including hyperactivity, inattention, restlessness/impulsivity and emotional lability.

Heirs and Dean (2009) also reported the significant benefit of homeopathy over placebo according to the Conners' Global Index (parent-rated), as examined by Frei et al (2005). Individualised homeopathy was also found be effective in reducing hyperactivity over ten days, compared to placebo (standard mean difference: -0.65; 95% confidence interval: -1.27, -0.03) in the Level III-1 study conducted by Lamont (1997). However, no other significant intergroup differences were found on any other outcomes (including subscales) across the four included studies. In the smallest, poorest-quality Level II study by Strass (2000), half of the participants in both the intervention and placebo arms received concomitant Ritalin.

Heirs and Dean (2009) also conducted a meta-analysis of the three Level II trials, despite the "significant heterogeneity" that existed between them in terms of "how the 'homeopathic treatment' was operationalised and implemented, as well as the effects". The results of the meta-analysis are presented in Table 46, and indicate that the pooling of results did not achieve any positive effects in terms of standard mean difference.

Heirs and Dean (2009) acknowledged the major limitations of their systematic review and the included studies. They suggested that the cross-over study design of Frei et al (2005) may have affected the results; possibly through a regression to the mean in phase one, or alternatively a carry-over effect in either phase one or two. The statistically significant benefit of homeopathy over placebo (parent-rated Conners' Global Index) reported in Frei et al (2005) may therefore be attributable to flawed methodology. It was also noted that Frei et al (2005) included an initial screening period to identify a subset of children who responded to homeopathy. An indefinite number of follow-ups were allowed at this stage and medicines could be prescribed or changed until a successful response was obtained. Participants who successfully responded to homeopathy (50% amelioration of symptoms on Conners' Global Index) were then entered into the Level II study.

In addition to the limitations of the included studies, Heirs and Dean (2009) acknowledged limitations of their meta-analysis. The data pooled in the meta-analysis came predominantly from two studies

that adopted different homeopathic approaches, including formulaic (Strauss, 2000) and individualised homeopathy (Jacobs et al, 2005). The authors felt that pooling was still appropriate since "all of the studies could be interpreted as addressing the ongoing controversy of whether homeopathic dilutions have any effect over a placebo dose". Nonetheless, Heirs and Dean concluded that there is "currently little evidence for the efficacy of homeopathy" and "insufficient evidence to recommend the use of homeopathy for children diagnosed with ADHD".

Finally, an earlier systematic review by Linde and Melchart (1998) (AMSTAR score 8/11) examined the efficacy of individualised homeopathy for the treatment of a variety of clinical conditions. The Level III-1 study of children with ADHD by Lamont (1997) was identified for inclusion in the systematic review; however, it was excluded from the meta-analysis due to "insufficient reporting of results" and a "problematic design" in which observation periods were not standardised. Lamont (1997) found a significantly better "mean response score" ($t=2.16$; $p<0.05$) in the homeopathy group (1.00) compared with placebo (0.35). Overall, Linde and Melchart (1998) concluded that, across all clinical conditions, any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

*Evidence statement*

Four systematic reviews of medium to good quality identified three randomised controlled trials (good quality; total of 125 participants, range: 20-62) and one very small prospectively designed, non-randomised controlled study (poor quality; 45 participants) that compared homeopathy with placebo for the treatment of children with attention deficit/hyperactivity disorder (ADHD).

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Very low - low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of children with ADHD.

**Table 45 Evidence summary table: the effectiveness of homeopathy for the treatment of children with attention deficit/hyperactivity disorder**

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Davidson et al (2011) [Level I] AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Frei et al (2005) [Level II] SIGN rating: Good N=62 | Children with ADHD | Individualised homeopathy | Placebo | CGI-P | Statistically significant benefit for homeopathy, particularly in behavioural and cognitive functions ($p<0.05$). | Overall there were mixed results for the efficacy of homeopathy on ADHD, making it difficult to generalise the results to this clinical area. |
| | Jacobs et al (2005) [Level II] SIGN rating: Good N=43 | Children with ADHD | Individualised homeopathy | Placebo | CGI-P | Placebo tended to be better than homeopathy, but not significantly better | |
| | Strauss (2000) [Level II] SIGN rating: Good N=20[d] | Children with ADHD | Individualised homeopathy | Placebo | CPSQ | Overall hyperactivity improved more on homeopathy than placebo; however effect was weak at best[e] | |
| | | | | | CCT | No significant difference between homeopathy and placebo | |
| Altunc et al (2007) [Level I] AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Frei et al (2005) [Level II] Jadad score 5[j] N=62 | Children with ADHD<br>• 89% male | Individualised homeopathy, material potencies, 6 weeks, treatment regimen not reported[f] | Placebo | CGI-P | Significant difference ($p=0.048$) | "The best evidence from double-blind RCTs shows no compelling data for any therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments."<br><br>"The evidence for ADHD… is mixed, showing both positive and negative |
| | | | | | Adverse events | Main adverse events causing withdrawal were 1 increasing tics, 2 behavioural disorders, 1 reactive depression | |
| | Jacobs et al (2005) [Level II] Jadad score 5[j] N=43 | Children with ADHD<br>• Mean age: 9.5 years<br>• 77% male | Individualised homeopathy, 18 weeks, homeopathic remedies prescribed with no limit, doses | Placebo | CGI-P | No significant difference | |
| | | | | | Adverse events | No adverse events | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | and potencies not reported[g] | | | | results for [the] main outcome measure."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to ADHD) |
| | Strauss (2000)<br>[Level II]<br>Jadas score 2[j]<br>N=20 | Children with ADHD<br>• Mean age: 10 years<br>• 90% male | Standardised homeopathy, material potencies, 2 months, treatment regimen not reported<br>Selenium-Homaccord[h] | Placebo | CPSQ | Significant difference (p=0.01) in favour of homeopathy | |
| | | | | | CCT | "Intergroup difference for improvement compared with baseline for CCT" (p=NR) | |
| Heirs and Dean (2009)<br>[Level I/III]<br>AMSTAR: 11/11<br><br>SR of homeopathy for ADHD | Frei et al (2005)<br>[Level II]<br>Quality score not specified<br>N=62 | Children with ADHD<br>• aged 7-15 yr<br>• symptoms had improved by ≥50% under homeopathic treatment during screening | Individual homeopathic medicine – prescribed according to Hahnemann and Bönninghausen, administered as daily liquid doses (LM potencies) | Placebo | CGI-P | Significant benefit of homeopathy over placebo in the cross-over. Generic inverse weighted average treatment effect:<br>-1.67 (95% CI -3.32, -0.02) | "Overall this review found no evidence that homeopathy has a significant impact on the overall severity, core symptoms or related outcomes of children diagnosed with Attention Deficit Hyperactivity Disorder."<br><br>Significant heterogeneity exists between the three trials included in the meta-analysis in terms of how "homeopathic treatment" was operationalised and implemented as well as the effects (one used a formula of medicines given without individualisation to patients over a relatively short period of time; one |
| | | | | | Inattention and impulsivity (using TAP) | Insufficient data to calculate effect size | |
| | Jacobs et al (2005)<br>[Level II]<br>Quality score not specified<br>N=43 | Children with ADHD<br>• mean age: 9 years | Individual homeopathic medicine – prescribed according to Hahnemann and Bönninghausen, administered as daily liquid doses (LM potencies) | Placebo | CGI-P | No evidence for effectiveness of homeopathy over placebo.<br>SMD 0.13 (95% CI -0.47, 0.73) | |
| | | | | | CPRS-R | No evidence of effectiveness of homeopathy over placebo.<br>SMD 0.17 (95% CI -0.43, 0.77) | |
| | | | | | Hyperactivity subscale from CPRS-R | No evidence of effectiveness of homeopathy on hyperactivity symptoms.<br>SMD 0.21 (95% CI -0.39, 0.81) | |
| | | | | | CPRS-R domain of inattention | No evidence of effectiveness was found. | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | SMD 0.39 (95% CI -0.21, 1.00) | used a form of individualised homeopathy similar to how 'classical' homeopathy is used in practice with freedom to vary the medicines as well as potency (strength) and frequency, although critics have suggested that the treatment period of 18 weeks was too short to show benefit hence the negative findings). However, "a trial of individualised homeopathy with minimised non-specific effects found a significant benefit from homeopathy" (Frei et al 2005)<br><br>"There is insufficient evidence to draw robust conclusions about the effectiveness of any particular form of homeopathy for ADHD at present given that only three randomised controlled trials have been carried out, and all were relatively small in size." |
| | | | | | Restlessness/ impulsivity (from the CPRS-R) | No significant evidence of effectiveness.<br>SMD 0.02 (95% CI -0.57, 0.62) | |
| | | | | | Conduct/ oppositional behaviour | No evidence of effectiveness.<br>SMD 0.10 (95% CI -0.50, 0.70) | |
| | | | | | Emotional Lability domain (from the CPRS-R) | No evidence of effectiveness.<br>SMD 0.21 (95% CI -0.39, 0.81) | |
| | | | | | Global total on the CGI-T | No significant differences.<br>SMD 0.41 (95% CI -0.20, 1.01) | |
| | | | | | Restless/ Impulsive behaviour (sub-domain of CGI-T) | No significant differences.<br>SMD 0.39 (95% CI -0.21, 1.00) | |
| | | | | | Emotional Lability (sub-domain of CGI-T) | No significant differences.<br>SMD 0.41 (95% CI -0.19, 1.02) | |
| | | | | | Inattention (measured by the Conners' CPT) | No significant difference.<br>SMD -0.12 (95% CI -0.72, 0.48) | |
| | | | | | Impulsivity (measured by the CPT) | No evidence of effectiveness.<br>SMD -0.07 (95% CI -0.67, 0.53) | |
| | Strauss (2000) [Level II]<br>Quality score not | Children with ADHD<br>• aged 7-10 years | Formula homeopathic combination medicine[h] – ten drops, three times daily for two | Placebo, with (n=5) or without | CRS (older version which included a domain termed the Hyperactivity Index | No evidence of effectiveness of homeopathy on ADHD Index score as rated by parents. | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | specified<br>N=20 | • half (n=10) taking Ritalin<br>• 18 boys; 2 girls | months, with (n=5) or without Ritalin (n=5) | Ritalin (n=5) | but has been renamed the ADHD Index in later revisions) | SMD -0.17 (95% CI -1.05, 0.71) | "There is at present insufficient evidence to recommend the use of homeopathy for children diagnosed with ADHD." |
| | | | | | Restlessness/ impulsivity (from the CRS) | No evidence of effectiveness.<br>SMD -0.14 (95% CI -1.02, 0.74) | |
| | | | | | Anxiety (based on a domain within the older CRS) | Non-significant difference in levels of anxiety.<br>SMD -0.55 (95% CI -1.45, 0.34) | |
| | | | | | Conduct/ oppositional behaviour | No evidence of effectiveness.<br>SMD 0.26 (95% CI -1.14, 0.63) | |
| | | | | | Inattention (converted from "successful attention" using CCT by Strauss 2000) | No significant difference.<br>SMD -0.53 (95% CI -1.42, 0.37) | |
| | Lamont (1997)<br>[Level III-1]<br>Quality score not specified<br>N=43 | Children with ADHD<br>• all lived in foster homes<br>• mean age 10 years<br>• 35% Black, 47% Hispanic; 18% Caucasian | Individualised homeopathic medicine – prescribed following a consultation using classical homeopathic prescribing and the RADAR repertory software. Administered as 6 x | Placebo | Change in hyperactivity over 10 days (measured by a five point rating scale completed by parents) | Effectiveness was found.<br>SMD -0.65 (95% CI -1.27, -0.03) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | 200c pills daily for up to 5 days. Ten days after the prescription progress was followed-up, with the option of changing the medicine on two further occasions. | | | | |
| Linde and Melchart (1998)<br>[Level I/III]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Lamont (1997)<br>[Level III-1]<br>Quality: 2,2[i]<br>N=45 | Children with ADHD<br>• mean age 10 years | Individual simillimum in C200 daily up to 5 days, computer-assisted (RADAR) | Placebo | Mean response score | Response scores in homeopathy group significantly better (mean scores 1.00 vs 0.35; t=2.16; p<0.05 | The authors did not provide any specific conclusions regarding the efficacy of homeopathy in children with ADHD. |

Abbreviations: ADHD, attention deficit/hyperactivity disorder; AMSTAR, Assessment of Multiple Systematic Reviews; CCT, Children's Checking Task; CGI-P, Conners' Global Index-Parent; CPRS-R, Revised Conners' Parent Rating Scale; CPSQ, Conners' Parent Symptom Questionnaire; NR, not reported; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review; TAP, Test battery for Attention Performance.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Refers to the number of participants who completed the study. Number of participants enrolled was not reported.

[e] Subsequent review in Cochrane analysis failed to find significance on any measure.

[f] 17 different remedies prescribed, potencies between Q3 and Q42: *Calcarea carbonica, sulphur, Chamomilla, Lycopodium, silica, Hepar-sulph., Nux vomica, China, Ignatia, Mercurius, Capsicum, Causticum, Hyoscyamus,* phosphorous, phosphoric acid, *sepia, Staphysagria*

[g] 41 different remedies prescribed: *Medorrhinum, Saccharum officinalis, Calcarea carbonica, Calcarea phosphorica, China officinalis, stramonium*; Concomitant treatment: stimulant medications (5H; 4P)

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

[i] Quality was assessed using (i) Jadad score, out of five; (ii) internal validity score, out of six.

[j] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

**Table 46 Meta-analysis results presented in Heirs and Dean (2009)**

| Homeopathy versus Placebo (Parent Ratings) | | | | |
|---|---|---|---|---|
| Outcome or subgroup | No. of studies | No. of participants | Statistical method | Effect size |
| CGI-P | 2 | | Mean Difference (Fixed, 95% CI) | -1.56 [-3.18, 0.06] |
| ADHD Index | 2 | 63 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.06 [-0.43, 0.56] |
| Hyperactivity: | 2 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| Randomised only | 1 | 43 | Std. Mean Difference (IV, Random, 95% CI) | 0.21 [-0.39, 0.81] |
| Quasi and fully randomised | 2 | 86 | Std. Mean Difference (IV, Random, 95% CI) | -0.22 [-1.06, 0.63] |
| Inattention | 1 | 43 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.39 [-0.21, 1.00] |
| Restless/Impulsive | 2 | 63 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.03 [-0.52, 0.46] |
| Oppositional/Conduct | 2 | 63 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.01 [-0.51, 0.48] |
| Emotional Lability | 1 | 43 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.21 [-0.39, 0.81] |
| Anxiety | 1 | 20 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.55 [-1.45, 0.34] |
| Global Index Scores | 1 | 43 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.13 [-0.47, 0.73] |
| Homeopathy versus Placebo (Teacher Ratings) | | | | |
| Outcome or subgroup | No. of studies | No. of participants | Statistical method | Effect size |
| Global Index Total | 1 | 43 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.41 [-0.20, 1.01] |
| Restless/Impulsive | 1 | 43 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.39 [-0.21, 1.00] |
| Emotional Lability | 1 | 43 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.41 [-0.19, 1.02] |
| Homeopathy versus Placebo (Child completed tests) | | | | |
| Outcome or subgroup | No. of studies | No. of participants | Statistical method | Effect size |
| Inattention | 2 | | Std. Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| Original figures | 2 | 63 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.25 [-0.74, 0.25] |
| Adjusted figures | 2 | 62 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.21 [-0.71, 0.29] |
| Impulsivity | 1 | 43 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.07 [-0.67, 0.53] |

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CGI-P, Conners' Global Index-Parent; CI, confidence interval

### 4.12.2 Anxiety or stress-related conditions

The effectiveness of homeopathy for the treatment of patients with anxiety or stress-related conditions was assessed in two systematic reviews as summarised in Table 47 and Table 48. In total, the systematic reviews included 11 Level II studies. Both systematic reviews received an AMSTAR score of 8/10 for quality. None of the systematic reviews performed a meta-analysis of the data.

**Table 47 Matrix indicating the studies that were included in the systematic reviews of anxiety or stress-related disorders**

| | | Systematic review | |
|---|---|---|---|
| | | **Pilkington et al (2006) [Level I]** | **Davidson et al (2011) [Level I]** |
| **Study ID** | **Ngobese (2006) [Level II]** | | ✓ |
| | **Thompson (2005) [Level II]** | ✓ | |
| | **Vaithilingam (2005) [Level II]** | | ✓ |
| | **Baker (2003) [Level II]** | ✓ | ✓ |
| | **Bonne (2003) [Level II]** | ✓ | ✓ |
| | **Traub (2000) [Level II]** | | ✓ |
| | **McCutcheon (1996) [Level II]** | ✓ | ✓ |
| | **Alibeu (1992) [Level II]** | ✓ | |
| | **Hariveau (1991) [Level II]** | ✓ | |
| | **Heulluy (1985) [Level II]** | ✓ | |
| | **Stanton (1981) [Level II]** | ✓ | |

Pilkington et al (2006) (AMSTAR score 8/10) performed a systematic review of the clinical evidence on homeopathy for the treatment of anxiety and anxiety disorders. It included the results of eight Level II studies of variable quality.

Test anxiety was assessed in two Level II studies (Stanton, 1981; Baker, 2003). Stanton (1981) was a placebo-controlled trial that examined the effect of a homeopathic preparation for test anxiety in 40 subjects. The study found a significant reduction in test anxiety (as measured by the Test Anxiety Scale (TAS)) in the homeopathy group compared with placebo. Pilkington et al (2006) noted, however, that “the original article was unavailable so that it was not possible to rate the quality”. Baker (2003) (Jadad score of 4) was an attempt to replicate the study by Stanton (1981). The Level II

study was conducted in an Australian University with 70 test anxious student volunteers. A revised version of the TAS was used, and the results found no significant difference in test anxiety between the homeopathy and placebo groups. A comparison of the results with the data by Stanton (1981) suggested that anxiety scores pre-treatment "might have been slightly higher" in the 1981 study; however, it was not clear whether the higher baseline anxiety scores related to the homeopathy or placebo treatment arm or the mean score across both groups.

Moderate anxiety or generalised anxiety disorder was assessed in two Level II studies (McCutcheon, 1996; Bonne, 2003). McCutcheon (1996) (Jadad score of 4) found no significant differences in either pre- or post-test State-Trait Anxiety Inventory (STAI) scores between the homeopathy and placebo groups. The homeopathy group, however, reported significantly less loss of sleep. The author concluded that "the homeopathic complex used may be useful for this aspect of anxiety, although it appeared to have little value in the reduction of either state or trait anxiety". Bonne (2003) (Jadad score of 3) reported no significant differences between adults with generalised anxiety disorder who were treated with individualised homeopathic remedies or placebo for 10 weeks. In fact, a significant improvement was observed in both the active and placebo groups. Pilkington et al (2006) noted, however, that this study may have been underpowered as a power calculation demonstrated that a minimum of 60 participants were required but only 44 were recruited.

Mixed anxiety and depressive disorder was assessed in two Level II studies of "proprietary homeopathic complexes" (Hariveau, 1991; Heulluy, 1985). Both Level II studies were rated a Jadad score of 1. The comparator arm for both studies used benzodiazepine, which primarily comprises an anxiolytic and thus the anxiety component of the condition was being treated in the comparator group. In both Level II studies, the homeopathic complex was reported to be as effective as benzodiazepine, but this may be a result of the studies being insufficiently powered to detect a difference. Pilkington et al (2006) also reported that "concerns over the initial diagnosis of participants together with a lack of detail about the methodology and outcome measures limit the usefulness of these findings".

Finally, anxiety associated with medical or physical conditions was assessed in two Level II studies (Alibeu, 1992; Thompson, 2005). Alibeu (1992) (Jadad score of 2) was a Level II study of homeopathic *aconite* for postoperative agitation in children. The results suggested that homeopathic *aconite* might be an appropriate treatment as "95% good results" were reported. However, Pilkington et al (2006) noted that "no clear objective outcome measures were provided and many of the methodological details such as randomisation, allocation concealment and blinding were unclear". In contrast, Thompson (2005) (Jadad score of 5) was a "rigorously conducted randomised placebo-controlled trial" of homeopathy for the treatment of symptoms of oestrogen withdrawal (including anxiety) in 53 breast cancer patients. The authors reported that both groups experienced clinically important improvements based on Measure Yourself Medical Outcome Profile (MYMOP) scores over the 16 week trial period. However, the study did not find that the specific effect of the remedy added further to the non-specific effects of the consultation, possibly due to lack of power.

Overall, the systematic review by Pilkington et al (2006) concluded that the Level II studies reported contradictory results and "the findings of many of the included studies were limited by the lack of detail about methodology and outcome measures as well as concerns that several of the studies were insufficiently powered to detect differences between treatments". Consequently, "no firm conclusions on the efficacy of homeopathy for anxiety can be drawn".

Davidson et al (2011) (AMSTAR score 8/10) was a systematic review of Level II studies of homeopathy for psychiatric conditions. For anxiety or stress-related conditions, six Level II studies were identified. Three Level II studies (Baker, 2003; Bonne, 2003; McCutcheon, 1996) overlapped with those identified in Pilkington et al (2006). The interpretation of those studies was consistent between the two systematic reviews.

Davidson et al (2011) also included three additional Level II studies that were not identified in Pilkington et al (2006): Ngobese (2006), Vaithilingam (2005) and Trabu (2003). Ngobese (2006) was reported to be a fair quality Level II study that investigated the effect of individualised homeopathy in patients with generalised anxiety disorder. The study reported no significant difference between the homeopathy and placebo groups for any outcome measure. Vaithilingam (2005) was a poor-quality Level II study that assessed individualised homeopathy in patients with job-related burnout. The results were that "homeopathy was worse than placebo on the depersonalisation scale of Maslach Burnout Inventory". Finally, Trabu (2003) was a poor-quality study that examined a combined three-remedy product in patients with test anxiety. While the outcome measure was unclear, Davidson et al (2011) reported "no effect on the total scores of the primary measures" and "weak evidence for homeopathy on scale items". Overall, Davidson et al (2011) concluded that there is "no support for the efficacy of homeopathy in anxiety- or stress-related conditions".

*Reviewer comments*

*Conflicting evidence exists for the effectiveness of homeopathic treatments in patients with anxiety or stress-related conditions. Many of the Level II studies that have investigated this indication are small in size and limited by poor methodological quality. The evidence reviewer notes that Pilkington et al (2006) also included one uncontrolled study (Davidson, 1997) in their assessment of anxiety and anxiety disorders. However, this study was excluded for the purposes of this overview as it is classed as Level III-3 evidence.*

*Evidence statement*

Two systematic reviews of medium quality identified nine randomised controlled trials (poor to good quality; total of 402 participants, range: 27-77) that compared homeopathy with placebo for the treatment of people with anxiety or stress-related conditions. LOC: Very low - low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with anxiety or stress-related conditions.

Two systematic reviews of medium quality identified three randomised controlled trials (poor to medium quality; total of 172 participants, range: 28-84) that compared homeopathy with other therapies (lorazepam, diazepam and cognitive behavioural therapy) for the treatment of people with anxiety or stress-related conditions.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Very low - low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is as effective as the other therapies for the treatment of people with anxiety or stress-related conditions.

**Table 48 Evidence summary table: the effectiveness of homeopathy for the treatment of anxiety or stress-related conditions**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Pilkington et al (2006)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for anxiety | Thompson (2005)<br>[Level II]<br>Jadad score 5[d]<br>N=53 | Breast cancer patients with symptoms of oestrogen withdrawal (including anxiety) | Individualised prescribing (60 minute initial consultation plus four 20 minute follow-up consultations, over 16 weeks) | Placebo | Mean HADS anxiety scores | No significant difference | The findings of many of the included studies were limited by the lack of detail about methodology and outcome measures as well as concerns that several of the studies were insufficiently powered to detect differences between treatments<br><br>No firm conclusions on the efficacy of homeopathy for anxiety can be drawn |
| | | | | | MYMOP | No significant difference | |
| | | | | | Menopausal Symptom Questionnaire | Significant clinical improvements in both groups; between-group differences not clear (p-value NR) | |
| | | | | | EORTC QLQ-C30 | Significant clinical improvements in both groups; between-group differences not clear (p-value NR) | |
| | Baker (2003)<br>[Level II]<br>Jadad score 4[d]<br>N=70 | Australian university students with test anxiety (score of 50+ on Benson RTA) | Traditionally prepared *Argentum nitricum* 12x, twice daily for 4 days | Radionically prepared *Argentum nitricum* 12x; or placebo (alcohol/water mixture as per treatments) | Benson Revised Test Anxiety Scale | No significant difference | |
| | | | | | TAS 36-item *Argentum nitricum* questionnaire pre- and post-treatment (1 week later) | No significant difference | |
| | Bonne (2003)<br>[Level II]<br>Jadad score 3[d]<br>N=44 | Adults with generalised anxiety disorder (DSM-IV diagnosis); HAM-A >20, HAM-D <18 | Individualised homeopathy (single remedy, all dilutions >$10^{-30}$) for 10 weeks | Placebo (non-medication impregnated globules) | HAM-A; HAM-D; BSI; PGWBI; BDI; STAI subjective distress (VAS) | Significant improvement in both groups (p-value NR)<br>No significant difference between groups | |
| | McCutcheon (1996)<br>[Level II] | Students with above average | Anti-Anxiety[e], 20 drops, four times | Placebo | STAI | No significant difference | |
| | | | | | Resting pulse rate | No significant difference | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Jadad score 4[d]<br>N=77 | anxiety scores (score of 18+ on part one of pre-test STAI) | daily for 15 days | | Sleep loss | Significantly less sleep loss in the homeopathy group<br>(p-value NR)[f] | |
| | Alibeu (1992)<br>[Level II]<br>Jadad score 2[d]<br>N=50 | Children (aged 6 months to 14 years) with post-operative agitation/anxiety | *Aconite* | Placebo | Physician-assessed improvement | "Effective with 95% good results" | |
| | Hariveau (1991)<br>[Level II]<br>Jadad score 1[d]<br>N=84 | Patients with reactive anxiety depression | Lithium Microsol, 3-4 ampoules per day, twice daily for 30 days | Lorazepam 2-4mg per day, twice daily | Sleep – measure not stated | Unclear | |
| | | | | | Delay in sleep onset – measure NR | Unclear | |
| | | | | | Heart rate | Unclear | |
| | | | | | "Emotionalism" – measure not stated | Unclear | |
| | Heulluy (1985)<br>[Level II]<br>Jadad score 1[d]<br>N=60 | Patients under consultation for depression, postmenopausal involution or thymo-effective dystonia | Non-individualised L72 (constituents not specified), 20 drops, four times daily for 31 days. Dose increased if required | Diazepam (dose and frequency unknown) | Ratio of pre and post scores for selected items on HAM scale – details not specified | No difference – L72 as effective as diazepam on all measures | |
| | | | | | Adverse events - drowsiness | 1 patient treated with L72 and two treated with diazepam suffered from drowsiness | |
| | Stanton (1981)<br>[Level II]<br>Quality not specified | Patients with test anxiety | *Argentum nitricum* 12x | Placebo | Test Anxiety Scale | Homeopathic preparation significantly improved test anxiety compared with placebo<br>(p-value NR) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | N=40 | | | | | | |
| Davidson et al (2011)<br>[Level I]<br>AMSTAR:8/10<br><br>SR of homeopathy for multiple conditions | Ngobese (2006)<br>[Level II]<br>SIGN score: fair<br>N=41 | Patients with GAD | Individualised homeopathy | Placebo or CBT | HARS, BAI, PPQ | No significant difference<br>• "A proven treatment for GAD, cognitive therapy, failed to work; study can be regarded as a "failed" study rather than a negative study for homeopathy. In other words, it is not informative. Length of treatment may have been inadequate". | There is no support for efficacy of homeopathy in anxiety- or stress-related conditions. |
| | Vaithilingam (2005)<br>[Level II]<br>SIGN score: poor<br>N=30[g] | Patients with job-related burnout | Individualised homeopathy | Placebo | Maslach Burnout Inventory subscales | Homeopathy worse than placebo on depersonalisation scale of Maslach Burnout Inventory | |
| | Baker et al (2003)<br>[Level II]<br>SIGN score: fair<br>N=62[g] | Patients with test anxiety | *Argentum nitricum* | Placebo | Benson Revised Test Anxiety Scale | Results favoured placebo (weak effect size) | |
| | Bonne et al (2003)<br>[Level II]<br>SIGN score: fair<br>N=44 | Patients with GAD | Individualised homeopathy | Placebo | Rate of response | No significant differences ("results unlikely to be different with a larger sample size")<br>• Homeopathy 40% vs. control 42% | |
| | Traub (2000)<br>[Level II]<br>SIGN score: poor<br>N=32[g] | Patients with test anxiety | Combined 3-remedy product | Placebo | Unclear | No effect on the total scores of the primary measures. Weak evidence for homeopathy on scale items | |
| | McCutcheon (1996)<br>[Level II]<br>SIGN score: fair<br>N=77 | Patients with high trait anxiety | Combined 9-remedy product | Placebo | STAI(T), STAI(S), sleep, pulse | Mixed results; significant improvement on sleep, but no benefit on state anxiety | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; BDI, Beck Depression Inventory; BSPS, Brief Social Phobia Scale; BSI, Brief Symptom Inventory; CBT, cognitive behavioural therapy; DSM, Diagnostic and Statistical Manual; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; GAD, generalised anxiety disorder; HADS, Hospital Anxiety and Depression Scale; HAM, Hamilton Rating Scale for Anxiety; ITT, intention-to-treat; MYMOP, Measure Yourself Medical Outcome Profile; NR, not reported; PGWBI, Psychological General Well-Being Index; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review; STAI, State-Trait Anxiety Inventory; TAS, Test Anxiety Scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

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

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

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

### 4.12.3 Borderline personality disorder

The effectiveness of homeopathy for the treatment of patients with borderline personality disorder was assessed in one systematic review that formed the basis of a NICE clinical practice guideline on borderline personality disorder (National Collaborating Centre for Mental Health, 2009; AMSTAR score 3/5). The systematic review aimed to evaluate the treatments that are associated with improvement in mental state and quality of life, reductions in self-harm, service use, risk-related behaviour, and/or improved social and personal functioning while minimising harm in people with borderline personality disorder. No studies were found from the search that was conducted in 2006, including a broadening of the search for studies on any personality disorder. The systematic review thus concluded that "there is no evidence on the use of complementary therapies as a treatment in people with a personality disorder".

*Evidence statement*

One systematic review (2006) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy in people with borderline personality disorder.

### 4.12.4 Dementia

The effectiveness of homeopathy for the treatment of patients with dementia was assessed in one systematic review (McCarney et al, 2009; AMSTAR score 5/5). This Cochrane review aimed to evaluate the effectiveness and safety profile of homeopathically prepared medications used in treating dementia, as established by Level II studies. The results of the literature search conducted in March 2009 identified no studies that fulfilled the criteria for inclusion. The authors thus concluded that "in view of the absence of evidence it is not possible to comment on the use of homeopathy in treating dementia".

*Evidence statement*

One systematic review (2009) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy in people with dementia.

### 4.12.5 Depression

The effectiveness of homeopathy for the treatment of depression was assessed in one systematic review (Pilkington et al, 2005; AMSTAR score 7/10) as summarised in Table 49. The systematic review, which focused specifically on the effectiveness of homeopathy for the treatment of depression, identified two Level II studies (Katz et al, 2005; Heulluy, 1985) and five uncontrolled studies that did not meet the standards for inclusion in this review. The systematic review did not identify any Level II, Level III-1 or Level III-2 studies that compared homeopathy to placebo for the treatment of depression.

The formal quality assessment was not specified for each individual trial by Pilkington et al (2005), although the authors did comment on the low methodological quality of the two Level II studies as well as the very small number of patients that were recruited (4 and 30 patients, respectively). In addition, Pilkington et al (2005) questioned whether Heulluy (1985) had used an appropriate comparator, stating "the use of an anxiolytic drug as a control appears inappropriate in a trial in patients with depression".

Ultimately, no results were presented from Katz et al (2005) due to low recruitment (4 patients) and the findings of the systematic review are largely based on the flawed Level II study by Heulluy (1985), which reported no difference between homeopathy (L72) and diazepam in terms of the ratio of pre- and post-treatment scores for selected items on the Hamilton Depression Scale. The systematic review authors conclude that the evidence base for homeopathy in depression is currently weak due to the "lack of clinical trials of high quality".

*Reviewer comments*

*Overall, the findings of the systematic review were limited by the low recruitment and methodological flaws within the included trials. The identification of only two very small Level II studies (one of which presented no results due to low recruitment), prevented the authors of the systematic review from presenting any strong evidence to indicate benefit or inferiority of homeopathy compared to other interventions.*

*The evidence reviewer supports the assertion by Pilkington et al (2005) that the studies identified in their review were inadequately randomised, controlled and powered in order to meet conventional measures of quality from which any meaningful clinical evidence could be drawn.*

*Evidence statement*

One systematic review (2005) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy compared with placebo for the treatment of people with depression.

One systematic review of medium quality identified two randomised controlled trials (poor quality; 4 and 30 participants) that compared homeopathy with diazepam or fluoxetine for the treatment of people with depression.

These studies are of insufficient quality and size to warrant further consideration of their findings. LOC: Very low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is as effective as diazepam or fluoxetine for the treatment of people with depression.

**Table 49 Evidence summary table: the effectiveness of homeopathy for the treatment of depression**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Pilkington et al (2005)<br>[Level I]<br>AMSTAR: 7/10<br><br>SR of homeopathy for depression | Katz et al (2005)<br>[Level II]<br>Low quality<br>N=4 | Patients with major depressive episodes of moderate severity (HAMD score 17+) | Homeopathic remedy selected from a list of 30 remedies by a trained homeopath (using decision support software) | Fluoxetine – 20 mg daily increased to 40 mg after 4 weeks if no improvement in HAMD score, or placebo matched tablets or capsules | • HAMD score<br>• CGI<br>• SF-12<br>• QoL questionnaire<br>• WSDS<br>• Pittsburgh Sleep<br>• Quality Index questionnaire<br>• Treatment Credibility Side Effects checklist | No results reported due to low recruitment | "Evidence for the effectiveness of homeopathy in depression is limited due to lack of clinical trials of high quality."<br><br>"Further research is required, and should include well-designed controlled studies with sufficient numbers of participants."<br><br>"The evidence base is currently weak." |
| | Heulluy (1985)<br>[Level II]<br>Low quality<br>N=30 | Patients currently under consultation for depression, postmenopausal involution or thymo-effective dystonia | L72 (constituents not specified) – 20 drops, 4 times daily for 31 days, dose increased if required | Diazepam – dose and frequency unknown | Ratio of pre and post scores for selected items on HAMD scale | No difference – L72 as effective as diazepam | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CGI, Clinical Global Improvement; HAMD, Hamilton Depression Scale; QoL, quality of life; SF-12, Short Form-12; SR, systematic review; WSDS, Work and Social Disability Scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.12.6 Heroin addiction

The effectiveness of homeopathy for the treatment of patients with a heroin addiction was assessed in one Level I/III systematic review (Linde and Melchart, 1998; AMSTAR score 8/11) as summarised in Table 50. The authors conducted a broad review of the efficacy of individualised homeopathy across a range of clinical areas. One study was identified that assessed the efficacy of homeopathy compared to placebo for heroin detoxification (Bakshi, 1990). The study was either a Level II or Level III-1 study; however, the method of allocation was not described and it is therefore not clear whether the study was randomised or pseudo-randomised. It was reported that overall homeopathy was "superior to placebo"; however, the outcome measure used to assess treatment superiority was not clear. Linde and Melchart (1998) gave the study a Jadad score of 1 and an internal validity score of 2. They stated that the reporting of the trial by Bakshi (1990) was "totally insufficient" and "completely inassessible".

*Evidence statement*

One systematic review of medium quality identified one small prospectively designed and controlled study (poor quality; 60 participants) that compared homeopathy (*Simillimum*) with placebo for the treatment of people with a heroin addiction. LOC: Very low.

Based on only one small poor quality study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with a heroin addiction.

**Table 50 Evidence summary table: the effectiveness of homeopathy for the treatment of heroin addiction**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998)<br>[Level I/III]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Bakshi (1990)<br>[Level II or Level III-1][d]<br>Quality: 1, 2[e]<br>N=60 | Patients with a heroin addiction | Individual simillimum | Placebo | Unclear | "Homeopathy superior to placebo." | "Totally insufficient report – completely inassessible." |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The study was either randomised or pseudo-randomised; however, the allocation of participants was not described.

[e] Quality assessed using (i) Jadad score (out of 5); (ii) internal validity score (out of 6)

# 4.13 Reproductive system and breast disorders

## 4.13.1 Premenstrual syndrome

The effectiveness of homeopathy for the treatment of women with premenstrual syndrome (PMS) was assessed in three systematic reviews as summarised in Table 51 and Table 52. In total, the systematic reviews included five Level II studies (Table 51).

**Table 51 Matrix indicating the studies that were included in the systematic reviews of premenstrual syndrome**

| | | Study ID | | | | |
|---|---|---|---|---|---|---|
| | | **Laister (2008) [Level II]** | **Yakir et al (2001) [Level II]** | **Chapman et al (1994) [Level II]** | **Kirtland (1994) [Level II]** | **Yakir et al (1994) [Level II]** |
| **Systematic review** | **Davidson et al (2011) [Level I]** | ✓ | ✓ | ✓ | ✓ | |
| | **Stevinson and Ernst (2001) [Level I]** | | | ✓ | | |
| | **Linde and Melchart (1998) [Level I]** | | | ✓ | | ✓ |

The systematic review by Davidson et al (2011) (AMSTAR score 8/10) analysed all Level II studies of homeopathy for psychiatric conditions. Four Level II studies were identified for the PMS indication. Laister (2008) (good quality), Yakir et al (2001) (fair quality), and Chapman et al (1994) (fair quality) were all Level II studies that investigated the effect of individualised homeopathy in women with PMS. The results of a Menstrual Distress Questionnaire (MDQ) in Yakir et al (2001) were "suggestive of greater benefit for homeopathy"; however the systematic reviewer noted the limitation of the small trial sample size (N=23). Laister (2008) found that "homeopathic simillimum was not effective in treating PMS". Chapman et al (1994) found that there was no significant difference in the rate of response between the homeopathy and placebo groups. Indeed, a high placebo response rate of 60% was noted. Kirtland (1994) was a poor-quality Level II study that examined the effect of homeopathic *Folliculinum* compared with placebo in women with PMS. The results of a MDQ and Premenstrual Assessment Form "suggested an effect for homeopathy"; however, no further details were provided. Overall, Davidson et al (2011) concluded that there is "little evidence of homeopathy for premenstrual problems, other than the one study with a small sample size".

Stevinson and Ernst (2001) (AMSTAR score of 6/10) conducted a systematic review that aimed to determine whether the use of complementary and alternative therapies for PMS is supported by evidence of effectiveness from rigorous clinical trials. The literature search identified one relevant Level II study (Chapman et al, 1994) for the homeopathy intervention. The authors commented that "a placebo response of 47% in the pre-treatment 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". Whilst the quality of Chapman et al (1994) was not specified, Stevinson and Ernst (2001) stated that "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". Consequently, Stevinson and Ernst (2001) concluded that "the current evidence for homeopathy is not particularly promising, with trial results indicating little more than a placebo response".

Linde and Melchart (1998) (AMSTAR score 8/11) performed a systematic review that examined the efficacy of individualised homeopathy on a variety of clinical conditions. The authors identified two Level II studies (Chapman et al, 1994; Yakir et al, 1994) for the PMS indication. Similar to all of the above systematic reviews, Linde and Melchart (1998) also reported that the homeopathy and placebo groups experienced a similar response in Chapman et al (1994). Whilst a Jadad score of 4 was given, it was noted that Chapman et al (1994) was a well-planned trial but "recruitment failed completely – totally insufficient sample size". In the second included Level II study (Yakir et al, 1994), Linde and Melchart (1998) observed that there was "greater improvement in homeopathy group". However, the significance of inter-group differences was not stated. A quality assessment of Yakir et al (1994) was not performed as the report was only available as an abstract. Linde and Melchart (1998) did not formulate a conclusion about the effect of homeopathy for the treatment of women with PMS.

*Evidence statement*

Three systematic reviews of medium quality identified five randomised controlled trials (poor to good quality; total of 103 participants, range: 10-39) that compared homeopathy with placebo for the treatment of women with premenstrual syndrome. LOC: Very low - low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of women with premenstrual syndrome.

**Table 52 Evidence summary table: the effectiveness of homeopathy for the treatment of premenstrual syndrome**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Davidson et al (2011)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Laister (2008)<br>[Level II]<br>Good quality<br>N=39 | Women with premenstrual syndrome | Individualised homeopathy | Placebo | MDQ | Homeopathic simillimum not effective in treating PMS | "Little evidence of efficacy of homeopathy for premenstrual problems, other than in one study with a small sample size." |
| | Yakir et al (2001)<br>[Level II]<br>Fair quality<br>N=23 | Women with premenstrual syndrome | Individualised homeopathy | Placebo | MDQ | Suggestive of greater benefit for homeopathy, but small sample size | |
| | Chapman et al (1994)<br>[Level II]<br>Fair quality<br>N=10 | Women with premenstrual syndrome | Individualised homeopathy | Placebo | Rate of response | No significant difference between treatment groups. High placebo response rate (homeopathy: 40%; placebo: 60%) | |
| | Kirtland (1994)<br>[Level II]<br>Poor quality<br>N=31 | Women with premenstrual syndrome | *Folliculinum* 15C | Placebo | Each item on MDQ, PAF | Suggests an effect for homeopathy | |
| Stevinson and Ernst (2001)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of CAM for PMS | Chapman et al (1994)<br>[Level II]<br>Quality not specified<br>N=10 | Not reported. Assumed to be women with premenstrual syndrome | Homeopathy, 3 doses monthly for 4 cycles | Placebo | Diary | "A placebo response of 47% in the pretreatment washout phase illustrates the powerful effect of placebo on premenstrual symptoms and suggests that the depth and empathy of the homeopathic interview may have a therapeutic | "The current evidence for homeopathy is not particularly promising, with trial results indicating little more than a placebo response." |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | effect." | |
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Chapman et al (1994)<br>[Level II]<br>Jadad score 4[d]<br>N=10 | Women aged between 18-45 years with premenstrual syndrome | Individual simillimum given in 3 doses at 12 hour intervals, repeated or new remedy at follow-up | Placebo | Number of patients assessed globally as improved | Similar response in both groups. Significance of inter-group differences not reported<br>• Intervention group: 2/5 (40%)<br>• Control group: 3/5 (60%) | Not reported |
| | Yakir et al (1994)<br>[Level II]<br>Quality not specified<br>N=23 | Women with premenstrual syndrome | Individual simillimum | Placebo | Number of patients assessed globally as improved | Greater improvement in homeopathy group. Significance of inter-group differences not reported<br>• Intervention group: 75%<br>• Control group: 25% | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CAM, complementary and alternative medicines; MDQ, Menstrual Distress Questionnaire; PAF, Premenstrual Assessment Form; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.13.2 Lactation in postpartum women who elect not to breastfeed

The effectiveness of homeopathy for suppressing the symptoms of lactation in postpartum women who elect not to breastfeed was assessed in one systematic review (Oladapo and Fawole, 2012; AMSTAR score 8/10) as summarised in Table 53. This Cochrane review aimed to evaluate the effectiveness and safety of interventions used for suppression of lactation in postpartum women (who have not breastfed or expressed breast milk) to determine which approach has the greatest comparative benefits with least risk. Whilst a number of different interventions were assessed, the results of a literature search on homeopathic preparations versus no treatment or placebo only identified one relevant Level II study (Berrebi et al, 2001).

Berrebi et al (2001) assessed the effect of an unspecified homeopathic treatment on milk secretion, breast engorgement and breast pain in postpartum women who elected not to breastfeed. The results "suggested a lower risk of treatment failure when homeopathic preparation (with anti-inflammatory and analgesic properties) was compared with placebo on days two and four postpartum". An overall quality rating for this Level II study was not specified; however, Oladapo and Fawole (2012) noted that "the risk of bias for most reports was uncertain as they contained little methodological description". Indeed, Berrebi et al (2001) received an "unclear" risk of bias rating for random sequence generation, allocation concealment, blinding for lactation and adverse events, selective reporting and other bias. Oladapo and Fawole (2012) concluded that "this review did not show sufficient evidence to indicate if other pharmacologic agents (including homeopathic preparations) are useful in suppressing the symptoms of lactation postpartum, as they are all based on individual small trials".

*Evidence statement*

One systematic review of medium quality identified one small randomised controlled trial (quality not reported; 71 participants) that compared homeopathy with placebo for suppression of lactation in postpartum women who had elected not to breastfeed. LOC: Very low.

Based on only one small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the suppression of lactation in postpartum women who elect not to breastfeed.

**Table 53 Evidence summary table: the effectiveness of homeopathy for suppressing lactation in postpartum women who elect not to breastfeed**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Oladapo and Fawole (2012)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of CAM for the suppression of lactation | Berrebi et al (2001)<br>[Level II]<br>Quality not specified<br>N=71 | Postpartum women who elected not to breastfeed | Five homeopathic pills twice daily for 10 days. All patients received an anti-inflammatory treatment (*naproxine-Apranax*) for 5 days. | Placebo. All patients received an anti-inflammatory treatment (naproxine-Apranax) for 5 days | Milk secretion (VAS)<br>Breast engorgement (VAS)<br>Breast pain (VAS) | "Berrebi 2001 (71 women) suggested a lower risk of treatment failure when homeopathic preparation (with anti-inflammatory and analgesic properties) was compared with placebo on days two and four postpartum." | "This review did not show sufficient evidence to indicate if other pharmacologic agents (includes homeopathic preparation) are useful in suppressing the symptoms of lactation postpartum, as they are all based on individual small trials." |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; SR, systematic review; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

# 4.14 Respiratory and allergic

## 4.14.1 Adenoid vegetation in children

The effectiveness of homeopathy for the treatment of children with adenoid vegetation was assessed in one systematic review (Altunc et al, 2007; AMSTAR score 6/10) as summarised in Table 54. The systematic review included two Level II studies (Furuta et al, 2003; Feuchter et al, 2001). In Furuta et al (2003) (Jadad score 4), there was no significant difference in the size of adenoid vegetation or symptom questionnaire between the homeopathy and placebo groups. There were also no adverse events reported. In Feuchter et al (2001) (Jadad score 5), there was no significant difference in the need for adenoidectomy after three months of treatment between the homeopathy and placebo groups. A number of adverse events were reported in both groups. The authors concluded that "homeopathic treatments were not effective for reducing the size of adenoid vegetations and preventing the need for adenoidectomy".

*Evidence statement*

One systematic review of medium quality identified two randomised controlled trials (medium to good quality; 40 and 97 participants) that compared homeopathy with placebo for the treatment of children with adenoid vegetation. LOC: Low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of children with adenoid vegetation.

**Table 54 Evidence summary table: the effectiveness of homeopathy for the treatment of adenoid vegetation**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Altunc et al (2007)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Furuta et al (2003)<br>[Level II]<br>Jadad score 4[d]<br>N=40 | Patients with adenoid vegetation; Intervention group and control group: 3-7 years old; 57% male | Standardised and individualised homeopathy, material potencies, 4 months, treatment regimen not reported<br>• *Agraphis nutans* 6C potency<br>• *Thuya* 6C potency<br>• Adenoid 21C potency in addition to individualised remedies | Placebo | Size of adenoid vegetation | No significant difference | "Homeopathic treatments were not effective for reducing the size of adenoid vegetations and preventing the need for adenoidectomy." |
| | | | | | Symptom questionnaire | No significant difference | |
| | | | | | Adverse events | No adverse events | |
| | Feuchter et al (2001)<br>[Level II]<br>Jadad score 5[d]<br>N=97 | Patients with adenoid vegetation; Intervention and control group: mean age 6 years; 65% male<br><br>Concomitant treatment: acute intercurrent diseases were treated homeopathically if possible so as not to compromise the effect of homeopathic remedies | Standardised homeopathy, material potencies, 3 months<br>• *Nux vomica* D200 potency, 5 globules once at the start of the study<br>• *Okoubaka* D3 potency, 15 globules daily before meals from the first day for 4 weeks<br>• *Tuberculinum* D200 potency, 5 globules once 4 weeks after the start of the study<br>• *Barium iodatum* D4 potency, 3 tablets daily before meals from weeks 4-8<br>• *Barium iodatum*, D6 potency, 3 tablets daily for 4 weeks from weeks 8-12 | Placebo | Need for adenoidectomy after 3 months of treatment | No significant difference | |
| | | | | | Adverse events | Main adverse events: acute inflammation of the middle ear (5 homeopathy, 6 placebo), influenza (4 in both groups), acute tonsillitis (3 homeopathy, 5 placebo), cough (5 homeopathy), scarlet fever (2 in both groups), rhinitis (2 in both groups), digestive complaints (1 in both groups) | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; D, decimal; NR, not reported; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.14.2 Allergic rhinitis

The effectiveness of homeopathy for the treatment of allergic rhinitis (also referred to as pollinosis and hay fever) was assessed in five systematic reviews (Bellavite et al, 2011; Cucherat et al, 2000; Ernst, 2011; Linde et al, 1997; Passalacqua et al, 2006) as summarised in Table 55 and Table 56. Overall, the six reviews included 14 Level II studies and two Level III-2 studies (see Table 55).

**Table 55 Matrix indicating the studies that were included in the systematic reviews of allergic rhinitis**

| | | Systematic review | | | | |
|---|---|---|---|---|---|---|
| | | Ernst (2011) [Level I] | Passalacqua et al (2006) [Level I] | Cucherat et al (2000) [Level I] | Linde et al (1997) [Level I] | Bellavite et al (2011) [Level I/III] |
| Study ID | Kim et al (2005) [Level II] | | ✓ | | | ✓ |
| | Aabel (2001) [Level II] | | | | | ✓ |
| | Aabel et al (2000) [Level II] | | ✓ | | | ✓ |
| | Aabel (2000) [Level II] | | ✓ | | | ✓ |
| | Taylor et al (2000) [Level II] | | ✓ | | | ✓ |
| | Weiser et al (1999) [Level II] | | ✓ | | | ✓ |
| | Wiesenauer & Ludtke (1995) [Level II] | ✓ | | | ✓ | ✓ |
| | Wiesenauer et al (1990) [Level II] | ✓ | | | ✓ | |
| | Wiesenauer & Ludtke (1987) [Level II] | | | | | ✓ |
| | Reilly et al (1986) [Level II] | | ✓ | ✓ | ✓ | ✓ |
| | Reilly and Taylor (1985) [Level II] | | | | ✓ | |
| | Wiesenauer and Gaus (1985) [Level II] | ✓ | ✓ | | ✓ | ✓ |
| | Hardy (1984) [Level II] | | | | | ✓ |
| | Wiesenauer et al (1983) [Level II] | ✓ | | | ✓ | |
| | Witt et al (2005) [Level III-2] | | | | | ✓ |
| | Micciche et al (1998) [Level III-2] | | | | | ✓ |

The systematic review by Bellavite et al (2011) (AMSTAR score 5/10) aimed to evaluate the effectiveness of homeopathy for the treatment of a range of conditions including respiratory allergies. The review included the majority of the Level II and III-2 trials (11 Level II studies and two Level III-2 studies). The method used to assess the quality of the included studies was unclear, although the relatively poor quality was alluded to throughout the review. The authors suggested that the "major quality problems in most trials" were the limited details provided about allocation concealment methods, imprecise outcomes, and the poor reporting of dropouts and withdrawals.

Bellavite et al (2011) stated that any meta-analysis was precluded due to the poor quality of many trials and the high level of heterogeneity. Instead, the systematic review authors offered a "semi-quantitative" evaluation when multiple studies on the same homeopathic approach and indication were available. They concluded that, for the treatment of allergic rhinitis, there was "strong positive evidence" for the effectiveness of homeopathic *Galphimia glauca*; "good positive evidence" for the effectiveness of individualised homeopathy; and "unclear or conflicting evidence" for the effectiveness of homeopathic immunotherapy.

Passalacqua et al (2006) (AMSTAR score 4/10) performed a broad systematic review of complementary and alternative medicines that are commonly used in patients with rhinitis and asthma. The review included seven Level II studies that examined various homeopathic interventions in patients with seasonal or perennial allergic rhinitis. Of the seven studies, six were given Jadad scores of 5 (Aabel, 2000; Aabel et al, 2000; Kim et al, 2005; Reilly et al, 1986; Taylor et al, 2000; Weiser et al, 1999) and one received a Jadad score of 4 (Wiesenauer and Gaus, 1985). The overwhelming majority of outcomes across the trials found no significant difference between the homeopathic interventions and placebo.

Passalacqua et al (2006) reported the results of the individual studies in a way that was difficult to interpret. For example, the results of Reilly et al (1986) were reported as a "decrease in symptom score, visual analog scale, and use of antihistamines"; however, it was not clear whether the decrease referred to a decrease within the homeopathy group compared to baseline, or a decrease relative to placebo. Overall, Passalacqua et al (2006) concluded that the few positive results described in allergic rhinitis in good-quality trials were counterbalanced by an equal number of negative trials.

Linde et al (1997) (AMSTAR score 9/11) conducted a systematic review and meta-analysis that aimed to "assess whether the effect seen with homeopathic remedies is equivalent to that seen with placebo". Linde et al (1997) identified six Level II studies that examined the effects of homeopathic treatments on patients with allergic rhinitis. Three studies received a Jadad score of 3 (Reilly and Taylor, 1985; Wiesenauer et al, 1990; Wiesenauer and Ludtke, 1995), two studies received Jadad scores of 4 (Wiesenauer et al, 1983; Wiesenauer and Gaus, 1985), and one study received a Jadad score of 5 (Reilly et al, 1986) (see Table 56). Linde et al (1997) noted that all of the trials that examined allergic rhinitis had a high number of dropouts and withdrawals.

In contrast to the approach taken by Bellavite et al (2011), Linde et al (1997) undertook a meta-analysis of the latter four Level II studies (by Wiesenauer and others) that examined homeopathic *Galphimia glauca* in patients with allergic rhinitis. The raw data from continuous outcomes were used to calculate odds ratios by the authors of the systematic review. The odds ratios of all of the four individual studies favoured homeopathy, and in two of the four studies the result was statistically significant. After the results were pooled, the odds ratio of 1.87 (95% CI 1.37, 2.56)

suggested that *Galphimia glauca* is significantly more effective than placebo in the treatment of allergic rhinitis. Nevertheless, the overall conclusion of the systematic review by Linde et al (1997) was that there is "insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition".

Ernst (2011) (AMSTAR score 5/10) performed a systematic review to assess the efficacy of homeopathic *Galphimia glauca* in patients with allergic rhinitis. The review included the same four Level II studies that were meta-analysed by Linde et al (1997) (Wiesenauer et al, 1983; Wiesenauer and Gaus, 1985; Wiesenauer et al, 1990; and Wiesenauer and Ludtke, 1995). Ernst (2011) reported that three of the Level II studies (two with Jadad scores of 4 and one with a Jadad score of 5) found significant improvements in the primary outcome (a non-validated symptom scale; self-assessed by the patient and verified by the physician) in favour of *Galphimia glauca* over placebo. However, one study (Wiesenauer and Gaus, 1985; Jadad score 5) found no significant inter-group differences. The conclusion drawn in the systematic review was that there is some evidence to suggest that *Galphimia glauca* may be effective for symptomatic treatment of allergic rhinitis; however the preliminary studies require independent replication.

Finally, Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The systematic review included one Level II study of acute allergic rhinitis (Reilly et al, 1986). Reilly et al (1986) used a visual analogue scale to compare overall symptom intensity between allergic rhinitis patients treated with homeopathy or placebo. A significant difference was reported between the groups that favoured homeopathy (p=0.018). The quality of the study was not reported by Cucherat et al (2000), although a comment was made that overall the studies of high methodological quality were more likely to have negative results in terms of the efficacy of homeopathy, compared to low quality studies. Cucherat et al (2000) concluded that there is insufficient evidence to conclude that homeopathy is clinically effective for any condition examined in their review, which included allergic rhinitis.

*Reviewer comments*

*Poor reporting of the individual study results was a major limitation of the systematic reviews, particularly those conducted by Bellavite et al (2011) and Passalacqua et al (2006). For example, it was commonly stated that homeopathy was "better than placebo" with no mention of the statistical significance of the results. It was unclear whether the lack of numerical data stemmed from the individual Level II studies or the review itself, however if the limitation was with the Level II studies then this should have been stated to clarify the omission. Similarly, it was difficult to ascertain whether results such as "significant relief in verum group" were referring to a significant improvement from baseline or a significant improvement compared to placebo. This made it difficult for the evidence reviewer to critique the overall conclusions drawn by the systematic review authors.*

*The evidence reviewer notes that it was often difficult to determine from the systematic reviews whether the studies examined allergic or non-allergic rhinitis. Where possible, studies that related to allergic rhinitis (where the systematic review explicitly used the word "allergic") have been discussed in Section 4.14.2 and studies that related to non-allergic rhinitis (where none of the systematic reviews explicitly used to word "allergic") have been discussed in Section 4.14.7; however, it is possible that the studies have not always been correctly categorised.*

*Evidence statement*

Five systematic reviews of poor to good quality identified 13 randomised controlled trials (unreported or medium to good quality; total of 1436 participants, range: 39-243) that compared homeopathy with placebo for the treatment of people with allergic rhinitis.

Though not the largest study identified in this body of evidence, and while it is below the agreed threshold for a sufficiently sized study, one good quality study with 144 participants (Reilly et al, 1986) reported a significant difference in favour of homeopathy over placebo. However, the findings of this study were not confirmed by other good quality, sufficiently sized studies.

Overall, these studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with allergic rhinitis.

Two systematic reviews of poor quality identified one small randomised controlled trial (good quality; 147 participants) and two prospectively designed, non-randomised controlled studies (quality not reported; 70 and 178 participants) that compared homeopathy with other therapies (including anti-histamines, cortisone and intranasal cromolyn sodium) for the treatment of people with allergic rhinitis.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is as effective as the other therapies for the treatment of people with allergic rhinitis.

**Table 56 Evidence summary table: the effectiveness of homeopathy for the treatment of allergic rhinitis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Ernst (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for allergic rhinitis | Wiesenauer and Ludtke (1995)<br>[Level II]<br>Jadad score 4[d]<br>N=164 | Patients with allergic rhinitis | *Galphimia glauca*-D4; dosage individualised; duration of 4 weeks | Placebo | Symptom rating scales (not validated; self-assessed by the patient and verified by the physician) | Differences between groups were statistically significant only for ocular symptoms.<br>Improvement by end of treatment in intervention group [89% ocular, 80% nasal] and comparator group [63% ocular, 69% nasal]. | "Three RCTs reported significant result in favour of GG over placebo, while one study failed to yield significant inter-group differences. No serious adverse effects were reported in any of the trials".<br><br>"In conclusion, three of the four currently available placebo-controlled RCTs of homeopathic GG suggest this therapy is an effective symptomatic treatment for hay fever. There are, however, important caveats. Most essentially, independent replication would be required before GG can be considered for the routine treatment of hay fever." |
| | | | | | Adverse events | No adverse events were reported in intervention group. | |
| | Wiesenauer et al (1990)<br>[Level II]<br>Jadad score 4[d]<br>N=243 | Patients with allergic rhinitis | *Galphimia glauca*-C2; dosage individualised; duration of 33 days on average | Placebo | Symptom rating scales (not validated; self-assessed by the patient and verified by the physician) | Statistically significant difference (p=NR)<br>Improvement by end of treatment in intervention group [88% ocular, 76% nasal] and comparator group [60% ocular, 67% nasal]. | |
| | Wiesenauer and Gaus (1985)<br>[Level II]<br>Jadad score 5[d]<br>N=213 | Patients with allergic rhinitis | *Galphimia glauca* -D6; dosage individualised; duration of 5 weeks on average | 2 groups:<br>Placebo;<br>*Galphimia glauca* diluted by factor of $10^{-6}$ | Symptom rating scales (not validated; self-assessed by the patient and verified by the physician) | No significant difference.<br>Improvement by end of treatment in intervention group [80% ocular, 78% nasal], diluted homeopathy remedy group [66% ocular, 51% nasal], placebo group [65% ocular, 58% nasal]. | |
| | | | | | Adverse events | No adverse events were noted | |
| | Wiesenauer et al (1983)<br>[Level II]<br>Jadad score 5[d]<br>N=121 | Patients with allergic rhinitis | *Galphimia glauca*-D4; dosage individualised; duration of 39 | Placebo | Symptom rating scales (not validated; self-assessed by the patient and verified by the | Statistically significant difference (p=NR)<br>Improvement by end of treatment in intervention group [81% (95% CI 65, 92)] and comparator group [57% (95% CI 39, 74)] | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | days on average | | physician) | | |
| | | | | | Adverse events | Adverse events were noted only in the comparator group | |
| Passalacqua et al (2006)<br>[Level I]<br>AMSTAR: 4/10<br><br>SR of homeopathy for allegeric rhinitis and allergic asthma | Kim et al (2005)<br>[Level II]<br>Jadad score 5[d]<br>N=40 | Patients with allergic rhinitis | Homeopathic grass, trees, weeds mix | Placebo | Three QoL questionnaires | Significant improvement in active group (compared to placebo or baseline?) | "Some positive results were described in rhinitis in good-quality trials, but an equal number of negative studies counterbalance the positive ones."<br><br>"It is not possible to provide evidence-based recommendations for the use of homeopathy to treat allergic rhinitis." |
| | Aabel (2000)<br>[Level II]<br>Jadad score 5[d]<br>N=80 | Patients with seasonal allergic rhinitis | *Birch* 30c | Placebo | Rhinitis symptoms | No effect on symptoms | |
| | Aabel et al (2000)<br>[Level II]<br>Jadad score 5[d]<br>N=70 | Patients with seasonal allergic rhinitis | *Birch* 30c | Placebo | Rhinitis symptoms | No effect on symptoms | |
| | Taylor et al (2000)<br>[Level II]<br>Jadad score 5[d]<br>N=51 | Patients with perennial allergic rhinitis | 30c dilution of various allergens | Placebo | VAS | No difference between groups | |
| | | | | | Symptom score | No difference between groups | |
| | | | | | PNIF morning and evenings | Increase (in homeopathy group?). No mention of placebo or between-group differences | |
| | Weiser et al (1999)<br>[Level II]<br>Jadad score 5[d]<br>N=147 | Patients with seasonal allergic rhinitis | Nasal *Luffa compositum Heel* | Nasal cromone | Rhinitis symptoms | Homeopathy and nasal cromone are equivalent | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Reilly et al (1986)<br>[Level II]<br>Jadad score 5[d]<br>N=144 (reported incorrectly in SR as N=158) | Patients with seasonal allergic rhinitis | 30c dilution grass pollen | Placebo | Symptom score | Decrease (presumably in homeopathy group?). No mention of placebo or between-group differences | |
| | | | | | VAS | Decrease (presumably in homeopathy group?). No mention of placebo or between-group differences | |
| | | | | | Use of antihistamines | Decrease (presumably in homeopathy group?). No mention of placebo or between-group differences | |
| | Wiesenauer and Gaus (1985)<br>[Level II]<br>Jadad score 4[d]<br>N=164 | Patients with allergic oculo-rhinitis | *Galphimia* homeopathic dilution | Conventional dilution/placebo | NR | No significant difference between active and placebo treatments | |
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Reilly et al (1986)<br>[Level II]<br>Quality not specified[e]<br>N=144 (reported incorrectly in SR as N=158) | Patients with allergic rhinitis | Fixed, mixed grass pollens 30°C | Placebo | VAS of overall symptom intensity | Significant difference in favour of homeopathy (p=0.018) | "The strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies. Further high quality studies are needed to confirm these results."<br><br>"It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | | all clinical conditions and is not specific to allergic rhinitis) |
| Linde et al (1997)<br>[Level I]<br>AMSTAR: 9/11<br><br>SR of homeopathy for multiple conditions | Reilly et al (1986)<br>[Level II]<br>Quality score 100/93[g]<br>N=144 (reported incorrectly in SR as N=162) | Patients with allergic rhinitis | Pollen C30 | Placebo | VAS improvement (mm) | Odds ratio[f] favoured homeopathy | The pooled fixed effects and pooled random effects of four Level II studies of *Galphimia glauca* for pollinosis found an odds ratio of 1.87 (95% CI 1.37, 2.56) at 4 weeks (as per Erratum in Linde, 1998)<br><br>"The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition." |
| | Reilly and Taylor (1985)<br>[Level II]<br>Quality score 60/50[g]<br>N=39 | Patients with allergic rhinitis | Pollen C30 | Placebo | Global assessment patient | Odds ratio[f] favoured homeopathy | |
| | Wiesenauer and Ludtke (1995)<br>[Level II]<br>Quality score 60/79[g]<br>N=164 | Patients with allergic rhinitis | *Galphimia* D4 | Placebo | Improvement ocular symptoms | Odds ratio[f] favoured homeopathy.<br>Intervention (responder/ randomised): 50/82<br>Control (responder/ randomised): 36/82<br>Odds ratio (95% CI): 2.00 (1.07, 3.72) | |
| | Wiesenauer et al (1990)<br>[Level II]<br>Quality score 60/86[g]<br>N=243 | Patients with allergic rhinitis | *Galphimia* C2 | Placebo | Improvement ocular symptoms | Odds ratio[f] favoured homeopathy.<br>Intervention (responder/ randomised): 75/121<br>Control (responder/ randomised): 52/122<br>Odds ratio (95% CI): 2.19 (1.31, 3.67) | |
| | Wiesenauer and Gaus (1985)<br>[Level II] | Patients with allergic | *Galphimia* D6 | Placebo | Improvement ocular symptoms | Odds ratio[f] showed no difference between homeopathy and placebo.<br>Intervention (responder/ randomised): | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Quality score 80/79[g]<br>N=142 | rhinitis | | | | 28/71<br>Control (responder/ randomised): 24/71<br>Odds ratio (95% CI): 1.28 (0.64, 2.53) | |
| | Wiesenauer et al (1983)<br>[Level II]<br>Quality score 80/79[g]<br>N=121 | Patients with allergic rhinitis | *Galphimia* D4 | Placebo | Improvement ocular symptoms | Odds ratio[f] favoured homeopathy.<br>Intervention (responder/ randomised): 30/61<br>Control (responder/ randomised): 20/60<br>Odds ratio (95% CI): 1.94 (0.93, 4.04) | |
| Bellavite et al (2011)<br>[Level I/III]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Kim et al (2005)<br>[Level II]<br>Quality not specified<br>N=40 | Patients with allergic rhinitis | H.I.T. prepared from individual allergen | Placebo | Symptoms, quality-of-life questionnaires | Better clinical changes in homeopathy group as compared with placebo | The results of the included studies were combined and classified into one of the following levels of evidence by the systematic reviewers:<br>• Strong positive evidence<br>• Good positive evidence<br>• Unclear or conflicting evidence<br>• Negative scientific evidence<br>The evidence for the effectiveness of homeopathy for the treatment of respiratory allergies was categorised by Bellavite et al (2011) as follows:<br><br>Strong positive evidence[h]: *Galphimia glauca* (low homeopathic dilutions) in allergic oculorhinitis<br><br>Good positive evidence[i]: Individualised homeopathy in allergic rhinitis |
| | Aabel (2001)<br>[Level II]<br>Quality not specified<br>N=51 | Patients with allergic rhinitis | Homeopathic birch pollen *Betula* 30c | Placebo | Symptoms (VAS) | Similar improvement in homeopathy and placebo | |
| | Aabel (2000)<br>[Level II]<br>Quality not specified<br>N=73 | Children with allergic rhinitis | Homeopathic birch pollen *Betula* 30c | Placebo | Symptoms (VAS) | Homeopathy significantly worse than placebo | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Aabel et al (2000)<br>[Level II]<br>Quality not specified<br>N=66 | Patients with allergic rhinitis | Homeopathic birch pollen *Betula* 30c | Placebo | Symptoms scores | Slightly less symptoms during 10 days; aggravation after taking homeopathy | Unclear or conflicting evidence[j]:<br>Homeopathic immunotherapy of allergic rhinitis |
| | Taylor et al (2000)<br>[Level II]<br>Quality not specified<br>N=50 | Patients with allergic rhinitis | Individual allergen | Placebo (H.I.T.) | Symptoms (VAS) and nasal air flux tests | Slightly better outcomes in homeopathy group | |
| | Weiser et al (1999)<br>[Level II]<br>Quality not specified<br>N=146 | Patients with allergic rhinitis | Low dilution homeopathic complex formulation *Luffa compositum* | Standard intranasal therapy based on cromolyn sodium | Symptoms and quality-of-life questionnaire | Equivalence of homeopathy and conventional therapy | |
| | Wiesenauer and Ludtke (1995)<br>[Level II]<br>Quality not specified<br>N=115 | Patients with allergic oculo-rhinitis | *Galphima* 4x | Placebo | Eye and nose symptoms | Significant relief in homeopathy group | |
| | Wiesenauer and Ludtke (1987)<br>[Level II]<br>Quality not specified<br>N=132 | Patients with allergic oculo-rhinitis | *Galphimia* 2c | Placebo | Eye and nose symptoms | Significantly less eye symptoms in homeopathy group | |
| | Reilly et al | Patients | Pollens 30c | Placebo | Symptoms | H.I.T. better than placebo | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | (1986)<br>[Level II]<br>Quality not specified<br>N=144 | with allergic oculo-rhinitis | (H.I.T.) | | (VAS) | | |
| | Wiesenauer and Gaus (1985)<br>[Level II]<br>Quality not specified<br>N=164 | Patients with allergic oculo-rhinitis | *Galphimia glauca* 6x dynamised | Placebo (e *Galphimia glauca* 6x non-dynamised) | Eye and nose symptoms | Trend to better improvement in the homeopathic group; not statistically significant; less symptoms in patients taking dynamised homeopathic medicine than other groups | |
| | Hardy (1984)<br>[Level II]<br>Quality not specified<br>N=70 | Patients with allergic oculo-rhinitis (house dust) | Homeopathic immunotherapy (H.I.T.) made with house dust potencies | Placebo | Symptoms | H.I.T. better than placebo | |
| | Witt et al (2005)<br>[Level III-2]<br>Quality not specified<br>N=178 | Patients with allergic diseases including rhinitis and asthma | Classic homeopathy | Conventional care | Symptoms, quality-of-life questionnaires, costs | Better outcomes in homeopathic group | |
| | Micciche et al (1998)<br>[Level III-2]<br>Quality not | Children with allergic oculo- | Homeopathic protocol based on three low-dilution drugs | Conventional therapy (anti-histaminic and cortisone | General assessment | Trend to better improvement in the homeopathic group | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | specified<br>N=70 | rhinitis | | treatment) | | | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CI, confidence interval; D, decimal; GG, *Galphimia glauca*; H.I.T, homeopathic immunotherapy; NR, not reported; SR, systematic review; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

[e] Quality of included studies was not formally assessed by the authors. The authors noted that "the only criterion for quality used for selection was adequate concealment of treatment allocation (by a suitable randomisation method)".

[f] Odds ratios were calculated by the systematic reviews based on raw data provided in Level II studies.

[g] Jadad score / IV score, where the scores are expressed as a percentage of the maxium possible score. Note: the maximum possible Jadad score is 5; the maximum possible internal validity score is 7.[h] Significant evidence of a clear benefit from >2 properly randomised trials, or from one properly conducted meta-analysis on homogenous trials.

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

[j] Conflicting evidence from multiple trials or observational studies without a clear majority of the properly conducted trials finding evidence of benefit or ineffectiveness.

### 4.14.3 Asthma

The effectiveness of homeopathy for the treatment of asthma (including allergic and non-allergic asthma) was assessed in six systematic reviews (Altunc et al, 2007; Bellavite et al, 2011; Cucherat et al, 2000; Linde and Melchart, 1998; McCarney et al, 2008; Passalacqua et al, 2006) as summarised in Table 57 and Table 58. Overall, the six systematic reviews included eight Level II studies (Freitas et al, 1995; Lara-Marquez et al, 1997; Lewith et al, 2002; Matusiewicz, 1995; Matusiewicz et al, 1999; Reilly et al, 1994; Riveron-Garrote et al, 1998; White et al, 2003).

**Table 57 Matrix indicating studies that were included in the systematic review of asthma**

| | | Systematic review | | | | | |
|---|---|---|---|---|---|---|---|
| | | Bellavite et al (2011) [Level I] | McCarney et al (2008) [Level I] | Altunc et al (2007) [Level I] | Passalacqua et al (2006) [Level I] | Cucherat et al (2000) [Level I] | Linde and Melchart (1998) [Level I] |
| Study IDs | White et al (2003) [Level II] | ✓ | ✓ | ✓ | ✓ | | |
| | Lewith et al (2002) [Level II] | ✓ | ✓ | | ✓ | | |
| | Matusiewicz et al (1999) [Level II] | ✓ | ✓ | | | | |
| | Riveron-Garrote et al (1998) [Level II] | ✓ | | | | | |
| | Lara-Marquez et al (1997) [Level II] | ✓ | | | | | ✓ |
| | Freitas et al (1995) [Level II] | | ✓ | ✓ | | | |
| | Matusiewicz (1995) [Level II] | ✓ | ✓ | | | | |
| | Reilly et al (1994) [Level II] | ✓ | ✓ | | ✓ | ✓ | |

McCarney et al (2008) (AMSTAR score 9/11) undertook a Cochrane review of homeopathy for chronic asthma. McCarney et al (2008) included six studies (see Table 58), comprehensive study details and a meta-analysis. Four of the Level II studies identified were assessed to be medium to good quality, including two with a Jadad quality assessment score of 4 (Freitas et al, 1995; Reilly et al, 1994) and two with a score of 5 (Lewith et al, 2002; White et al, 2003). White et al (2003) compared the efficacy of individualised homeopathy with placebo in patients with allergic asthma, aged five to 15 years. No statistically significant differences were found between the treatment arms on any of the reported

outcomes, which included lung function (measured by peak expiratory volume), quality of life, medication use, global assessment, and days off school. Similarly, the good quality trial by Lewith et al (2002) examined lung function, medication use and subjective symptoms and found no significant differences between the homeopathy and placebo groups.

Freitas et al (1995) reported no significant difference between homeopathy (*blatta officinalis* 6C) and placebo on any outcome. However, the systematic review authors questioned whether the patient population of that trial were truly asthmatic (eligible participants were children aged one to 12 years who had experienced at least three bronchospastic episodes or who had a continuous wheeze for at least three months). Finally, Reilly et al (1994) examined homeopathy in patients with allergic asthma, the majority of whom were sensitive to house dust mite. Reilly et al (1994) reported significant differences in favour of homeopathy based on the severity of symptoms measured on a visual analogue scale (p=0.003) and also between the medians of the groups based on forced vital capacity (p=0.03).

In addition to the studies outlined above, McCarney et al (2008) also identified two low quality studies that examined the efficacy of homeopathy in patients with bronchial asthma. Matusiewicz et al (1995) and Matusiewicz (1999) received Jadad scores of 1 and 2, respectively. In addition to significant methodological flaws, the methods and results were difficult to interpret in both studies due to poor reporting. Matusiewicz et al (1999) reported a "significant effect" for immune functioning, global ratings and number of infections; however no p-values were reported and it was unclear whether the "significant effect" referred to inter-group differences or differences in the homeopathy arm from baseline to follow-up. Matusiewicz et al (1995) reported a significant benefit in the homeopathy group based on peak expiratory flow; however, no p-value was provided to support the finding. In addition, the authors of that study reported a "clear difference" in forced expiratory volume, forced vital capacity and steroid use in favour of the homeopathy group; although no p-values or standard deviations were reported.

Overall, the ability to pool the results of the six included studies was limited due to disparate reporting of outcomes. The only outcome for which pooled effect sizes were estimable was forced expiratory volume in adults. McCarney et al (2008) pooled the results from Lewith et al (2002), Matusiewicz et al (1999) and Matusiewicz et al (1995) and no significant difference was observed between treatment groups, based on a total of 366 participants (effect size: -0.06 litres; 95% CI -0.17, 0.04; p=0.24), see Table 59. McCarney et al (2008) concluded that there is "not enough evidence to reliably assess" the efficacy of homeopathy in asthma. The authors highlighted the fact that the results regarding lung function were mixed and that no trials included in their systematic review found a significant difference between homeopathy and placebo on a validated symptom scale. Finally, McCarney et al (2008) stated that although there is no plausible scientific rationale behind homeopathy, there may be "non-specific benefits associated with a 'holistic' package of care".

Altunc et al (2007) (AMSTAR score 6/10) performed a systematic review to assess the efficacy of homeopathy in various conditions that commonly affect children and adolescents, including asthma. Two of the Level II studies discussed above (Freitas et al, 2005; White et al, 2003) were identified that compared the efficacy of homeopathy to placebo. One of the studies (Freitas et al, 2005; Jaded score 4) adopted a formulaic approach in which all patients received homeopathic *blatta orentalis* (6C potency) for six months, and found no significant difference between the homeopathic remedy and placebo in terms of intensity, frequency and duration of asthma attacks. Patients recruited into the

study by White et al (2003) (Jadad score 5) received individualised homeopathy for one year, and reported no significant difference between the homeopathy and placebo groups on the "active quality of living" subscale on the Childhood Asthma Questionnaire.

The Level II study by White et al (2003) was also included in the systematic review by Passalacqua et al (2006) (AMSTAR score 4/10). The review examined the efficacy of homeopathy for the treatment of asthma and rhinitis. Passalacqua et al (2006) reported that White et al (2003) found no significant differences between homeopathy and placebo on any of the four outcomes presented (asthma-related quality of life, peak expiratory flow, use of $\beta_2$-agonists, and missing days). The Level II studies by Lewith et al (2002) and Reilly et al (1994) examined asthma-related outcomes (forced expiratory volume, peak expiratory flow, asthma symptoms and use of other asthma medications) in patients with allergic asthma. The only significant inter-group difference on any outcome was a significant improvement of asthma symptoms according to a visual analogue scale (Reilly et al, 1994), although the p-value was not reported. Passalacqua et al (2006) concluded that "three well-conducted trials showed no or marginal effects in asthmatic patients".

In addition to most of the aforementioned studies (namely Lewith et al, 2002; Matusiewicz, 1995; Matusiewicz et al, 1999; Reilly et al, 1994; White et al, 2003), Bellavite et al (2011) (AMSTAR score 5/10) also included a further two Level II studies (Lara-Marquez et al, 1997; Riveron-Garrote et al, 1998) in their systematic review. The review aimed to evaluate the effectiveness of homeopathy for the treatment of upper airways and ear-nose-throat ailments, respiratory allergies, arthrorheumatic diseases and osteoarthritis. According to Bellavite et al (2011), Riveron-Garrote et al (1998) reported a higher reduction of asthma attacks in the homeopathy group compared to placebo; however it was not clear from the systematic review whether this reduction was clinically or statistically significant. Similarly, it was reported that Lara-Marquez et al (1997) found "significant changes" in laboratory markers in favour of homeopathy; however, the clinical and statistical significance was also not clear and there were only 19 participants in the study.

Linde and Melchart (1998) (AMSTAR score 8/11) conducted a systematic review that examined the efficacy of individualised homeopathy across a number of clinical conditions. They also identified the study of homeopathy for the treatment of allergic asthma by Lara-Marquez et al (1997) which, according to Linde and Melchart (1998), was available as an abstract only. Based on the limited information available, Linde and Melchart (1998) reported that homeopathy was "better than placebo"; however, the outcome used to measure treatment superiority and the magnitude of the difference between treatment groups was not clear.

Cucherat et al (2000) (AMSTAR score 10/11) conducted a broad review that aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". Cucherat et al (2000) included one Level II study in their review (Reilly et al, 1994), which showed a significant difference in favour of homeopathy based on the severity of symptoms measured on a visual analogue scale (p=0.003). The authors provided an overall, generalised conclusion that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Reviewer comments*

*McCarney et al (2008) provided a detailed discussion of the major limitations of the included studies. Importantly, homeopathy was assessed in addition to conventional medications (in some cases for ethical reasons), making it hard to determine whether homeopathy itself provides any benefit.*

*In addition, the interventions varied substantially between the included trials and the evidence reviewer thought that some of the studies examined interventions that were not representative of normal homeopathic treatment strategies. For example, Lewith et al (2002) and Reilly et al (1994) used "one off" treatments, while in White et al (2003) patients were involved in six consultations, extensive telephone contact and as many remedy changes as were deemed appropriate.*

*The evidence reviewer also notes that it was often difficult to determine from the systematic reviews whether the studies examined allergic or non-allergic asthma. As such, only one 'asthma' section has been included in the Overview Report which includes studies that probably examine both allergic and non-allergic asthma.*

*Evidence statement*

Six systematic reviews of poor to good quality identified eight randomised controlled trials (poor to good quality; total of 675 participants, range: 19-242) that compared homeopathy with placebo for the treatment of people with asthma.

The one medium-sized, good-quality trial (242 participants) did not detect a difference between homeopathy and placebo in the treatment of people with asthma. LOC: Low - moderate.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with asthma.

**Table 58 Evidence summary table: the effectiveness of homeopathy for the treatment of asthma**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | White et al (2003)<br>[Level II]<br>Quality not specified<br>N=96 | Children with allergic asthma (mild to moderate) | Individualised homeopathy | Placebo | Quality-of-life questionnaires, symptoms and tests | No changes in quality of life, small not significant improvement of symptoms in homeopathy group | The results of the included studies were combined and classified into one of the following levels of evidence by the systematic reviewers:<br>• Strong positive evidence<br>• Good positive evidence<br>• Unclear or conflicting evidence<br>• Negative scientific evidence<br>The evidence for the effectiveness of homeopathy for the treatment of respiratory allergies was categorised by Bellavite et al (2011) as follows:<br><br>Good positive evidence[d]: Individualised homeopathy in asthma<br><br>Unclear or conflicting evidence[e]: Homeopathic immunotherapy of asthma |
| | Lewith et al (2002)<br>[Level II]<br>Quality not specified<br>N=242 | Allergic asthma | Allergen (dust mite) 30c | Placebo H.I.T. | Symptoms (VAS) and expiration flux (FEV) | No final therapeutic effect, initial aggravation | |
| | Matusiewicz et al (1999)<br>[Level II]<br>Quality not specified<br>N=84 | Patients with allergic asthma | Homeopathic complex Asthma H Inj. Plfugerplex, subcutaneously | Placebo | Use of unspecified 'standard' drugs, laboratory and spirometric tests | Slight decrease of conventional medication and infections; no change in spirometric tests | |
| | Riveron-Garrote et al (1998)<br>[Level II]<br>Quality not specified<br>N=80 | Patients with allergic asthma | Individualised homeopathy | Placebo | General symptoms and attack intensity | Higher reduction of asthma attacks in homeopathy group | |
| | Lara-Marquez et al (1997)<br>[Level II]<br>Quality not | Patients with allergic asthma | Individualised homeopathy | Placebo | Symptoms, spirometry parameters and immunological | Homeopathy better than placebo, significant changes of laboratory markers | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | specified<br>N=19 | | | | markers | | |
| | Matusiewicz (1995)<br>[Level II]<br>Quality not specified<br>N=40 | Patients with allergic asthma | Homeopathic complex Engystol-N | Placebo | Respiratory tests | Clinical improvement only in homeopathy group | |
| | Reilly et al (1994)<br>[Level II]<br>Quality not specified<br>N=28 | Patients with allergic asthma | Unspecified 'standard' drugs + allergen 30C (H.I.T.) | Unspecified 'standard' drugs + placebo | Symptoms (VAS) and respiratory tests | Less symptoms in the homeopathy group than placebo, no differences in tests | |
| McCarney et al (2008)<br>[Level I]<br>AMSTAR: 9/11<br><br>SR of homeopathy for asthma | White et al (2003)<br>[Level II]<br>Jadad score 5[f]<br>N=93 | • Children with allergic asthma diagnosed by GP and prescription for either beta-agonist or corticosteroid inhaler in previous 3 months<br>• aged 5-15 years | Any number of individualised homeopathy prescriptions | Placebo | Days off school (measured as a change from the previous month; increased, no change, or reduced) | No statistically significant differences between the treatment groups | "There is not enough evidence to reliably assess the possible role of homeopathy in asthma. As well as randomised trials, there is a need for observational data to document the different methods of homeopathic prescribing and how patients respond. This will help to establish to what extent people respond to a 'package of care' rather than the homeopathic intervention alone". |
| | | | | | PEF | No significant difference between treatment groups in terms of improvement | |
| | | | | | Asthma-related QoL | No significant difference between treatment and control | |
| | | | | | Use of $\beta_2$-agonists | No significant difference in terms of use of inhaler | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | Global assessment of change | No significant difference between treatment groups | "The currently available evidence is insufficient to assess reliably the possible role of homeopathy in the treatment of asthma. Whilst the scientific rationale behind homeopathy remains unproven, non-specific benefits associated with a 'holistic' package of care may exist".<br><br>"The effect of homeopathy on asthma has yet to be proven in a randomised study. However, the varied quality of the studies precludes us from extrapolating any effects observed to the general population level".<br><br>"No trials reported a significant difference on validated symptoms scales. There were conflicting results in terms of lung function between the studies"<br><br>"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 individualised |
| | | | | | Adverse events | No significant intergroup differences reported | |
| | Lewith et al (2002)<br>[Level II]<br>Jadad score 5[f]<br>N=242 | Patients with mild to severe allergic asthma<br>• positive skin prick test to house dust mite with response greater than aeroallergens tested | Isopathy (30C house dust mite), 3 doses orally in 24 hours | Placebo | Lung function | No significant difference | |
| | | | | | Use of $\beta_2$-agonists | No significant difference in bronchodilator usage after treatment of at 15 week follow-up | |
| | | | | | Subjective symptoms | No adverse events reported | |
| | Matusiewicz et al (1999)<br>[Level II]<br>Jadad score 2[f]<br>N=84 | Patients with chronic bronchial asthma<br>• diagnosis based on history, spirometry, physical examination and medication use<br>• Triamcinolone | 1 ampoule of Asthma H (a complex remedy consisting of 14 homeopathic potencies of D3, D4, D5 and D6) injected subcutaneously at intervals of 5 to 7 days | Placebo | Immune functioning | "Significant effect" reported – unclear whether this was between treatment groups of from baseline to follow-up | |
| | | | | | Global ratings | "Significant effect" reported – unclear whether this was between treatment groups of from baseline to follow-up | |
| | | | | | Number of infections | "Significant effect" reported – unclear whether this was between treatment groups of from baseline to follow-up | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | use for last 5 years | | | FVC | No significant differences (2.7 litres, SD: 0.91 in treatment group; 2.74 litres, SD: 0.7 in the control group) | homeopathic practice)"<br><br>See Table 59 for results of the meta-analysis. |
| | | | | | Medication use | Study reported "inhaled triamcinolone usage with treatment leading to a significant reduction (baseline 4.73mg versus 2.3mg in the treatment group; p<0.01; and 4.38mg versus 4.51mg in the control group; p>0.01. | |
| | | | | | PEF | Significant difference between homeopathy and control in favour of homeopathy (no p-value reported). PEF increased from 200ml to 330ml in the treatment group and decreased from 210ml to 190ml in the placebo group | |
| | Freitas et al (1995)<br>[Level II]<br>Jadad score 4[f]<br>N=69 | Patients with at least 3 bronchospastic episodes with intervals of 3 months or less, or | *Blatta officinalis* C6, 2 globules 3 times per day for 6 months | Placebo | Intensity of asthma attack | No significant difference between treatment groups | |
| | | | | | Frequency of asthma attack | No significant difference between treatment groups | |
| | | | | | Duration of asthma attack | No significant difference between treatment groups | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | continuous wheeze for at least 3 months[g]<br>• aged 1-12 years<br>• approx. 50% males and females | | | | | |
| | Matusiewicz (1995)<br>[Level II]<br>Jadad score 1[f]<br>N=40 | Patients with corticosteroid-dependent bronchial asthma diagnosis confirmed by history and spirometry<br><br>Patients received methylxanthines for mucolysis and tetracycline in case of exacerbations | 1 ampoule Engystol N (a complex remedy consisting of the homeopathic remedies *Vincetoxin* D6/D10/ D30, Sulfur D4/D10) injected subcutaneously at intervals of 5 to 7 days. | Placebo | FEV | There was a "clear difference" between treatment and control. FEV litres improved from 1.7 at baseline to 2.4 after treatment in the homeopathy group; placebo group changed from 1.9 to 1.8 litres, no SDs reported. | |
| | | | | | FVC | There was a "clear difference" between treatment and control (treatment group: +1.3 litres versus control group: 0 litres); no p-values reported | |
| | | | | | Medication use | There was a "clear difference" between treatment and control in terms of oral steroid use (3 mg per day in the treatment group versus 7 mg in the control group). No SD or p-values reported | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Reilly et al (1994)<br>[Level II]<br>Jadad score 4[f]<br>N=28 | Patients with allergic asthma<br>• most with sensitivity to house-dustmite<br>• age > 16 years | Homeopathic preparation of the individual allergens in potency C30 (30 dilution steps 1:100) prepared in a water-alcohol solution and impregnated on lactose/sucrose globules (placebo impregnated with diluent only). Treatment consisted of 3 doses of globules within 24 hours (once). | Placebo | Severity symptoms quantified by a 100 mm VAS | Highly significant difference between treatment groups (p=0.003). Improvement of 7.2mm (SD: 10.6mm) in the treatment group; deterioration by 7.8mm (SD: 10.8mm) in the placebo group. | |
| | | | | | PEF | No significant difference between groups | |
| | | | | | FVC | Significant difference between the medians of the groups (0.36 litres; 95% CI 0.03, 0.73; p-value 0.03) | |
| Altunc et al (2007)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | White et al (2003)<br>[Level II]<br>Jadad score 5[f]<br>N=93 | Children with allergic asthma<br>• 5-15 years old<br>• 54% male<br>• Concomitant treatment: β-Adrenergic inhalers (all patients), inhaled steroids (33H; 36P), sodium cromoglycate (6H; 2P), salbutamol nebules (1H) | Individualised homeopathy, potency not reported, 1 year<br>Various remedies in different potencies (no details reported). | Placebo | Active quality of living subscale of CAQ | No significant difference | "Both RCTs reported no differences compared with placebo on several outcome measures, including the intensity, frequency and duration of asthma attacks".<br><br>"The evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition". |
| | | | | | Adverse events | Main adverse events include exacerbation of eczema (4H, 2P0 and asthma (3 both), headache (3H), fever (1H), sickness (1H), rash (1P), depression and irritability (3P), sleeping difficulties (2P); 1 patients was withdrawn because of adverse events (cough, behaviour and sleeping disorders) | |
| | Freitas et al | Patients with | Standardised | Placebo | Intensity of asthma | No significant difference | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | (1995)<br>[Level II]<br>Jadad score 4[f]<br>N=86 | asthma<br>• 1-12 years old<br>• 51% male<br>• Concomitant treatment: conventional asthma medicines (for prevention or crisis). | homeopathy, material potencies, 6 months. *Blatta orientalis* 6C potency, two globules delivered 3 times daily. | | attack | | |
| | | | | | Frequency of asthma attack | No significant difference | |
| | | | | | Duration of asthma attack | No significant difference | |
| Passalacqua et al (2006)<br>[Level I]<br>AMSTAR: 4/10<br><br>SR of homeopathy for rhinitis and asthma | White et al (2003)<br>[Level II]<br>Jadad score 5[f]<br>N=93 | Children with allergic asthma | Individual homeopathy plus drugs | Placebo plus drugs | Asthma-related QoL | No difference between active group and placebo | Three well-conducted trials found no or marginal effects in asthmatic patients |
| | | | | | PEF | No difference between active group and placebo | |
| | | | | | Use of $\beta_2$-agonists | No difference between active group and placebo | |
| | | | | | Days off school (measured as a change from the previous month; increased, no change, or reduced) | No difference between active group and placebo | |
| | Lewith et al (2002)<br>[Level II]<br>Jadad score 5[f]<br>N=242 | Patients with allergic asthma | Dust mite homeopathy | Placebo | FEV | No difference between active group and placebo | |
| | | | | | PEF | No difference between active group and placebo | |
| | | | | | Asthma symptoms | No difference between active group and placebo | |
| | | | | | Use of $\beta_2$-agonists | No difference between active | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | group and placebo | |
| | | | | | Asthma score | No difference between active group and placebo | |
| | Reilly et al (1994)<br>[Level II]<br>Jadad score 4[f]<br>N=28 | Patients with allergic asthma | 30c dilution of allergens | Placebo | Severity symptoms quantified by a 100 mm VAS | Significant improvement (no p-value) | |
| | | | | | PEF | No change | |
| | | | | | Pulmonary function | No change | |
| | | | | | Histamine challenge | No change | |
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Reilly et al (1994)<br>[Level II]<br>Quality not specified[h]<br>N=28 | Patients with allergic asthma | Individualised homeopathic immunotherapy | Placebo | VAS of overall symptom intensity | Significant difference in favour of homeopathy (p=0.003) | "The strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies. Further high quality studies are needed to confirm these results."<br><br>"It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to asthma) |
| Linde and | Lara-Marquez et | Patients with | Individualised | Placebo | Unclear | "Homeopathy better than | No specific conclusions provided |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | al (1997)<br>[Level II]<br>Quality not assessed[i]<br>N=19 | allergic asthma | simillimum | | | placebo" | regarding the efficacy of homeopathy for allergic asthma were provided.<br><br>The study was not included in the meta-analysis as it was available as an abstract only. |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CAQ, Childhood Asthma Questionnaire; D, decimal; FEV, forced expiratory volume; FVC, forced vital capacity; NR, not reported; PEF, peak expiratory flow; QoL, quality of life; SD, standard deviation; SR, systematic review; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

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

[e] Conflicting evidence from multiple trials or observational studies without a clear majority of the properly conducted trials finding evidence of benefit or ineffectiveness

[f] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

[g] The authors of the systematic review question whether this is truly asthma.

[h] Quality of included studies was not formally assessed by the authors. The authors noted that "the only criterion for quality used for selection was adequate concealment of treatment allocation (by a suitable randomisation method)"

[i] Quality not assessed as the study was available as an abstract only at the time of publication

**Table 59 Pooled results presented in McCarney et al (2008)**

| Outcome | Patient population | Intervention group | Control group | Measure of effect (95% CI) | p-value Heterogeneity[a] |
|---|---|---|---|---|---|
| FEV1<br>(1 Level II study, 2 Level III-2 studies; N=366) | Patients with chronic asthma | Formula homeopathy<br>Mean (SD): NR<br>N=203 | Placebo<br>Mean (SD): NR<br>N=163 | Mean difference: -0.06<br>(-0.17 to 0.04) | Effect size: p=0.24<br>Heterogeneity: p=0.68 ($I^2$=0%) |

Abbreviations: CI, confidence interval; FEV, forced expiratory volume; NR, not reported; SD, standard deviation.

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

### 4.14.4 Bronchitis

The effectiveness of homeopathy for the treatment of patients with bronchitis was assessed in one systematic review (Cucherat et al, 2000; AMSTAR score 10/11) as summarised in Table 60. Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The review included one Level II study (Diefenbach, 1997) that had investigated the effect of the homeopathic treatment, Bronchiselect, in patients with bronchitis. Cucherat et al (2000) reported that in this Level II study, there was no significant difference in the length of productive cough between patients in the homeopathy and placebo groups. The quality of Deifenbach (1997) was not formally assessed; however, a general comment was made in reference to all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Evidence statement*

One systematic review of good quality identified one medium-sized randomised controlled trial (quality not reported; 258 participants) that compared homeopathy (*Bronchiselect*) with placebo for the treatment of people with bronchitis. LOC: Low.

Based on only one study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with bronchitis.

**Table 60 Evidence summary table: the effectiveness of homeopathy for the treatment of bronchitis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Diefenbach (1997)<br>[Level II]<br>Quality not specified<br>N=258[d] | Patients with bronchitis | Bronchiselect | Placebo | Length of productive cough | No significant difference (p=0.86) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective"<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to bronchitis) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] 209 participants evaluated.

### 4.14.5 Cough

The effectiveness of homeopathy for the treatment of cough was assessed in one systematic review (Bellavite et al, 2011) (AMSTAR score 5/10) as summarised in Table 61. The authors conducted a broad review of homeopathy and immunology across a range of clinical areas. One Level II study was identified that assessed the efficacy of homeopathy (*Drosera*) compared to placebo in patients with a cough (Bordes and Dorfman, 1986). Patients were assessed for symptoms, and it was reported that 67% of patients in the homeopathy group and 27% of patients in the placebo group experienced a reduction or disappearance of symptoms after one week. However, the significance of the findings was unknown. The quality of the included study was not formally assessed by Bellavite et al (2011). Bellavite et al (2011) did not provide any overall conclusion regarding the efficacy of homeopathy for the treatment of cough in their systematic review.

*Evidence statement*

One systematic review of poor quality identified one small randomised controlled trial (quality not reported; 60 participants) that compared homeopathy (*Drosera)* with placebo for the treatment of people with a cough. LOC: Very low.

Based on only one small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with a cough.

**Table 61 Evidence summary table: the effectiveness of homeopathy for the treatment of a cough**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Bordes and Dorfman (1986)<br>[Level II]<br>Quality result not reported<br>N=60 | Patients with a cough | Low-dilution (3C) homeopathic complex in syrup (*Drosera*) | Placebo | Number of patients with significant reduction or disappearance of symptoms after one week | Homeopathy group: 20/30 patients (66.67%); Placebo group: 8/30 patients (26.67%). No level of significance reported | Bellavite et al (2011) did not provide an overall conclusion for the efficacy of homeopathy in patients with a cough. |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.14.6 Oral lichen planus

The effectiveness of homeopathy for the treatment of oral lichen planus was assessed in one systematic review (Bellavite et al, 2011; AMSTAR score 5/10) as summarised in Table 62. The authors conducted a broad review of homeopathy and immunology across a range of clinical areas. One Level II study was identified that assessed the efficacy of homeopathy (*Ignatia* 30c) in patients with oral lichen planus (Mousavi et al, 2009). The systematic review did not provide any details regarding the treatment that the comparator arm received, despite stating that Mousavi et al (2009) was a "single blind randomised controlled clinical trial". Mousavi et al (2009) assessed mean pain score and mean lesion size and reported a significant difference in favour of *Ignatia* ($p<0.05$). The quality of the included study was not formally assessed by Bellavite et al (2011). Bellavite et al (2011) did not provide an overall interpretation of the evidence regarding the treatment of oral lichen planus with homeopathy.

*Reviewer comments*

*The comparator was not specified in the systematic review; however, the evidence reviewer obtained a copy of the abstract of Mousavi et al (2009), which revealed that the unspecified comparator was placebo.*

*Evidence statement*

One systematic review of poor quality identified one very small randomised controlled trial (quality not reported; 30 participants) that compared homeopathy (*Ignatia*) with placebo for the treatment of people with oral lichen planus. LOC: Very low.

Based on only one very small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with oral lichen planus.

**Table 62 Evidence summary table: the effectiveness of homeopathy for the treatment of oral lichen planus**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Mousavi et al (2009)<br>[Level II]<br>Quality result not reported<br>N=30 | Patients with oral lichen planus | *Ignatia* 30C | NR | Mean pain score and mean lesion size (not reported separately) | Significant improvement in favour of *Ignatia* after 4 months of treatment; p<0.05 | The authors of the systematic review did not provide a conclusion about the use of *Ignatia* in patients with oral lichen planus |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; NR, not reported; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.14.7 Non-allergic rhinitis

The effectiveness of homeopathy for the treatment of acute and chronic rhinitis was assessed in one systematic review (Bellavite et al, 2011; AMSTAR score 5/10) as summarised in Table 63. Additional systematic reviews were identified that examined homeopathy for the treatment of allergic rhinitis; however, the evidence pertaining to allergic rhinitis/hay fever is presented in the "Allergic rhinitis" evidence summary (see Section 4.14.2).

Bellavite et al (2011) conducted a broad review of homeopathy and immunology across a range of clinical areas. Two Level II studies (Gassinger et al, 1981; Maiwald, 1988) and two Level III-2 studies (Ammerschlager et al, 2005; Schmiedel and Klein, 2006) were identified that assessed the efficacy of homeopathy compared to conventional treatments in patients with chronic or acute rhinitis. No Level II, Level III-1 or Level III-2 studies were identified that compared homeopathy with placebo for the treatment of non-allergic rhinitis. The quality of the included studies was not formally assessed by Bellavite et al (2011).

Gassinger et al (1981) and Maiwald (1988) both compared the efficacy of homeopathic remedies (*Eupatorium perfoliatum* and Gripp-heel, respectively) to aspirin. Both studies reported equivalence between the homeopathic treatments and aspirin in terms of symptom severity score; however, no quantitative results were presented in Bellavite et al (2011).

The Level III-2 study by Schmiedel and Klein (2006) assessed patient-reported improvement within three days in patients that received either "conventional treatment" (antihistamines, antitussives and nonsteroidal anti-inflammatory drugs) or the homeopathic complex Engystol. The systematic review indicated that a higher proportion of patients who received Engystol reported an improvement (77.1%) compared to those treated with conventional therapies (61.7%); however, the significance of the results was not reported in Bellavite et al (2011).

Finally, a large Level III-2 study was performed by Ammerschlager et al (2005) in patients with rhinitis and sinusitis. Patients that received the homeopathic intervention were treated with low-dilution homeopathic *Euphorbium compositum*, and their disease specific symptoms were compared to patients treated with xylometazoline. Bellavite et al (2011) reported that "clinical relevant reductions" were observed in both treatment groups and that the treatments had equivalent efficacy. The results were not reported separately according to rhinitis and sinusitis patient populations in Bellavite et al (2011).

The systematic review by Bellavite et al (2011) concluded that there was "good positive evidence" for the efficacy of *Euphorbium compositum* for the treatment of rhinitis, based on results that reported equivalence with conventional therapy in one Level II study, and non-inferiority to xylometazoline in one Level III-2 study.

*Reviewer comments*

*The evidence reviewer notes that the results of the four included studies should be interpreted with caution, as they all used 'active' comparators and the authors of the systematic review did not comment on the appropriateness of the chosen comparators. In particular, the evidence reviewer questions the use of aspirin for the treatment of rhinitis as there is some evidence that aspirin can cause or exacerbate rhinitis.*

*The evidence reviewer also notes that it was often difficult to determine from the systematic reviews whether the studies examined allergic or non-allergic rhinitis. Where possible, studies that related to allergic rhinitis (where the systematic review explicitly used the word "allergic") have been discussed in Section 4.14.2 and studies that related to non-allergic rhinitis (where none of the systematic reviews explicitly used to word "allergic") have been discussed in Section 4.14.7; however, it is possible that the studies have not always been correctly categorised.*

*Evidence statement*

One systematic review (2011) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy compared with placebo for the treatment of people with non-allergic rhinitis.

One systematic review of poor quality identified two randomised controlled trials (quality not reported; 53 and 170 participants) and two prospectively designed, non-randomised controlled studies (quality not reported; 397 and 739 participants) that compared homeopathy with other therapies (including aspirin and xylometazoline) for the treatment of people with non-allergic rhinitis.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is as effective as the other therapies for the treatment of people with non-allergic rhinitis.

**Table 63 Evidence summary table: the effectiveness of homeopathy for the treatment of non-allergic rhinitis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Maiwald (1988)<br>[Level II]<br>Quality not reported<br>N=170 | Patients with acute rhinitis | Homeopathic complex Gripp-heel | Aspirin | Symptom severity score | Equivalence between homeopathy and aspirin | "Good positive evidence" for *Euphorbium compositum* in rhinitis, based on positive evidence from one Level II study and one Level III-2 study |
| | Gassinger et al (1981)<br>[Level II]<br>Quality not reported<br>N=53 | Patients with acute rhinitis | *Eupatorium perfoliatum* 2x | Aspirin | Symptom severity score | Equivalence between homeopathy and aspirin | |
| | Schmiedel and Klein (2006)<br>[Level III-2]<br>Quality not reported<br>N=397 | Patients with acute rhinitis | Homeopathic complex Engystol | Conventional therapies (antihistamines, antitussives, and nonsteroidal anti-inflammatory drugs) | Patient-reported improvement within 3 days | Significant benefit in homeopathy group ($p<0.05$)<br>• Homeopathy group: 77.1%<br>• Conventional treatment group: 61.7% | |
| | | | | | General and local symptoms | Homeopathic medicine equivalent to the conventional treatment | |
| | Ammerschlager et al (2005)<br>[Level III-2]<br>Quality not reported<br>N=739 | Patients with rhinitis and sinusitis | Low-dilution homeopathic complex formulation *Euphorbium compositum* (nasal spray) | Xylometazoline | Disease specific symptoms | Treatments had equivalent efficacy. Clinically relevant reductions observed in both groups. Non-inferiority of the homeopathic complex was demonstrated. | |
| | | | | | Tolerability | Treatments were equivalent. Good tolerability in both therapies | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.14.8 Sinusitis

The effectiveness of homeopathy for the treatment of patients with rhinosinusitis/chronic sinusitis was assessed in two systematic reviews (Bellavite et al, 2011; Cucherat et al, 2000) as summarised in Table 64 and Table 65. In total, the systematic reviews included three Level II studies (Table 64).

**Table 64 Matrix indicating the studies that were included in the systematic reviews of sinusitis**

| | | Study ID | | |
|---|---|---|---|---|
| | | **Zabolotnyi et al (2007) [Level II]** | **Weiser and Clasen (1994) [Level II]** | **Wiesenauer et al (1989) [Level II]** |
| **Systematic review** | **Bellavite et al (2011) [Level I]** | ✓ | ✓ | ✓ |
| | **Cucherat et al (2000) [Level I]** | | ✓ | |

The systematic review by Bellavite et al (2011) (AMSTAR score 5/10) aimed to evaluate the effectiveness of homeopathy for the treatment of a range of diseases including infections of the upper airways and ear-nose-throat ailments. Three Level II studies of unspecified quality were included for the sinusitis indication. Zabolotnyi et al (2007) tested the effect of a homeopathic complex compared with placebo in patients with maxillary sinusitis. The study found a significant effect of homeopathy over placebo in the improvement of symptoms. Weiser and Clasen (1994) was a double-blind, placebo-controlled Level II study that examined the effect of a homeopathic *Euphorbium composition S* nasal spray in patients with rhinosinusitis/chronic sinusitis, compared to placebo. This Level II study also reported a "significantly greater improvement in the homeopathy group (21.1%) compared to placebo (14.4%)". The third included Level II study by Wiesenauer et al (1989) investigated the effect of a low-dilution homeopathic complex in patients with sinusitis. The study found no effect of homeopathy in a global evaluation and analysis of symptoms. Bellavite et al (2011) did not formulate a specific conclusion on the effectiveness of homeopathy for the treatment of sinusitis, but it noted that there was "good positive evidence for *Euphorbium compositum* in rhinitis-sinusitis" from the one Level II study (Weiser and Clasen, 1994).

Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The systematic review included one Level II study (Weiser and Clasen, 1994) that focused on chronic sinusitis. Cucherat et al (2000) stated that there was a significant difference in cumulative scores in Weiser and Clasen (1994) that favoured homeopathy (p=0.016). The quality of Weiser and Clasen (1994) was not formally assessed; however, a general comment was made in reference to all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Evidence statement*

Two systematic reviews of poor and good quality identified three randomised controlled trials (quality not reported; total of 420 participants, range: 113-155) that compared homeopathy with placebo for the treatment of people with sinusitis.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with sinusitis.

**Table 65 Evidence summary table: the effectiveness of homeopathy for the treatment of sinusitis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Zabolotnyi et al (2007)<br>[Level II]<br>Quality not specified<br>N=113 | Patients with maxillary sinusitis | Homeopathic complex Sinfrontal | Placebo | Symptoms | Significant improvement over placebo (p-value not reported) | Good positive evidence for *Euphorbium compositum* in rhinitis-sinusitis. Positive evidence from one Level II study |
| | Weiser and Clasen (1994)<br>[Level II]<br>Quality not specified<br>N=155 | Patients with chronic sinusitis | *Euphorbium compositum* | Placebo | Overall percentage improvement | Significantly greater improvement in homeopathy group (21.1%) compared to placebo (14.4%) (p=0.016) | |
| | Wiesenauer et al (1989)<br>[Level II]<br>Quality not specified<br>N=152 | Patients with sinusitis | Low-dilution (3x-4x) homeopathic complex *Luffa, Cinnabaris, Kalium bichromicum* | Placebo | Global evaluation and symptoms | No effect over placebo | |
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Weiser and Clasen (1994)<br>[Level II]<br>Quality not specified<br>N=155 | Patients with chronic sinusitis | *Euphorbium compositum S* nasal spray | Placebo | Overall percentage improvement | Significant difference in favour of homeopathy (p=0.016) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective."<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to sinusitis) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.14.9 Upper respiratory tract infection

The effectiveness of homeopathy for the treatment of patients with an URTI was assessed in three systematic reviews as summarised in Table 67. In total, the systematic reviews included four Level II studies and three Level III-2 studies (Table 66).

**Table 66 Matrix indicating the studies that were included in the systematic reviews of upper respiratory tract infection**

| | | Study ID | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Steinsbekk et al (2007) [Level II] | Steinsbekk et al (2005) [Level II] | de Lange et al (1994) [Level II] | Lecoq (1985) [Level II] | Haidvogl et al (2007) [Level III-2] | Rabe et al (2004) [Level III-2] | Riley et al (2001) [Level III-2] |
| Systematic review | Altunc et al (2007) [Level I] | | ✓ | ✓ | | | | |
| | Linde and Melchart (1998) [Level I] | | | ✓ | | | | |
| | Bellavite et al (2011) [Level I/III] | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |

Altunc et al (2007) (AMSTAR score 6/10) performed a systematic review to assess the efficacy of homeopathy in various conditions that commonly affect children and adolescents, including URTIs. Two Level II studies were identified for the treatment of URTI. The authors noted that both Steinsbekk et al (2005) (Jadad score of 5) and de Lange et al (1994) (Jadad score of 3) were double-blind Level II studies that examined the effect of homeopathy compared to placebo in children aged 3 to 4 years with URTI. Neither of the studies reported significant differences compared with placebo for the main outcome measures, which included daily symptom scores. Altunc et al (2007) concluded that "the evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition".

Linde and Melchart (1998) (AMSTAR score 8/11) aimed to give an overview of the methods and results of the available Level II studies of individualised homeopathy for a range of clinical conditions. It included only de Lange et al (1994) (Jadad score 5) for the URTI indication (Steinsbekk et al (2005) was published after the time of the systematic review). Linde and Melchart (1998) reported that de Lange et al (1994) found "trends in favour of homeopathy" but no statistically significant differences between homeopathy and placebo in the number of patients assessed globally as improved (RR 1.08; 95% CI 0.81, 1.42). Overall, Linde and Melchart (1998) concluded that, across all clinical conditions, any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

The systematic review by Bellavite et al (2011) (AMSTAR score 5/10) aimed to evaluate the effectiveness of homeopathy for the treatment of a range of diseases including common upper respiratory tract infections. Three Level II (de Lange et al, 1994; Lecoq, 1985; Steinsbekk et al, 2007) and three Level III-2 studies (Haidvogl et al, 2007; Oberbaum et al, 2001; Rabe et al, 2004) were included in the review for URTIs; however, the quality of the studies was not formally assessed by the authors of the systematic review. Steinsbekk et al (2007) tested the effect of individualised homeopathy compared with parents-selected medicines in children with URTI. The study reported no significant difference in the prevention of new symptoms and symptom scores between the two methods of prescription. Similar to the systematic review by Altunc et al (2007), Bellavite et al (2011) also reported no significant difference between the homeopathy and placebo groups (based on the mean number of infective episodes) in de Lange et al (1994). However, it was noted that the percentage of children who did not require antibiotics was higher in the homeopathy group (62%) compared to placebo (49%). The third included Level II study (Lecoq, 1985) investigated the effect of a homeopathic complex in patients with URTI compared with placebo. Whilst the statistical significance of the results was not reported, Bellavite et al (2011) noted that "patients rated more relief in verum group".

Amongst the three Level III-2 studies, both Haidvogl et al (2007) and Rabe et al (2004) assessed the effect of homeopathy compared with various conventional therapies (including anti-inflammatory drugs and antibiotics) in patients with URTI. In Haidvogl et al (2007), it was reported that homeopathic treatment was not inferior to standard treatments (e.g. anti-inflammatory drugs and antibiotics) and was best tolerated. Rabe et al (2004) reported equivalence between homeopathy and anti-inflammatory agents. The third included Level III-2 study (Riley et al, 2001) tested the effect of individualised homeopathy compared with conventional therapies in patients with respiratory tract complaints or ear complaints. Thus, the evidence reviewer notes that the patient population may not be exclusive to those with an URTI. The significance of the results was not specified, but healing or major improvement after 14 days of treatment was observed in 82.6% of patients in the homeopathy group and 68% in the conventional treatment group. The rate of adverse events was 7.8% in the homeopathy group and 22.3% in the conventional treatment group. Overall, Bellavite et al (2011) concluded that "the evidence for individualised homeopathy for upper respiratory tract infections is defined as conflicting, but if we exclude from consideration the trials of de Lange and coworkers (trend to positive effect, but not statistically significant) and of Steinsbekk (where the self-treatment was investigated), a "good" positive evidence in favour of homeopathy can be suggested in these conditions".

*Reviewer comments*

*The evidence reviewer notes that the systematic reviews provided contradicting reports of the results of de Lange et al (1994). Nevertheless, none of the reviews stated an effect of homeopathy in the treatment of URTI in this Level II study. It is also of interest to note that Altunc et al (2007) rated de Lange et al (1994) a Jadad quality score of 3, in comparison to Linde and Melchart (1998), who gave a Jadad quality score of 5 (good quality).*

*Evidence statement*

Three systematic reviews of poor to medium quality identified three randomised controlled trials (unreported or medium to good quality; total of 486 participants, range: 60-251) that compared homeopathy with placebo for the treatment of people with upper respiratory tract infections.

The one medium-sized, good-quality trial (251 participants) did not detect a difference between homeopathy and placebo in the treatment of children with upper respiratory tract infection. LOC: Low - moderate.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with upper respiratory tract infection.

One systematic review of poor quality identified one medium-sized randomised controlled trial (quality not reported; 208 participants) and three prospectively designed, non-randomised controlled studies (quality not reported; total of 2498 participants, range: 456-1557) that compared homeopathy with other therapies (including anti-inflammatory drugs and antibiotics) for the treatment of people with upper respiratory tract infections.

These studies are of insufficient quality to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is as effective as the other therapies for the treatment of people with upper respiratory tract infection.

**Table 67 Evidence summary table: the effectiveness of homeopathy for the treatment of upper respiratory tract infection**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Altunc et al (2007)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Steinsbekk et al, (2005)<br>[Level II]<br>Jadad score 5[d]<br>N=251 | Children with URTI<br>• Mean age 3.6 years<br>• 41% male<br>• Concomitant treatment: antibiotics, painkiller/ antipyretic drugs if needed | *Calcarea carbonica, Pulsatilla,* sulfur in C30 potency; 2 pills 2 days per week for 12 weeks. In addition, 1 pill up to once every hour if the child had an acute episode of URTI but reduce the intake if the URTI was mild or when there was an improvement | Placebo | Total daily symptom score | No significant difference | "The evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition" |
| | | | | | Adverse events | "Mild and transient" adverse events in 4 placebo and 9 homeopathy patients | |
| | de Lange et al (1994)<br>[Level II]<br>Jadad score 3[d]<br>N=170 | Children with recurrent URTI<br>• Mean age 4.2 years<br>• 56% male<br>• Concomitant treatment: adequate nutrition advice, antibiotics, adenoidectomy, tonsillectomy if needed | Individualised homeopathy. Remedies in various potencies, mainly D6, D30 and D200 (remedies not reported) for 1 year. Homeopathic medicines and follow up prescriptions were based on the clinical course | Placebo | Daily symptom scores | No significant difference | |
| | | | | | Number of antibiotic treatment courses | No significant difference | |
| | | | | | Adenoidectomies and tonsillectomies after 1 year follow up | No significant difference | |
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11 | de Lange et al (1994)<br>[Level II]<br>Jadad score 5[d]<br>N=175 | Patients with recurrent upper respiratory tract infection<br>• Median age: 4.2 years<br>• 53% male | Constitutional and acute individual simillimum as necessary (changes possible, dosage and potency variable) | Placebo | Number of patients assessed globally as improved | RR 1.08 (95% CI 0.81,1.42)<br>"Trends in favour of homeopathy"<br>• Intervention group: 48/88 (55%)<br>• Control group: 44/87 (51%) | A meta-analysis found an overall trend in favour of homeopathy. The rate ratio was 1.62 (95% CI 1.17, 2.23) and the odds ratio was 2.62. |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| SR of homeopathy for multiple conditions | | | | | Difference in daily symptom score | RR 0.41 (95% CI 0.02, 0.83)<br>"Trends in favour of homeopathy" | The pooled rate ratio of the methodologically best studies was clearly smaller and not statistically significant (RR 1.12; 95% CI 0.87, 1.44)<br><br>(Note: Results of meta-analysis refer to all clinical conditions and are not specific to upper respiratory tract infections) |
| Bellavite et al (2011)<br>[Level I/III]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Steinsbekk et al (2007)<br>[Level II]<br>Quality not specified<br>N=208 | Children with upper respiratory tract infections | Individualised homeopathy | Parents-selected medicines | Total daily symptom score | No difference between groups | "The evidence for individualized homeopathy for upper respiratory tract infections is defined as conflicting, but if we exclude from consideration the trials of de Lange and coworkers (trend to positive effect, but not statistically significant) and of Steinsbekk (where the self-treatment was investigated), a "good" positive evidence in favour of homeopathy can be suggested in these conditions" |
| | | | | | Prevention of new episodes | No difference between the two methods of prescription | |
| | de Lange et al (1994)<br>[Level II]<br>Quality not specified<br>N=170 | Children with pharyngitis or tonsillitis | Individualised homeopathy | Placebo | Mean number of infective episodes | No significant inter-group differences:<br>• Homeopathy group: 7.9/year<br>• Placebo group: 8.4/year | |
| | | | | | Percentage of children not requiring antibiotics | Significance of results not reported<br>• Homeopathy group: 62%<br>• Placebo group: 49% | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Lecoq (1985)<br>[Level II]<br>Quality not specified<br>N=60 | Patients with upper respiratory tract infections | Homeopathic complex L52 | Placebo | Symptom severity score | Patients rated more relief in homeopathy group | |
| | Haidvogl et al (2007)<br>[Level III-2]<br>Quality not specified<br>N=1557 | Patients with upper respiratory tract infections | Homeopathic strategy | Standard treatments (e.g. anti-inflammatory drugs, antibiotics) | Healing or major improvement after 14 days of treatment | Homeopathic treatment not inferior to standard treatments and best tolerated | |
| | Rabe et al (2004)<br>[Level III-2]<br>Quality not specified<br>N=485 | Patients with mild upper respiratory tract infections | Homeopathic complex Gripp-heel | Anti-inflammatory agents | Symptoms | Equivalence between homeopathy and anti-inflammatory agents | |
| | Riley et al (2001)<br>[Level III-2]<br>Quality not specified<br>N=456 | Patients with respiratory tract complaints or ear complaints | Individualised homeopathy | Conventional medicine | Healing or major improvement after 14 days of treatment | Significance of results not reported<br>• Homeopathy group: 82.6%<br>• Conventional medicine group: 68% | |
| | | | | | Rate of adverse events | Significance of results not reported<br>• Homeopathy group: 7.8%<br>• Conventional medicine group: 22.3% | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CI, confidence interval; D, decimal; RR, relative risk; SR, systematic review; URTI, upper respiratory tract infection.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

## 4.15 Skin and subcutaneous tissue disorders

### 4.15.1 Acne vulgaris

The effectiveness of homeopathy for the treatment of patients with acne vulgaris was assessed in one Level I systematic review (Linde and Melchart, 1998; AMSTAR score 8/11) as summarised in Table 68. The authors conducted a broad review of the efficacy of individualised homeopathy across a range of clinical areas. One Level II study was identified that assessed the efficacy of individualised homeopathic simillimum compared to placebo for the treatment of acne vulgaris (McDavid, 1994). McDavid (1994) measured efficacy using a patient-reported global assessment. A higher proportion of patients treated with placebo reported global improvements (73%) compared to the homeopathy group (60%), although the trend was not significant. Linde and Melchart (1998) stated that the trial seemed to be of "acceptable quality" (Jadad score 2; internal validity score 3); however, McDavid (1994) provided an "insufficient report" of the trial.

*Evidence statement*

One systematic review of medium quality identified one very small randomised controlled trial (poor quality; 30 participants) that compared homeopathy (*Simillimum*) with placebo for the treatment of people with acne vulgaris. LOC: Very low.

Based on only one very small poor quality study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with acne vulgaris.

**Table 68 Evidence summary table: the effectiveness of homeopathy for the treatment of acne vulgaris**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | McDavid (1994)<br>[Level II]<br>Quality: 2,3[d]<br>N=30 | Patients with acne vulgaris | Individualised simillimum | Placebo | Number of patients with improvement in global assessment (patient-reported) | No significant difference between treatment groups.<br>Intervention group: 9/15 (60%);<br>Control group: 11/15 (73%).<br>Rate ratio (95% CI): 0.82 (0.49, 1.37) | "Insufficient report"<br><br>"Trial seems to be of acceptable quality" |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CI, confidence interval; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality assessed using (i) Jadad score (out of 5); (ii) internal validity score (out of 6).

### 4.15.2 Boils and pyoderma

The effectiveness of homeopathy for the treatment of patients with boils and pyoderma was assessed in one systematic review (Cucherat et al, 2000; AMSTAR score 10/11) as summarised in Table 69. Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The review included one Level II study (Mossinger, 1980) that had investigated the effect of homeopathic *Hepar sulfuris calcareum* D4 compared to placebo in patients with boils and pyoderma. The systematic review found no significant difference (p=0.318) in healing time between the homeopathy and placebo groups. The quality of Mossinger (1980) was not formally assessed by Cucherat et al (2000); however, a general comment was made about all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Evidence statement*

One systematic review of good quality identified one very small randomised controlled trial (quality not reported; 46 participants) that compared homeopathy (*Hepar sulfuris calcareum*) with placebo for the treatment of people with boils and pyoderma. LOC: Very low.

Based on only one very small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with boils and pyoderma.

**Table 69 Evidence summary table: the effectiveness of homeopathy for the treatment of boils and pyoderma**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Cucherat (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Mossinger (1980)<br>[Level II]<br>Quality not specified<br>N=46[d] | Patients with boils and pyoderma | *Hepar sulfuris calcareum* D4 | Placebo | Healing time | No significant difference (p=0.318) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective"<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to boils and pyoderma) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; D, decimal; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] N equals the number of participants evaluated. The number of participants randomised was not reported.

### 4.15.3 Bruising

The effectiveness of homeopathy for the treatment of patients with bruising was assessed in one systematic review (Ernst and Pittler, 1998; AMSTAR score 6/10) as summarised in Table 70. Ernst and Pittler (1998) aimed to review the clinical efficacy of homeopathic *Arnica* in a range of clinical areas, and identified two Level III-2 studies that had examined the effect of this treatment in healthy volunteers with experimentally inflicted mechanical bruising (Campbell, 1976; Savage and Roe, 1978). Both of these trials were very small and rated as low quality by the systematic reviewers. Ernst and Pittler (1998) reported that in both studies "results numerically favoured *Arnica*" over placebo with regards to the extent of bruising and the subjective symptoms outcomes. However, their overall conclusion across the various clinical conditions they assessed was that "the hypothesis claiming that homeopathic *Arnica* is clinically effective beyond a placebo effect is not based on methodologically sound placebo-controlled trials".

*Evidence statement*

One systematic review of medium quality identified two prospectively designed, non-randomised controlled studies (poor quality; 10 and 13 participants) that compared homeopathy (*Arnica*) with placebo for the treatment of people with bruising.

These studies are of insufficient quality and size to warrant further consideration of their findings. LOC: Very low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with bruising.

**Table 70 Evidence summary table: the effectiveness of homeopathy for the treatment of bruising**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Ernst and Pittler (1998)<br>[Level I/III]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Savage and Roe (1978)<br>[Level III-2]<br>Jadad score 2[d]<br>N=10 | Healthy volunteers for the treatment of experimentally inflicted mechanical bruising | *Arnica* 30C, one tablet before being bruised and 2 after, on the same day, and 2 more tablets on the next day | Placebo | Extent of bruising | Results numerically favoured *Arnica* | "The claim that homeopathic *Arnica* is efficacious beyond a placebo effect is not supported by rigorous clinical trials"<br><br>"The hypothesis claiming that homeopathic *Arnica* is clinically effective beyond a placebo effect is not based on methodologically sound placebo-controlled trials".<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to bruising) |
| | | | | | Subjective symptoms | Results numerically favoured *Arnica* | |
| | Campbell (1976)<br>[Level III-2]<br>Jadad score 1[d]<br>N=13 | Healthy volunteers for the treatment of experimentally inflicted mechanical bruising | *Arnica* 10M, one tablet before being bruised and 2 after, on the same day, and 2 more tablets on the next day | Placebo | Extent of bruising | Results numerically favoured *Arnica* | |
| | | | | | Subjective symptoms | Results numerically favoured *Arnica* | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; M, the number 1000 in Latin; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.15.4 Second and third degree burns

The effectiveness of homeopathy for the treatment of patients with second and third degree burns was assessed in one systematic review (Cucherat et al, 2000) (AMSTAR score 10/11) as summarised in Table 71. Cucherat et al (2000) (AMSTAR score 10/11) aimed to answer the question of "whether there is any evidence from randomised controlled trials that homeopathy is efficacious for the treatment of disease in humans". The review did not identify any Level II, Level III-1 or Level III-2 studies that compared homeopathy to placebo; however it included one Level II study (Lievre, 1992) that investigated the effect of homeopathic *Calendula* compared with Vaseline in patients with second and third degree burns. The quality of Lievre (1992) was not formally assessed by Cucherat et al (2000); however, a general comment was made about all of the included studies that "the strength of this evidence is low because of the low methodological quality of the trials". The authors of the trial reported no significant difference between homeopathic *Calendula* and Vaseline in the composite criteria of treatment success outcome (p=0.147). Overall, the authors concluded that "it is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective".

*Evidence statement*

One systematic review (2000) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy compared with placebo for the treatment of people with second and third degree burns.

One systematic review of good quality identified one small randomised controlled trial (quality not reported; 103 participants) that compared homeopathy (*Calendula*) with Vaseline for the treatment of people with second and third degree burns. LOC: Very low.

Based on only one small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to Vaseline for the treatment of people with second and third degree burns.

**Table 71 Evidence summary table: the effectiveness of homeopathy for the treatment of second and third degree burns**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Cucherat et al (2000)<br>[Level I]<br>AMSTAR: 10/11<br><br>SR of homeopathy for multiple conditions | Lievre (1992)<br>[Level II]<br>Quality not specified<br>N=103 | Patients with second and third degree burns | *Calendula* | Vaseline | Composite criteria of treatment success | No significant difference (p=0.147) | "It is clear that the strength of available evidence is insufficient to conclude that homeopathy is clinically effective"<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to second and third degree burns) |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.15.5 Eczema

The effectiveness of homeopathy for the treatment of patients with eczema was assessed in two Level I/III systematic reviews as summarised in Table 73. Both systematic reviews included one Level II study (Siebenwirth et al, 2009) and two Level III-2 studies (Keil et al, 2008; Witt et al, 2009) (Table 72). Neither of the systematic reviews performed a meta-analysis of the data.

**Table 72 Matrix indicating the studies that were included in the systematic reviews of eczema**

| | | Study ID | | |
|---|---|---|---|---|
| | | **Siebenwirth et al (2009) [Level II]** | **Witt et al (2009) [Level III-2]** | **Keil et al (2008) [Level III-2]** |
| **Systematic review** | **Ernst (2012) [Level I/III]** | ✓ | ✓ | ✓ |
| | **Simonart et al (2011) [Level I/III]** | ✓ | ✓ | ✓ |

Ernst (2012) (AMSTAR score 6/10) performed a systematic review of evidence from controlled clinical trials of any type of homeopathic treatment for any type of eczema. The one Level II study that was identified (Siebenwirth et al, 2009; Jadad score 3) examined the effect of individualised homeopathic treatment in patients with atopic eczema. Ernst (2012) reported that it found a non-significant trend that favoured placebo over homeopathy. Two Level III-2 studies each with a Jadad score of 1 were also included. Both Witt et al (2009) and Keil et al (2008) examined the effect of treatment by homeopaths in children with eczema compared with conventional treatment (including corticosteroids and antihistamines). The study found no significant difference between homeopathy and conventional treatment in either symptom scores or quality of life in both trials. Ernst (2012) concluded that "the available data do not demonstrate homeopathic remedies to be efficacious as a treatment of eczema".

Simonart et al (2011) (AMSTAR score 8/10) conducted a systematic review of evidence for the efficacy of homeopathic treatments in dermatology. A number of different dermatological conditions were examined, including atopic dermatitis (a form of eczema), which included the same three studies as Ernst (2012). Simonart et al (2011) reported no significant difference between homeopathy and the comparator (which was placebo in one of the trials and unspecified 'conventional therapy' in the other two trials) for any of the outcomes examined in Siebenwirth et al (2009), Witt et al (2009) or Keil et al (2008). The only exception was in Keil et al (2008), where a significant difference ($p<0.001$) was reported for the extent of improvement of signs/symptoms of eczema as assessed by the physician. However, it is unclear if this difference favoured homeopathy or the other therapy (the other therapy was not specified in Simonart et al, 2011). Simonart et al (2011) also noted some of the limitations of the included trials. Siebenwirth et al (2009) had a high percentage of ineligible patients and a high proportion of dropouts. The patient population in both Keil et al (2008) and Witt et al (2009) were recruited at the homeopathic or conventional doctor's practices, which presents a bias as the patients had already made their own choice of preferred therapeutic approach. Further, the use of conventional therapies was allowed in the homeopathic group in Witt et al (2009), which would make it difficult to ascertain any effect of homeopathic treatment. Simonart et al (2011) concluded that "the hypothesis that any dermatological condition

responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".

*Evidence statement*

Two systematic reviews of medium quality identified one very small randomised controlled trial (medium quality; 24 participants) that compared homeopathy with placebo for the treatment of people with eczema. LOC: Very low.

Based on only one very small study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with eczema.

Two systematic reviews of medium quality identified two prospectively designed, non-randomised controlled studies (poor quality; 118 and 135 participants) that compared homeopathy with other therapies (corticosteroids, antihistamines and other unspecified therapies) for the treatment of people with eczema.

These studies are of insufficient quality and power to warrant further consideration of their findings. LOC: Very low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is as effective as the other therapies for the treatment of people with eczema.

**Table 73 Evidence summary table: the effectiveness of homeopathy for the treatment of eczema**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Ernst (2012)<br>[Level I/III]<br>AMSTAR: 6/10<br><br>SR of homeopathy for eczema | Siebenwirth et al (2009)<br>[Level II]<br>Jadad score 3[d]<br>N=24 | Patients with atopic eczema | Individualised homeopathic treatment for 32 weeks | Placebo | Not reported | A non-significant trend favoured placebo over homeopathy | "The available data do not demonstrate homeopathic remedies to be efficacious as a treatment of eczema" |
| | Witt et al (2009)<br>[Level III-2]<br>Jadad score 1[d]<br>N=135 | Children with atopic eczema | Treatment by homeopaths (not specified) | Conventional treatment | Symptom scores | No significant difference | |
| | | | | | Quality of life | No significant difference | |
| | Keil et al (2008)<br>[Level III-2]<br>Jadad score 1[d]<br>N=118 | Children with eczema | Treatment by homeopaths (not specified) | Conventional treatment | Symptom scores | No significant difference | |
| | | | | | Quality of life | No significant difference | |
| Simonart et al (2011)<br>[Level I/III]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Siebenwirth et al (2009)<br>[Level II]<br>Quality not specified<br>N=24 | Young adults aged 18-35 years with atopic dermatitis | Individually selected homeopathic remedies for 32 weeks | Placebo | MP score | No significant difference | "The hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to eczema) |
| | | | | | Quality of life | No significant difference | |
| | | | | | Coping and global assessments of treatment success | No significant difference | |
| | Witt et al (2009)<br>[Level III-2]<br>Quality not specified<br>N=135 | Children aged 1-14 years with atopic dermatitis | Individually selected homeopathic remedies for 12 months | Conventional therapy | SCORAD | No significant difference | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | Keil et al (2008)<br>[Level III-2]<br>Quality not specified<br>N=118 | Children less than 17 years of age with atopic dermatitis | Individually selected homeopathic remedies for 12 months | Conventional therapy | Extent of improvement of signs/symptoms of eczema as assessed by the patients or their parents on a 0-10 numerical scale | No significant difference | |
| | | | | | Extent of improvement of signs/symptoms of eczema as assessed by the physician on a 0-10 numerical scale | Significant difference ($p<0.001$)<br>• Intervention group: 1.8-4.5<br>• Comparator group: 2.6-3.6 | |
| | | | | | Quality of life | No significant difference | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; MP score, Costa and Saurat's multiparameter atopic dermatitis score; SCORAD, Scoring Atopic Dermatitis; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

### 4.15.6 Seborrhoeic dermatitis

The effectiveness of homeopathy for the treatment of patients with seborrhoeic dermatitis was assessed in one systematic review (Simonart et al, 2011; AMSTAR score 8/10) as summarised in Table 74. This systematic review aimed to assess the evidence for the efficacy of homeopathic treatments in dermatological conditions. For the seborrhoeic dermatitis indication, one relevant Level II study of unspecified quality was identified. Smith et al (2002) investigated the effect of a homeopathic combination product in adults with seborrhoeic dermatitis. The study reported a significant difference that favoured homeopathy in the percentage improvement in Seborrhoea Area and Severity Index (SASI) compared with placebo (p=0.03). However, Simonart et al (2011) noted that "this trial methodology reveals some serious shortcomings. A high withdrawal rate and the non-inclusion of data from the withdrawal group are factors that combine to suggest that the results may not be as robust as first indicated. The brief discussion section of the report does not include any mention of possible errors or weaknesses". The systematic review concluded that "the hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".

*Evidence statement*

One systematic review of medium quality identified one very small randomised controlled trial (quality not reported; 41 participants) that compared homeopathy with placebo for the treatment of people with seborrhoeic dermatitis. LOC: Very low.

Based on only one very small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with seborrhoeic dermatitis.

**Table 74 Evidence summary table: the effectiveness of homeopathy for the treatment of seborrhoeic dermatitis**

| Study<br>Level of evidence[a]<br>Quality[b] | Included studies<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcomes | Results | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Simonart et al, 2011<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Smith et al, 2002<br>[Level II]<br>Quality not specified<br>N=41 | Patients aged 20-77 years with typical seborrhoeic dermatitis or dandruff | Homeopathic mineral therapy (potassium bromide 1X, sodium bromide 2X, nickel sulphate 3X, sodium chloride 6X) for 10 weeks | Placebo | SASI improvement | Significant difference in favour of homeopathy (p=0.03)<br>• SASI improvement 38±42% in homeopathy group and -10±66% in placebo group | "The hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to seborrhoeic dermatitis) |

Abbreviations: NR, not reported; SASI; Seborrhoea Area and Severity Index; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer according to the AMSTAR criteria.

[c] Study quality as reported in the systematic review.

### 4.15.7 Ulcers

The effectiveness of homeopathy for the treatment of patients with ulcers was assessed in two systematic reviews as summarised in Table 76. In total, the systematic reviews included one Level II study and one Level III-2 study (Table 75). Neither of the systematic reviews specified the quality of the included studies.

**Table 75 Matrix indicating the studies that were included in the systematic reviews of ulcers**

| | | Study ID | |
|---|---|---|---|
| | | **Mousavi et al (2009) [Level II]** | **Garrett et al (1997) [Level III-2]** |
| **Systematic review** | **Bellavite et al (2011) [Level I]** | ✓ | |
| | **Simonart et al (2011) [Level I/III]** | ✓ | ✓ |

The systematic review by Bellavite et al (2011) (AMSTAR score 5/10) aimed to evaluate the effectiveness of homeopathy for the treatment of a range of diseases including infections of the upper airways and ear-nose-throat ailments. One Level II study was identified for aphthous ulcers. Mousavi et al (2009) was a single-(patient) blind Level II study that investigated the efficacy of individualised homeopathy in the treatment of patients with minor recurrent aphthous ulceration for 6 days. The study found that pain intensity and ulcer size were significantly lower in the homeopathy group compared with placebo at day 4 and day 6 of treatment ($p<0.05$). Bellavite et al (2011) did not formulate an overall conclusion on the effectiveness of homeopathy for the treatment of ulcers.

Simonart et al (2011) (AMSTAR score 8/10) aimed to assess the evidence for the efficacy of homeopathic treatments in dermatology. For the ulcers indication, two relevant Level II studies of unspecified quality were identified. Consistent with Bellavite et al (2011), Simonart et al (2011) also reported a significant effect of homeopathy in the Level II study by Mousavi et al (2009). However, Simonart et al (2011) noted that "the open-label design is the major limitation of this study", which may have subjected the results to bias. Garrett et al (1997) was a small, Level III-2 study that investigated the effect of homeopathy in patients with leg ulcers. Of importance, each patient had conventional local or systemic therapy continued during the trial period. The study reported no significant difference in improvement in ulcer size between the homeopathy and placebo groups. Simonart et al (2011) noted that poor randomisation, small sample size, inadequate statistical methodology and the absence of blinding were the major limitations of this study. Overall, Simonart et al (2011) concluded that "the hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".

*Evidence statement*

Two systematic reviews of poor and medium quality identified one small randomised controlled trial (quality not reported; 100 participants) and one very small prospectively designed, non-randomised controlled study (quality not reported; 23 participants) that compared homeopathy with placebo for the treatment of people with ulcers.

These studies are of insufficient quality and size to warrant further consideration of their findings. LOC: Very low - low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with ulcers.

**Table 76 Evidence summary table: the effectiveness of homeopathy for the treatment of ulcers**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Mousavi et al (2009)<br>[Level II]<br>Quality not specified<br>N=100 | Patients with minor aphthous ulcer | Individualised homeopathy | Placebo | Improvement in ulcer size and mean pain score | Significant improvement in the homeopathy group at day 4 and day 6 of treatment ($p<0.05$) | No final conclusions were drawn |
| Simonart et al (2011)<br>[Level I/III]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Mousavi et al (2009)<br>[Level II]<br>Quality not specified<br>N=100 | Patients aged 18-65 years with 1-5 aphthous ulcers of <24 hours duration | Individually selected homeopathic remedies (two doses) for 6 days | Placebo | Improvement in ulcer size | Significant difference in favour of homeopathy ($p<0.05$)<br>• Proportion of responders: 96% in homeopathy group and 72% in placebo | "The hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence"<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to ulcers) |
| | | | | | Mean pain score | Significant difference in favour of homeopathy (lower pain intensity) ($p<0.05$) | |
| | Garrett et al (1997)<br>[Level III-2]<br>Quality not specified<br>N=23 | Patients aged 53-87 years with leg ulcers | Sulphur, silica and carbo-vegetabilis 6 cH for a mean duration of 4.2 weeks | Placebo | Improvement in ulcer size | No significant difference | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; cH, Hahnemannian centesimal scale; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.15.8 Uraemic pruritis

The effectiveness of homeopathy for the treatment of patients with uraemic pruritis was assessed in one systematic review (Simonart et al, 2011; AMSTAR score 8/10) as summarised in Table 77. This systematic review aimed to assess the evidence for the efficacy of homeopathic treatments in dermatology. For the uraemic pruritis indication, one relevant Level II study of unspecified quality was identified. Cavalcanti et al (2003) investigated the effect of individually selected homeopathic remedies in patients with uraemic pruritis, compared with placebo. The study reported no significant difference between the homeopathy and placebo groups with reference to the percentage of maximum pruritis score before and during treatment, the percentage of pruritis reduction as evaluated by the homeopathic physician, dermatologist or patient, or the percentage of responders (i.e. those with a reduction in pruritis score of greater than 50%) at the end of the follow-up period (60 days). There was a significant difference, however, in the percentage of responders at 30 days that favoured homeopathy (p=0.038). Simonart et al (2011) noted that randomisation resulted in significant differences between the two groups; the placebo patients were significantly older and had a higher dialysis dose than patients in the homeopathy group. Whether the difference in rate of responders is a truly significant result thus remains uncertain. The systematic review concluded that "the hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".

*Evidence statement*

One systematic review of medium quality identified one very small randomised controlled trial (quality not reported; 28 participants) that compared homeopathy with placebo for the treatment of people with uraemic pruritis. LOC: Very low.

Based on only one very small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with uraemic pruritis.

**Table 77 Evidence summary table: the effectiveness of homeopathy for the treatment of uraemic pruritis**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Simonart et al (2011)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Cavalcanti et al (2003)<br>[Level II]<br>Quality not specified<br>N=28 | Patients with uraemic pruritis | Individually selected homeopathic remedies for 2 months | Placebo | Percentage of maximum pruritis score before and during treatment | No significant difference | "The hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence"<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to uraemic pruritis) |
| | | | | | Percentage of responders (>50% reduction in pruritis score) | Significant difference in favour of homeopathy (p=0.038)<br>• 0% responders in placebo group, 45% responders in homeopathy group after 30 days | |
| | | | | | | No significant difference (p=0.370)<br>• 7/11 responders in homeopathy group<br>• 3/9 responders in placebo group | |
| | | | | | Pruritus score | No significant difference (p=0.260)<br>• 38 ± 33 in homeopathy group<br>• 57 ± 39 in placebo group | |
| | | | | | Percentage of pruritis reduction as evaluated by the homeopathic physician, dermatologist and patients | No significant difference | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; SR, systematic review; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

### 4.15.9 Warts

The effectiveness of homeopathy for the treatment of patients with warts was assessed in four systematic reviews as summarised in Table 79. In total, the systematic reviews included two Level II studies (Kainz et al, 1996; Labrecque et al, 1992) and one Level III-2 study (Villeda et al, 2001) (Table 78). One systematic review (Linde and Melchart, 1998) performed a meta-analysis of the data; however it included a variety of clinical conditions and was not specific to warts.

**Table 78 Matrix indicating the studies that were included in the systematic reviews of warts**

| | | Study ID | | |
|---|---|---|---|---|
| | | **Kainz et al (1996) [Level II]** | **Labrecque et al (1992) [Level II]** | **Villeda et al (2001) [Level III-2]** |
| **Systematic review** | **Loo and Tang (2009) [Level I]** | ✓ | ✓ | |
| | **Altunc et al (2007) [Level I]** | ✓ | | |
| | **Linde and Melchart (1998) [Level I]** | ✓ | | |
| | **Simonart and de Maertelaer (2012) [Level I/III]** | ✓ | ✓ | ✓ |

Loo and Tang (2009) (AMSTAR score 6/10) performed a systematic review of the effects of treatments for non-genital warts. For homeopathy as a treatment, it included the results of two poor quality Level II studies (Kainz et al, 1996; Labrecque et al, 1992). In both studies, there was no significant difference in the proportion of participants with wart clearance between the homeopathy and placebo groups. In Labrecque et al (1992), there was also no significant difference in adverse effects experienced by participants in the homeopathy and placebo groups. As a result, Loo and Tang (2009) concluded that "we don't know whether homeopathy increases cure rates compared with placebo, as few high-quality studies have been found" and "we don't know whether homeopathy is more effective at increasing the proportion of people with wart clearance after 8-18 weeks".

Altunc et al (2007) (AMSTAR score 6/10) performed a systematic review to assess the efficacy of homeopathy in various conditions that commonly affect children and adolescents, including warts. One Level II study given a Jadad score of 4 (Kainz et al, 1996) was identified for the treatment of warts. The systematic review noted that this Level II study "failed to demonstrate the effectiveness of individualised homeopathic treatment for reducing the size of warts". It concluded that "the evidence from rigorous clinical trials of any type of therapeutic or preventive intervention testing homeopathy for childhood and adolescence ailments is not convincing enough for recommendations in any condition".

Linde and Melchart (1998) (AMSTAR score 8/11) performed a systematic review of the efficacy of individualised homeopathy across a range of clinical conditions. They identified the same Level II study by Kainz et al (1996) (given a Jadad score of 4) that has been discussed above. Linde and Melchart (1998) reported that 27% of participants treated with homeopathy achieved at least a 50% reduction in the size of warts, compared to 21% of patients who received placebo. The

corresponding rate ratio was 1.29 (95% CI 0.55, 3.00), indicating no significant difference between the treatment groups. The authors of the systematic review were critical of the fact that the trial only had one outcome measure and that some details were lacking in the report. They also stated that the study suffered from a lack of statistical power.

Simonart and De Maertelaer (2012) (AMSTAR score 6/10) is a systematic review that assessed the evidence for the efficacy of systemic treatments for cutaneous warts. It included two Level II studies (Kainz et al, 1996; Labrecque et al, 1992) and also one Level III-2 study (Villeda et al, 2001). Whilst the quality of the individual studies was not specified, comment was made that "many of the trials reviewed concerning systemic treatment for cutaneous warts were of limited quality". In all three included studies, there was no significant difference in the complete clearance of warts between the homeopathy and placebo groups. In Labrecque et al (1992), there was also no significant difference in adverse effects experienced by participants in the homeopathy and placebo groups. Simonart and De Maertelaer (2012) concluded that "evidence for the efficacy of homeopathy is lacking".

*Reviewer comments*

*The evidence reviewer notes that one of the Level II studies (Kainz et al, 1996) was given a Jadad score of 4 by Linde and Melchart (1998) and Altunc et al (2007); however, Loo and Tang (2009) stated that the trial was of "low quality". There is no apparent reason for the discrepancy between the reviews.*

*Evidence statement*

Four systematic reviews of medium quality identified two randomised controlled trials (poor to medium quality; 77 and 174 participants) and one very small prospectively designed, non-randomised controlled study (quality not reported; 26 participants) that compared homeopathy with placebo for the treatment of people with warts. LOC: Very low - low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with warts.

**Table 79 Evidence summary table: the effectiveness of homeopathy for the treatment of warts**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Loo and Tang (2009)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of CAM for non-genital warts | Kainz et al (1996)<br>[Level II]<br>Low quality<br>N=67 | Not specified. Assumed to be patients with non-genital warts | Oral homeopathy (individually selected regimen) | Placebo | Proportion of people with wart clearance | No significant difference<br>• RR 4.85 (95% CI 0.60, 39.35)<br>• 5/34 (15%) patients in homeopathy group, and 1/33 (3%) patients in placebo group had wart clearance at 8 weeks | "We don't know whether homeopathy increases cure rates compared with placebo, as few high-quality studies have been found." |
| | Labrecque et al (1992)<br>[Level II]<br>Low quality<br>N=174 | Not specified. Assumed to be patients with non-genital warts | Oral homeopathy for 6 weeks (*Thuya* 30cH plus antimony crudum 7cH plus nitricium acidum 7cH) | Placebo | Proportion of people with wart clearance | No significant difference<br>• ARR 4% (95% CI -8, 17)<br>• 16/80 (20%) patients in homeopathy group, and 20/82 (24%) patients in placebo group had wart clearance at 18 weeks | |
| | | | | | Adverse effects | No significant difference<br>• RR 0.51 (95% CI 0.10, 2.72)<br>• 2/86 (2%) patients in homeopathy group and 4/88 (5%) patients in placebo group experienced adverse effects<br>• Adverse effects included stomach ache, loose stools, fatigue and acne | |
| Altunc et al (2007)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for multiple conditions | Kainz et al (1996)<br>[Level II]<br>Jadad score 4[d]<br>N=60 | Patients with warts. Gender not reported.<br>• Intervention group: mean age 8 years<br>• Control group: mean age 9 years | Individualised homeopathy, material potencies, 8 weeks<br>• 10 different remedies were preselected: sulfur 12X potency, Calcium carbonicum 30X potency, Natrium muriaticum 30X potency, sepia 12X potency, Causticum 12X potency, *Staphysagria* 12X potency, *Thuja* 12X potency. Globuli 12X potency were administered once a day; globuli 30X potency every other | Placebo | Number of responders (50% reduction in warts area) | No significant difference | "A single RCT was identified for treating warts. It failed to demonstrate the effectiveness of individualised homeopathic treatment for reducing the size of warts". |
| | | | | | Adverse events | Main adverse events include thrombosis of a capillary hemangioma (1 placebo), exacerbation (1 in both homeopathy and placebo groups) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | day | | | | |
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Kainz et al (1996)<br>[Level II]<br>Quality: 4,4[e]<br>N=77 | Children (aged 6-12 years) with common warts on the hands | Best-fitting simillimum out of predefined set of 10 constitutional remedies in D12 (once a day) and D30 (once every other day) | Placebo | Number of responders (50% reduction in warts area) | No significant difference<br>• Intervention group: 9/33 (27%); comparator group: 7/34 (21%)<br>•<br>• Rate ratio (95% CI): 1.29 (0.55, 3.00) | "Only one outcome measure; lack of statistical power".<br><br>"Simple, straightforward trial with some details lacking in the report". |
| Simonart and De Maertelaer (2012)<br>[Level I/III]<br>AMSTAR: 6/10<br><br>SR of CAM for warts | Kainz et al (1996)<br>[Level II]<br>Quality not specified<br>N=67 | Children aged 6-12 years. Ordinary warts on the back of the hands only | Homeopathic therapy (individually selected regimen) for 6 weeks | Placebo | Complete clearance of warts | No significant difference<br>• Complete clearance of warts in 9/30 (30%) patients in intervention group and 7/30 (23%) patients in control group | "Evidence for the efficacy of homeopathy is lacking" |
| | Labrecque et al (1992)<br>[Level II]<br>Quality not specified<br>N=174 | Children and adults. Ordinary warts on the feet only | Homeopathic therapy (*Thuya* 30CH plus antimonium crudum 7cH plus nitricium acidum 7cH) for 6 weeks | Placebo | Complete clearance of warts | No significant difference<br>• Complete clearance of warts in 4/74 (5%) patients in intervention group and 4/71 (5%) patients in control group | |
| | | | | | Adverse events | No significant difference | |
| | Villeda et al (2001)<br>[Level III-2]<br>Quality not specified<br>N=26 | Children and adults. Ordinary warts anywhere | Homeopathic therapy (*Thuya* 6cH) for 1 month | Placebo | Complete clearance of warts | No significant difference<br>• Complete clearance of warts in 1/12 (8%) patients in intervention group and 0/14 (0%) patients in control group) | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; ARR, absolute risk reduction; CAM, complementary and alternative medicines; cH, Hahnemannian centesimal scale; CI, confidence interval; D, decimal; RCT, randomised controlled trial; RR, relative risk; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.
[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.
[c] Study quality as reported in the systematic review.
[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

# 4.16 Sleep disorders and fatigue

## 4.16.1 Chronic fatigue syndrome

The effectiveness of homeopathy for the treatment of patients with CFS was assessed in six systematic reviews as summarised in Table 80 and Table 81. In total, the systematic reviews included three Level II studies (Awdry, 1996; Saul, 2005; Weatherley-Jones, 2004). The quality of the Level I evidence was variable and ranged from an AMSTAR score of 5/10 to 9/10. One of the systematic reviews (Linde and Melchart, 1998) performed a meta-analysis; however it was not specific to homeopathy in patients with chronic fatigue syndrome.

**Table 80 Matrix indicating the studies that were included in the systematic reviews of chronic fatigue syndrome**

| | | Study ID | | |
|---|---|---|---|---|
| | | **Saul (2005) [Level II]** | **Weatherley-Jones (2004) [Level II]** | **Awdry (1996) [Level II]** |
| **Systematic review** | **Alraek et al (2011) [Level I]** | | ✓ | ✓ |
| | **Davidson et al (2011) [Level I]** | ✓ | ✓ | ✓ |
| | **Reid et al (2011) [Level I]** | | ✓ | |
| | **Porter et al (2010) [Level I]** | | ✓ | ✓ |
| | **Turnbull et al (2007) [Level I]** | | ✓ | ✓ |
| | **Linde and Melchart (1998) [Level I]** | | | ✓ |

Davidson et al (2011) (AMSTAR score 8/10) conducted a systematic review that examined the effectiveness of homeopathy for the treatment of a range of clinical conditions, including three Level II studies (Awdry, 1996; Saul, 2005; Weatherley-Jones, 2004) that examined homeopathy for the treatment of CFS. The largest trial included 103 patients (Weatherley-Jones, 2004) and was considered to be of good quality by the authors of the systematic review. Davidson et al (2011) reported that the Level II study produced "mixed results, but the most rigorous measure supports homeopathy" and stated there was "weak, but equivocal evidence favouring homeopathy". The systematic review also presented results from a "fair quality" Level II study by Awdry (1996), stating that while homeopathy seemed to be effective on many measures, no statistical analyses were carried out and "some of the published numbers do not add up in subscales". Therefore, Davidson et al (2011) were "guarded in stating advantages for homeopathy" based on Awdry (1996).

The smallest Level II study (Saul, 2005) included 30 CFS patients and was judged to be the methodologically weakest Level II study by Davidson et al (2011). The study reported no benefit for individualised homeopathy compared to placebo. Davidson et al (2011) provided a broad conclusion across all trials that assessed homeopathy for functional somatic syndromes that "all except one of

the six functional somatic syndrome studies yielded positive evidence that homeopathy was superior to placebo, and that was the smallest and methodologically weakest".

Alraek et al (2011) (AMSTAR score 7/10) examined the effectiveness of a variety of CAM in relieving symptoms of CFS. The systematic review included two Level II studies (Weatherley-Jones, 2004; Awdry, 1996) that examined the effectiveness of homeopathy compared with placebo for six months and one year, respectively. As reported above, Awdry (1996) did not conduct statistical analyses, although Alraek et al (2011) reported that Awdry (1996) found "beneficial effects of homeopathy on symptom improvement". Weatherley-Jones (2004) found that homeopathy significantly improved function and fatigue compared to placebo. Across all eight measures of methodological quality assessed by Alraek et al (2011), Weatherley-Jones (2004) had a low risk of bias, whereas Awdry (1996) had a mixture of low, unclear and high risk of bias. Overall, Alraek et al (2011) concluded that homeopathy had "insufficient evidence of symptom improvement in CFS" compared with placebo.

Porter et al (2010) (AMSTAR score 9/10) included the same two Level II studies as Alraek et al (2011) in their review of CAM for the treatment of several functional somatic syndromes, including CFS. No additional results were reported, although Porter et al (2010) assessed the quality of the studies using Jadad scores. Awdry (1996) and Weatherley-Jones (2004) received Jadad scores of 2 and 5, respectively. Porter et al (2010) concluded that "given the limited number of studies and mixed outcomes, no conclusions can be drawn on homeopathy for chronic fatigue syndrome".

Turnbull et al (2007) (AMSTAR score 5/10) also conducted a systematic review of CAM for CFS, including the same results from the same two Level II studies as Alraek et al (2011) and Porter et al (2010) (Awdry, 1996; Weatherley-Jones, 2004). Overall, Turnbull et al (2007) concluded that "the evidence found on the effects of complementary therapies for CFS is inadequate in terms of quantity and/or quality".

Similarly, the conclusion from the systematic review of CAM and CFS by Reid et al (2011) was that "there is insufficient evidence to recommend homeopathy as a treatment in CFS", based on the Level II study of "moderate quality" by Weatherley-Jones (2004).

Finally, the much earlier systematic review by Linde and Melchart (1998) (AMSTAR score 8/11) of homeopathy and multiple clinical conditions only included the older Level II study by Awdry (1996; Jadad score 3). Linde and Melchart reported results from Awdry (1996) that favoured homeopathy; however, the systematic review authors stated that although the trial seemed to be rigorous, the reporting of results was "partly detailed but confusing". Overall, Linde and Melchart (1998) concluded that, across all clinical conditions, any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

*Evidence statement*

Six systematic reviews of poor to good quality identified three randomised controlled trials (poor to good quality; total of 197 participants, range: 30-103) that compared homeopathy with placebo for the treatment of people with chronic fatigue syndrome.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with chronic fatigue syndrome.

**Table 81 Evidence summary table: the effectiveness of homeopathy for the treatment of chronic fatigue syndrome**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Alraek et al (2011)<br>[Level I]<br>AMSTAR: 7/10<br><br>SR of CAM for CFS | Weatherley-Jones (2004)<br>[Level II]<br>Quality not specified<br>N=93 | Patients over 18 years of age diagnosed with CFS according to the Oxford criteria | Homeopathy for 6 months | Placebo | MFI | No significant difference except general fatigue (p=0.04) | "Compared to placebo, homeopathy had insufficient evidence of symptom improvement in CFS" |
| | | | | | FIS | No significant difference | |
| | | | | | FLP | Significant difference (p=0.04) | |
| | Awdry (1996)<br>[Level II]<br>Quality not specified<br>N=61 | Patients less than 65 years of age diagnosed with CFS according to the Oxford criteria | Homeopathy for 1 year | Placebo | Daily graphs completed by each patient | No significant differences reported (no between-group analysis) | |
| | | | | | Symptom score | No significant differences (no between-group analysis) | |
| Davidson et al (2011)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Saul (2005)<br>[Level II]<br>Poor quality<br>N=30 | Patients with CFS | Individualised homeopathy | Placebo | CFS-Q | No benefit for homeopathy | "All except one of the six functional somatic syndromes studies yielded positive evidence that homeopathy was superior to placebo and that one was one of the smallest and methodologically weakest"<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to CFS) |
| | | | | | F-VAS | No benefit for homeopathy | |
| | Weatherley-Jones (2004)<br>[Level II]<br>Good quality<br>N=103 | Patients with CFS | Individualised homeopathy | Placebo | MFI scales (general fatigue, physical fatigue, mental fatigue, reduced activity, reduced motivation) | Mixed results, but the most rigorous measure supports homeopathy – no further information provided | |
| | | | | | Effect size (95% CI) and NNT based on MFI - fatigue | ES (95% CI): 0.40 (-0.03 to 0.83)<br>NNT: 6.14 | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | Effect size (95% CI) based on MFI – reduced motivation | ES (95% CI): -0.08 (-0.34 to 0.50) | |
| | Awdry (1996)<br>[Level II]<br>Fair quality<br>N=64 | Patients with CFS | Individualised homeopathy | Placebo | Global response | Homeopathy group 43%; placebo group 4%.<br>"Advantages seem evident on many measures, but statistical analysis not carried out" | |
| | | | | | NNT | 2.49 | |
| Reid et al (2011)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of CAM for CFS | Weatherley-Jones (2004)<br>[Level II]<br>Moderate quality<br>N=103 | Adults with CFS (Oxford criteria) | Individualised homeopath | Placebo | 5 MFI scales: general fatigue, physical fatigue, mental fatigue, reduced activity, reduced motivation | No significant difference except general fatigue (favours homeopathy; p=0.04)<br>• Homeopathy group: mean change 2.7<br>• Placebo group: mean change 1.35 | "There is insufficient evidence to recommend homeopathy as a treatment in CFS" |
| Porter et al (2010)<br>[Level I]<br>AMSTAR: 9/10<br><br>SR of CAM for multiple conditions | Weatherley-Jones (2004)<br>[Level II]<br>Jadad score 5[d]<br>N=103 | Patients with CFS | Homeopathy – details not specified | Placebo | Physical outcomes | Positive results for homeopathy | "Given the limited number of studies and mixed outcomes, no conclusions can be drawn on homeopathy for CFS" |
| | Awdry (1996)<br>[Level II[<br>Jadad score 2[d]<br>N=64 | Patients with CFS | Homeopathy – details not specified | Placebo | Overall beneficial effect or reduction in symptoms | Null result for homeopathy | |
| | | | | | Quality of life | Null result for homeopathy | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Turnbull et al (2007)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of CAM for CFS | Weatherley-Jones (2004)<br>[Level II]<br>SIGN EL 1++[e]<br>N=103 | Patients aged over 18 years who were diagnosed with CFS using the Oxford criteria | Homeopathic consultations over a 6 month period with consultations at monthly periods when individualised prescriptions were made | Placebo | MFI | Significant difference for the general fatigue scale of the MFI (p=0.04)<br>• 26% of patients in treatment group showed clinical improvements on all subscales of the MFI compared to 9% of the placebo group | "The evidence found on the effects of complementary therapies for CFS is inadequate in terms of quantity and/or quality." |
| | | | | | FIS | No significant difference | |
| | | | | | FLP | Significant difference in score changes for physical dimension scale (p=0.04) | |
| | Awdry (1996)<br>[Level II]<br>SIGN EL 1[e]<br>N=64 | Patients aged less than 65 years who were diagnosed with CFS using the Oxford criteria and had the illness for less than 10 years duration | Variety of homeopathic remedies "as indicated", assessed by homeopath | Placebo | Daily graphs completed by each patient | "Cumulative results presented graphically for a small part of the scale - not clear on how to extract data or how meaningful this is" | |
| | | | | | End of trial self-assessment charts completed by each patient | Homeopathy group: 6 recovered, 4 greatly improved, 3 improved, 6 were slightly better and 11 largely unchanged.<br>Placebo group: 0 recovered, 1 greatly improved, 0 improved, 4 were slightly better and 26 largely unchanged | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Awdry (1996)<br>[Level II]<br>Quality:3,4 [f]<br>N=64 | Patients with postviral fatigue syndrome (mean age 40 years; 70% female) | Individual simillimum | Placebo | Number of patients assessed globally as improved | Intervention group: 13/32 (41%); Control group: 1/32 (3%).<br>• Rate ratio (95% CI): 13.0 (1.81, 93.6) | "Apparently rigorous trial, partly detailed but confusing reporting".<br><br>"Homeopathy superior regarding sleep, fatigue, disability, mood". |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; CFS, chronic fatigue syndrome; CFS-Q, Chronic Fatigue Syndrome Questionnaire; CI, confidence interval; EL, evidence level; F-VAS, Fatigue Visual Analogue Scale; FIS, Fatigue Impact Scale; FLP, Functional Limitations Profile; MFI, Multidimensional Fatigue Inventory; NNT, number needed to treat; SIGN, Scottish Intercollegiate Guidelines Network; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

[e] SIGN evidence level assesses the quality of the evidence based on study design and risk of bias. The range of possible scores is 4 (low) to $1^{++}$ (high). Studies with a level of evidence '–' should not be used as a basis for making a recommendation due to high risk of bias.

[f] Quality was assessed using two measures (i) Jadad score, out of 5; (ii) internal validity score, out of 6.

### 4.16.2 Sleep or circadian rhythm disturbances

The effectiveness of homeopathy for the treatment of sleep or circadian rhythm disturbances was assessed in five systematic reviews (Cooper and Relton, 2010; Davidson et al, 2011; Ernst, 2011; Linde and Melchart, 1998; Sarris and Byrne, 2011). The review of complementary medicines and insomnia by Sarris and Byrne (2011) (AMSTAR score 3/5) did not identify any relevant studies. The remaining systematic reviews are summarised in Table 82 and Table 83. In total, the systematic reviews included eight Level II studies.

**Table 82 Matrix indicating the studies that were included in the systematic reviews of sleep or circadian rhythm disturbances**

| | | Systematic reviews | | | |
|---|---|---|---|---|---|
| | | Ernst (2011) [Level I] | Davidson et al (2011) [Level I] | Cooper and Relton (2010) [Level I] | Linde and Melchart (1998) [Level I] |
| Study IDs | Kumar (2010) [Level II] | | ✓ | | |
| | Naude et al (2010) [Level II] | ✓ | ✓ | | |
| | Kolia-Adam et al (2008) [Level II] | ✓ | ✓ | ✓ | |
| | La Pine et al (2006) [Level II] | ✓ | ✓ | | |
| | Cialdella et al (2001) [Level II] | ✓ | | ✓ | |
| | Lipman et al (1999) [Level II] | | ✓ | | |
| | Wolf (1992) [Level II] | ✓ | | ✓ | |
| | Carlini et al (1987) [Level II] | ✓ | | ✓ | ✓ |

The systematic review by Davidson et al (2011) (AMSTAR score 8/10) examined the effectiveness of homeopathy in treating a number of clinical conditions, including five Level II studies (Kolia-Adam, 2008; Kumar, 2010; La Pine et al, 2006; Lipman et al, 1999; Naude et al, 2010) that investigated the effect of various homeopathic remedies on sleep- and circadian rhythm-related problems. The quality assessment conducted by the authors of the systematic review (using the SIGN assessment tool) indicated that three of the trials were of "poor" quality (Kolia-Adam, 2008; Kumar, 2010; La Pine et al, 2006). Of those three trials, one (Kumar, 2010) reported significant results in favour of homeopathy ($p<0.05$) on the Profile of Mood Score (fatigue sub-scale). However, the authors noted that the trial reported inconsistent and ambiguous p-values, so the reliability of those significant results is not clear. The trials by Kolia-Adam (2008) and La Pine et al (2006) reported no significant difference between treatment groups for any outcome.

In contrast, the trials by Naude et al (2010) and Lipman et al (1999) were determined to be of "fair" quality by Davidson et al (2011). Naude studied the efficacy of individualised homeopathy compared to placebo in patients with primary insomnia and found a statistically significant benefit of homeopathy compared to placebo according to two outcomes (Sleep diary, $p<0.05$; Severity of Insomnia Index, $p<0.0001$). Similarly, Lipman et al reported a significant improvement ($p<0.001$) in Snoring Daily Score in the homeopathy group (80%) compared to placebo (46%).

Overall, Davidson et al (2011) found that there is mixed evidence for the efficacy of homeopathy in sleep- and circadian rhythm-related problems. The authors stated that their confidence in the results of the individual trials was either moderate or low and concluded that the cumulative evidence does not warrant a "positive or a negative overall recommendation for this group".

Ernst (2011) (AMSTAR score 6/10) performed a systematic review that focused specifically on homeopathy for insomnia and sleep-related disorders. Three of the studies discussed above (Kolia-Adam et al, 2008; La Pine et al, 2006; Naude et al, 2010) were also identified for inclusion by Ernst (2011) and given quality ratings of "poor", "moderate" and "moderate", respectively. No significant differences were reported for any outcome in the three trials; however, Naude et al (2010) did not report the statistical significance of the difference in total hours of sleep (as measured by the sleep diary), that favoured homeopathy over placebo. Three additional Level II studies by Carlini et al (1987), Cialdella et al (2001) and Wolf (1992) investigated the efficacy of various homeopathic remedies compared to placebo. The specific sleep-related disorder that these trials examined could not be ascertained from the systematic review. No significant differences were reported between homeopathy and placebo in any of the three trials for any outcome, including sleep duration, sleep quality, improvement in night awakenings, or other clinical ratings.

Overall, Ernst (2011) concluded that the best available evidence does not support the notion that homeopathic remedies are effective for the treatment of insomnia. Ernst (2011) also stated that proponents of homeopathy should not make claims about positive therapeutic effects until trials with rigorous study designs and consistently positive findings are available.

The efficacy of homeopathy in patients with insomnia was also investigated in a systematic review by Cooper and Relton (2010) (AMSTAR score 7/10). The review included four Level II trials (Carlini et al, 1987; Cialdella et al, 2001; Kolia-Adam et al, 2008; Wolf, 1992) that were all included in the systematic review by Ernst (2011). The review reported that none of the trials found significant differences between homeopathy and placebo on any outcome. Cooper and Relton (2010) concluded that the limited evidence available is flawed due to low sample sizes (as a result of poor recruitment), high withdrawal rates and poor reporting of results in the Level II studies; however, they did not provide quality scores for each of the included studies. Based on the available evidence, Cooper and Relton (2010) found that there is no evidence to suggest a statistically significant effect of homeopathic medicines for patients with insomnia.

Finally, Linde and Melchart (1998) (AMSTAR score 8/11) conducted an earlier systematic review that examined the efficacy of homeopathy in a wide range of clinical conditions. The Level II study by Carlini et al (1987) was the only study of insomnia or other sleep or circadian rhythm disturbances included in the review. No significant differences were found between the patients who received individual homeopathic simillimum and those who received placebo; however, the outcomes used to measure inter-group differences were not clear. More than half of the patients (26/44) dropped out of the study. As a result, only 18 patients were included in the analysis which draws into question the reliability of the results.

*Reviewer comments*

*Due to the limited evidence base and the heterogeneity of the data set, Davidson et al (2011) decided that a meta-analysis of the results was not meaningful. The evidence reviewer supports the decision not to pool results, as the patient populations that were included in the "sleep or circadian rhythm disturbances" group included patients with insomnia, severe snoring, jet lag, and shift lag in night shift workers. The homeopathic approach adopted in each of the five Level II trials also varied greatly.*

*Some statistically significant differences between homeopathy and placebo were achieved for patients with severe snoring and jet lag; although there was only one trial available for each condition, with flaws in the methodology and small sample sizes (N=23 and N=44 in jet lag and severe snoring, respectively).*

*Evidence statement*

Four systematic reviews of medium quality identified eight randomised controlled trials (poor to medium quality; total of 330 participants, range: 23-96) that compared homeopathy with placebo for the treatment of people with sleep or circadian rhythm disturbances.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Very low - low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with sleep or circadian rhythm disturbances.

**Table 83 Evidence summary table: the effectiveness of homeopathy for the treatment of sleep or circadian rhythm disturbances**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Ernst (2011)<br>[Level I]<br>AMSTAR: 6/10<br><br>SR of homeopathy for insomnia and sleep-related disorders | Naude et al (2010)<br>[Level II]<br>Moderate quality[d]<br>N=30 | Not reported – assumed to be patients with insomnia or sleep-related disorders | Individualised homeopathy for 4 weeks | Placebo | Sleep diary | "Change in total hours of sleep per week favoured homeopathy" | "In conclusion, the notion that homeopathic remedies are effective for the treatment of insomnia and sleep-related disorders is not supported by the best available evidence. It is recommended that future trials of homeopathy and insomnia be conducted using adequate and rigorous study designs. Until consistently positive evidence emerges, proponents of homeopathy should abstain from making such therapeutic claims". |
| | Kolia-Adam et al (2008)<br>[Level II]<br>Poor quality[d]<br>N=30 | Not reported – assumed to be patients with insomnia or sleep-related disorders | *Coffea cruda* 200C for 1 month | Placebo | Sleep duration | No significant difference | |
| | | | | | Sleep pattern | No significant difference | |
| | La Pine et al (2006)<br>[Level II]<br>Moderate quality[d]<br>N=34 | Nurses doing shift work | No-Shift-Lag for 1 week | Placebo | Sleep quality | No significant difference | |
| | | | | | Fatigue | No significant difference | |
| | Cialdella et al (2001)<br>[Level II]<br>Poor quality[d]<br>N=96 | Not reported – assumed to be patients with insomnia or sleep-related disorders | Homeogene or Sedatif PC for 1 month | Placebo | Clinical Global Impression Improvement scale | No significant difference | |
| | Wolf (1992)<br>[Level II]<br>Poor quality[d]<br>N=29 | Not reported – assumed to be patients with insomnia or sleep-related disorders | Requiesan for 1 month | Placebo | Sleep duration | No significant difference | |
| | | | | | Sleep quality | No significant difference | |
| | | | | | Decrease in sleep latency (baseline; 1 month) | No significant difference | |
| | | | | | Percentage of patients | No significant difference | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | reporting improvement, night awakenings | | |
| | Carlini et al (1987)<br>[Level II]<br>Poor quality[d]<br>N=44 | Not reported – assumed to be patients with insomnia or sleep-related disorders | Individualised homeopathy for 45 days | Placebo | Sleep duration | No significant difference | |
| | | | | | Sleep quality | No significant difference | |
| | | | | | Evaluation by clinician | No significant difference | |
| Davidson et al (2011)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Kumar (2010)<br>[Level II]<br>SIGN score: poor<br>N=23 | Patients with jet lag | Combined multiple remedy product | Placebo | POMS-Fatigue | Results favour homeopathy (p<0.05). Effect size: 0.24. | There is mixed evidence for sleep- and circadian rhythm-related problems.<br><br>Two studies (Lipman et al 1999; Naude et al, 2010), with relatively high scores on GRADE evaluation, yielded predominantly positive results. However they addressed different conditions, so the authors do not believe that "the cumulative evidence for any one condition warrants with a positive or a negative overall recommendation for this group". |
| | | | | | POMS-Vigor | No significant difference between treatment arms. Inconsistently reported p-values; ambiguous, but results warrant further study. Effect size: 0.17. | |
| | Naude et al (2010)<br>[Level II]<br>SIGN score: fair<br>N=16 | Patients with primary insomnia | Individualised homeopathy | Placebo | Sleep diary | Benefit for homeopathy (p<0.05). | |
| | | | | | SII | Effect size (95% CI): 2.40 (1.46, 3.34). Benefit for homeopathy (p<0.0001). | |
| | | | | | DBAS | No significant difference between treatment arms. | |
| | Kolia-Adam (2008)<br>[Level II]<br>SIGN score: poor<br>N=15 | Patients with insomnia of less than 1 year in duration | *Coffea cruda* 200C | Placebo | Unclear | "Rate of response": Homeopathy – 33%; Placebo – 50%. Significance not reported. | |
| | | | | | Sleep duration | No significant difference between treatment groups. | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | Effect size (95% CI): 0.24 (-0.53, 1.02). | There is positive evidence that homeopathy is effective in severe snoring.<br><br>"Mainly because of the limited number of studies in any single category and heterogeneity of the data set, we decided that meta-analysis was not meaningful"<br><br>Overall, confidence in the results was graded as moderate or low, suggesting that further research could well change the estimate of effect" |
| | | | | | Sleep satisfaction | No significant difference between treatment groups.<br>NNT: -5.99 (placebo was more effective). | |
| | | | | | Sleep pattern | No significant difference between treatment groups. | |
| | La Pine et al (2006)<br>[Level II]<br>SIGN score: poor<br>N=34 | Night shift workers with shift lag | Combined 5-remedy product | Placebo | CAVT | No significant difference between treatment groups | |
| | | | | | IIQ | No significant difference between treatment groups | |
| | | | | | Fatigue | Effect size: 0.03 (-0.49, 0.56) | |
| | Lipman et al (1999)<br>[Level II]<br>SIGN score: fair<br>N=44[e] | Patients with severe snoring | Combined 9-remedy product | Placebo | Snoring daily score | Statistically significant difference favouring homeopathy. Homeopathy group: 80%; Control group: 46%; p<0.001 | |
| | | | | | Global rating | NNT: 2.95 | |
| Cooper and Relton (2010)<br>[Level I]<br>AMSTAR: 7/10<br><br>SR of homeopathy for insomnia | Kolia-Adam (2008)<br>[Level II]<br>Quality not reported<br>N=30 | Patients with insomnia >1 year<br>• mean age 32-33 years | Formulaic homeopathic medicine: *Coffea cruda* 200C | Placebo | Increase in sleep duration compared to baseline | Significant improvement compared to baseline (homeopathy: 38 minutes, p=0.003; placebo: 35 minutes, p=0.007). No significant inter-group differences were reported | The limited evidence available does not indicate a statistically significant effect of homeopathic medicines for insomnia treatment.<br><br>Two studies reported a trend towards better outcomes in the homeopathy group, however the differences |
| | | | | | Improvement in sleep pattern | Both groups experienced a significant improvement from baseline. No inter-group differences reported | |
| | Cialdella et al (2001) | Patients with insomnia<br>• receiving low-dose | Formulaic homeopathic medicines: | Placebo | Proportion of patients completing the | No significant intergroup differences. Homeogene-46: 10/15 (67%); Sedatif-PC: 12/20 (60%); Placebo 13/36 (50%) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | [Level II]<br>Quality not reported<br>N=96 | benzodiazepines for ≥3 months prior to baseline<br>• mean age 54 years | Homeogene-46[f] or Sedatif-PC[g] | | study and showing improvement or no change in symptoms at 1 month | | were non-significant.<br><br>Major flaws existed in the Level II studies in terms of concealment of allocation, accrual of participants to sufficiently power the studies, and reporting of statistical differences (e.g. in one studies it was unclear whether the p-values referred to differences between groups or from baseline, in another the p-values were misinterpreted).<br><br>All four Level II studies involved small patient numbers, with the largest study reporting a lack of statistical power due to accrual difficulties. The included Level II studies were poorly reported with high patient withdrawal rates. |
| | | | | | Proportion of patients preferring:<br>(i) study treatment<br>(ii) prior BZD treatment<br>(iii) no treatment/other treatment/no preference | Homeopathy groups:<br>(i) 33% (ii) 30% (iii) 37%<br><br>Placebo group:<br>(i) 19% (ii) 38% (iii) 43% | |
| | | | | | Number of patients requesting a return to BZD treatment | No significant difference between patients in the homeopathy compared to placebo groups | |
| | | | | | Clinical Global Impression Improvement scale | No significant difference between patients in the homeopathy compared to placebo groups | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Wolf (1992)<br>[Level II]<br>Quality not reported<br>N=29 | Patients with difficulty falling asleep or staying asleep<br>• aged 19 to 73 years | Formulaic homeopathic medicine: Requiesan[h] | Placebo | Percentage of patients reporting improvement | No significant difference between groups, although a higher proportion of patients in the homeopathy group reported improvement (n=8/14; 57%) compared to the placebo group (n=4/14; 29%) | |
| | | | | | Sleep duration | No significant difference between groups, although the homeopathy group had an increase of 30 minutes, and the placebo group had no change | |
| | | | | | Decrease in sleep latency (baseline; 1 month) | Both groups experienced significant decreases from baseline (homeopathy: 1 hour to 30 minutes; placebo: 30 minutes to 20 minutes), although no significant inter-group differences were reported. | |
| | | | | | Sleep quality | Both groups experienced significant improvement from baseline; no significant inter-group differences were reported | |
| | | | | | Night awakenings | Both groups experienced significant improvement from baseline to 1 month; no significant inter-group differences were reported | |
| | Carlini et al (1987)<br>[Level II] | Patients with severe insomnia | Individualised homeopathic medicine | Placebo | Sleep duration | Both groups experienced significant improvement from baseline to Day 15 and at all timepoints until 3 months. | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Quality not reported<br>N=44 | | (agreed by 2 homeopaths) | | | No significant difference between patients starting on intervention or placebo | |
| | | | | | Sleep latency | Both groups experienced significant improvement from baseline to Day 15 and at all timepoints until 3 months. No significant difference between patients starting on intervention or placebo | |
| | | | | | Sleep quality | Both groups experienced significant improvement from baseline to Day 15 and at all timepoints until 3 months. No significant difference between patients starting on intervention or placebo | |
| | | | | | Clinical evaluation by a homeopath | Both groups experienced significant improvement from baseline to Day 15 and at all timepoints until 3 months. No significant difference between patients starting on intervention or placebo | |
| Linde and Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | Carlini et al (1987)<br>[Level II]<br>Quality:3, 4.5[i]<br>N=44 | Patients with insomnia | Individual simillimum in potencies C6 to C200 | Placebo | Unclear | No difference between groups | The authors did not provide an overall conclusion regarding the efficacy of homeopathy in insomnia; however they did state that the trial had an “extremely high drop-out (rate)”. |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; CAVT, Computer-Assisted Vigilance Test; DBAS, Dysfunctional Beliefs About Sleep; IIQ, Impact of Intervention Questionnaire; NNT, number needed to treat; POMS, Profile of Mood States scale; SIGN, Scottish Intercollegiate Guidelines Network; SII, Severity of Insomnia Index; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Risk of bias was assessed using the Cochrane criteria

[e] Number of participants who completed evaluation. Total number randomised not reported.

[f] Contains *Stramonium* 3DH, *Hyoscyamus niger* 3DH, *Passiflora incarnata* 3DH, *Ballota foetida* 3DH and *Nux moschata* 4CH.

[g] Contains *Aconitum napellus* 6CH, *Belladonna* 6CH, *Calendula officinalis* 6CH, *Abrus precatorius* 6CH, *Chelidonium majus* 6CH and *Viburnum opulus* 6CH.

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

[i] Quality was assessed according to (i) Jadad score (out of five); (ii) internal validity score (out of six).

# 4.17 Adverse effects of cancer treatments

## 4.17.1 Adverse effects of venous cannulation

The effectiveness of homeopathy for the treatment of adverse effects of venous cannulation in women undergoing chemotherapy for breast cancer was assessed in one systematic review (Kassab et al, 2011) as summarised in Table 84. Kassab et al (2011) (AMSTAR score 9/10) conducted a Cochrane review to examine the efficacy of homeopathic medicines for the treatment of adverse effects of cancer treatments. The systematic review identified one Level II study (Bourgois, 1984) that assessed homeopathy for the treatment of side effects of venous cannulation in women receiving chemotherapy for breast cancer.

Women who responded positively to homeopathic *Arnica* in an earlier open-label study were recruited and randomised to receive homeopathic *Arnica* 5c or placebo. Efficacy was assessed based on pain produced by the injection or haematoma(s), venous tone, and venous accessibility; none of which were associated with statistically significant differences between the homeopathy and placebo groups.

Kassab et al (2011) were unable to determine whether an adequate method of sequence generation was used in Bourgois (1984). Similarly, details regarding allocation concealment and blinding were not clear to the authors of the systematic review, although the blinding of patients and care providers was implied. Kassab et al (2011) rated the study to have a high risk of bias and concluded that overall there was "no convincing evidence" for the efficacy of homeopathy for the treatment of adverse effects of venous cannulation in breast cancer patients receiving chemotherapy.

*Evidence statement*

One systematic review of good quality identified one very small randomised controlled trial (poor quality; 29 participants) that compared homeopathy (*Arnica*) with placebo for the treatment of the adverse effects of venous cannulation in people undergoing chemotherapy. LOC: Very low.

Based on only one very small poor quality study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of the adverse effects of venous cannulation in people undergoing chemotherapy.

**Table 84 Evidence summary table: the effectiveness of homeopathy for the treatment of adverse effects of venous cannulation**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Kassab et al (2011)<br>[Level I]<br>AMSTAR: 9/10<br><br>SR of homeopathy for adverse effects of cancer treatments | Bourgois (1984)<br>[Level II]<br>High risk of bias[d]<br>N=29 | Women with breast cancer<br>• mean age (SD): 54.41 years (7.61 years)<br>• receiving chemotherapy<br>• suffering adverse effects of venous cannulation<br>• previously responded to *Arnica* in an open-label trial | Homepathic *Arnica* 5C – three granules 4 times a day for 3 days before and 3 days after treatment, for 2 chemotherapy cycles | Placebo – 3 granules 4 times a day for 3 days before and 3 days after treatment, for 2 chemo-therapy cycles | Improvements from baseline assessed by:<br>• pain produced by the injection or haematoma(s)<br>• venous tone assessed by the no. of haematomas<br>• venous accessibility assessed by the no. of attempts at cannulation | No significant inter-group differences | In general there were mixed findings or unclear risk of bias.<br><br>Overall the authors concluded that there is no evidence to support the efficacy of homeopathic medicines for adverse effects of cancer treatments (other than preliminary data to support the use of Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis). |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; C, centesimal; NR, not reported; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality assessed using the Delphi List and Cochrane Collaboration tool for assessing bias.

### 4.17.2 Chemotherapy-associated nausea/vomiting

The effectiveness of homeopathy for the treatment of nausea and vomiting in women with breast cancer was assessed in one systematic review (Kassab et al, 2011; AMSTAR score 9/10) as summarised in Table 85. This Cochrane review was a broad review of the effectiveness of homeopathy for the treatment of adverse effects of cancer treatments. One Level II study (Daub et al, 2005) with an "unclear risk of bias" was identified by Kassab et al (2011) that compared two homeopathic remedies (Vomitusheel S and Gastricumeel) with another homeopathic remedy (*Sambucus nigra* D3) for the treatment of nausea and vomiting in breast cancer patients undergoing chemotherapy. *Sambucus nigra* D3 was chosen as the comparator because it has "no antiemetic properties". No Level II, Level III-1 or Level III-2 studies were identified that compared homeopathy to placebo for the treatment of chemotherapy-associated nausea and vomiting.

In Daub et al (2005), participants in each of the three arms received conventional antiemetics on the first day followed by one of the three homeopathic interventions if nausea or vomiting persisted on the second day. The primary outcome was the number of patients requiring additional conventional treatments for nausea/vomiting, which were administered if symptoms had not resolved within two hours of receipt of homeopathic medicines or placebo.

Kassab et al (2011) reported that the trial found no significant difference between the interventions (p=0.6), with 68.2% requiring additional medication in the intervention group compared to 59.1% in the control group. Kassab et al (2011) stated that there was no explicit information on blinding in the report of the trial by Daub (2005); however, the fact that there was no placebo suppository available implied that blinding was not possible. Overall, Kassab et al (2011) concluded that there was "no convincing evidence" for the efficacy of homeopathy in the treatment of nausea and vomiting in women undergoing chemotherapy for breast cancer.

*Evidence statement*

One systematic review (2011) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy compared with placebo for the treatment of people with chemotherapy-associated nausea/vomiting.

One systematic review of good quality identified one small randomised controlled trial (quality unclear; 65 participants) that compared two homeopathic medicines (*Vomitusheel S* and *Gastricumeel*) with another homeopathic medicine with no claimed antiemetic properties for the treatment of people with chemotherapy-associated nausea/vomiting. LOC: Very low.

Based on only one small study of unknown quality there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of people with chemotherapy-associated nausea/vomiting.

**Table 85 Evidence summary table: the effectiveness of homeopathy for the treatment of chemotherapy-associated nausea/vomiting**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Kassab et al (2011)<br>[Level I]<br>AMSTAR: 9/10<br><br>SR of homeopathy for adverse effects of cancer treatments | Daub et al (2005)<br>[Level II]<br>Unclear risk of bias[d]<br>N=65 | Women with breast cancer<br>• aged 28-67 years<br>• undergoing chemotherapy<br>• all participants received standard antiemetics on day 1. If nausea or vomiting occurred on subsequent days, participants received either the homeopathic intervention or the comparator. | Vomitusheel S[e] given as a suppository and Gastricumeel[f] given as oral tablets | *Sambucus nigra* D3 oral tablets[g] | Percentage of patients requiring additional conventional treatment for nausea/vomiting[h] | No significant difference between groups. Intervention group: 68.2%; control group: 59.1% (p=0.6) | In general there were mixed findings or unclear risk of bias.<br><br>Overall the authors concluded that there is no evidence to support the efficacy of homeopathic medicines for adverse effects of cancer treatments (other than preliminary data to support the use of Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis). |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; D, decimal; NR, not reported; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality assessed using the Delphi List and Cochrane Collaboration tool for assessing bias.

[e] Vomitushell S is a proprietary complex homeopathic medicine containing *Ipecacuanha* D2 (1.1mg), *Aesthusea* D2 (1.1mg), *Nux vomica* D2 (1.1mg), *Apomorphium hydrochloricum* D4 (1.65mg), *Colchicum* D4 (2.75mg), *Ignatia* D4 (3.3mg)

[f] Gastricumeel is a proprietary complex homeopathic medicine containing *Argentum nitricum* D6 (30mg), *Acidum arsenicosum* D6 (30mg), *Pulsatilla* D4 (60mg), *Nux vomica* D4 (60mg), *Carbo vegetablis* D6 (60mg), *Antimonium crudum* D6 (60mg)

[g] The "placebo" was another homeopathic medicine that the authors chose because "no antiemetic properties had been described".

[h] Additional conventional treatment was given if nausea/vomiting had not resolved within two hours of receipt of intervention or "placebo".

### 4.17.3 Chemotherapy-induced stomatitis

The effectiveness of homeopathy for the treatment of chemotherapy-induced stomatitis in patients with cancer was assessed in three systematic reviews (Bellavite et al, 2011; Kassab et al, 2011; Milazzo et al, 2006) as summarised in Table 86 and Table 87.

**Table 86 Matrix indicating the studies that were included in the systematic reviews of chemotherapy-induced stomatitis**

| | | Systematic review | | |
|---|---|---|---|---|
| | | **Bellavite et al (2011) [Level I]** | **Kassab et al (2011) [Level I]** | **Milazzo et al (2006) [Level I/III]** |
| **Study ID** | **Oberbaum et al (2001) [Level II]** | ✓ | ✓ | ✓ |
| | **Oberbaum (1998) [Level III-2]** | | | ✓ |

Milazzo et al (2006) (AMSTAR score 7/10) carried out a systematic review that assessed the efficacy of homeopathic therapy as a sole or additional therapy in cancer care and identified two studies (Oberbaum, 1998; Oberbaum et al, 2001) that examined homeopathic TraumeelS as a treatment for chemotherapy-induced stomatitis. The Level III-2 study by Oberbaum (1998) was a pilot, case-control study conducted in order to inform the later Level II study by Oberbaum et al (2001). Oberbaum (1998) reported a highly statistically significant reduction in the homeopathy group in terms of the duration of symptoms, however no numerical evidence was provided to support the findings. The study received a Jadad score of 0 in the quality assessment by Milazzo et al (2006), and therefore reliability and validity of the results is questionable.

The Level II study identified by Milazzo et al (2006) (Oberbaum et al, 2001; Jadad score 4) examined homeopathic TraumeelS in patients aged 3 to 25 that had malignant blood cancer and underwent allogeneic or autologous stem-cell transplantation. Oberbaum et al (2001) found that the reduction of severity and/or duration of stomatitis, mean “area under the curve”, and mean time to worsening of symptoms all significantly favoured homeopathy. Milazzo et al (2006) did not report p-values for a number of other outcomes, including median time to worsening of symptoms, oral pain and discomfort, and difficulty to swallow. Overall Milazzo et al (2006) concluded that cancer patients “appear to have benefited from homeopathic interventions for chemotherapy-induced stomatitis” and that “encouraging results” in Oberbaum et al (2001) highlighted the need to perform a larger trial.

Kassab et al (2011) (AMSTAR score 9/10) conducted a Cochrane review that examined the effectiveness of homeopathy for the treatment of adverse effects of a variety of cancer treatments. The Level II study by Oberbaum et al (2001) was included in the review, although Kassab et al (2011) reported fewer outcomes from the trial than Milazzo et al (2006). Overall, Kassab et al (2011) stated that there was “preliminary data in support of TraumeelS mouthwash in the treatment of chemotherapy-induced stomatitis” that needs replication to provide any firm conclusions.

Finally, Bellavite et al (2011) (AMSTAR score 5/10) performed a systematic review of the effectiveness of homeopathy for a variety of clinical conditions, including chemotherapy-associated stomatitis from one Level II study (Oberbaum et al, 2001). Bellavite only reported the results of two outcomes (percentage of patients who did not develop stomatitis and mean area under the curve for

stomatitis scores), the latter of which was found to significantly favour homeopathy ($p<0.01$). Based on the results of the Level II study by Oberbaum et al (2001), Bellavite et al (2011) concluded that TraumeelS "may reduce the severity and duration of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation".

*Reviewer comments*

*The results of the Level II study (Oberbaum et al, 2001) were reported inconsistently between the three systematic reviews. For example, Bellavite et al (2011) reported "percentage of patients who did not develop stomatitis" as an outcome, suggesting that the trial was, in fact, examining Traumeel as a prophylactic intervention. However, the description of the trial in the other two systematic reviews (Kassab et al, 2011; Milazzo et al, 2006) and the outcomes reported suggested that the trial examined the treatment of existing stomatitis.*

*Evidence statement*

Three systematic reviews of poor to good quality identified one very small randomised controlled trial (good quality; 32 participants) and one very small prospectively designed, non-randomised controlled study (poor quality; 27 participants) that compared homeopathy (*Traumeel S*) with placebo for the treatment of people with chemotherapy-induced stomatitis.

These studies are of insufficient quality and/or size to warrant further consideration of their findings. LOC: Very low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of people with chemotherapy-induced stomatitis.

**Table 87 Evidence summary table: the effectiveness of homeopathy for the treatment of chemotherapy-induced stomatitis**

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Bellavite et al (2011) [Level I] AMSTAR: 5/10<br><br>SR of homeopathy for multiple conditions | Oberbaum et al (2001) [Level II] Quality not specified N=32 | Children and young adults with chemotherapy-associated stomatitis who had undergone stem cell transplantation | Homeopathic complex Traumeel-S | Placebo (local therapy with mouth rinsing) | Percentage of patients who did not develop stomatitis | Significance of results not reported<br>• Homeopathy: 33%<br>• Placebo: 7% | "These results suggest that this homeopathic complex may reduce the severity and duration of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation" |
| | | | | | Mean AUC (severity and duration of stomatitis) | Significant difference in favour of homeopathy (p<0.01)<br>• Homeopathy: 10.4<br>• Placebo: 24.3 | |
| Kassab et al (2011) [Level I] AMSTAR: 9/10<br><br>SR of homeopathy for adverse effects of cancer treatments | Oberbaum et al (2001) [Level II] Low risk of bias[d] N=32 | Patients suffering from malignant disease who had undergone allogeneic or autologous stem cell transplantation<br>• aged 3-25 years | TraumeelS®[e] – supplied as 2.2ml ampoules used as a mouthwash for a minimum of 30 seconds, 5 times per day, alongside standard mouthcare | Placebo – supplied as 2.2ml ampoules used as a mouthwash for a minimum of 30 seconds, 5 times per day, alongside standard mouthcare | Mean AUC (severity and duration of stomatitis) | Homeopathy group: 10.4; Placebo group: 24.3. Wilcoxon rank-sum score: 167.5; expected score 232.5; p<0.01) | In general there were mixed findings or unclear risk of bias.<br><br>There is preliminary data to support the efficacy of Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis, but there is no evidence to support the efficacy of homeopathic medicines for other adverse effects of cancer treatments. |
| | | | | | Time to worsening of symptoms | Log-rank test indicated a statistically significant difference between the two groups (chi-square test, 13.4 with 1 degree of freedom; p<0.001) | |
| | | | | | Median time to worsening in those patients whose symptoms worsened | Homeopathy group: 4.7 days; Placebo group: 4.0 days. Significance NR. | |

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | Patient-reported score | Reduction in all three symptoms (pain, dryness, dysphagia) in Traumeel group compared to placebo (p=NR). | |
| Milazzo et al (2006) [Level I/III] AMSTAR: 7/10<br><br>SR of homeopathy for cancer treatment | Oberbaum et al (2001) [Level II] Jadad score 4[f] N=30 | Patients with blood malignant cancer who underwent allogeneic or autologous stem-cell transplantation<br>• aged 3-25 years | TraumeelS®[g] | Placebo | Mean AUC (severity and duration of stomatitis) | Statistically significant difference between groups. Homeopathy: 10.4; Placebo: 24.3; p<0.01 | "Cancer patients appear to have benefited from homeopathic interventions specifically for chemotherapy-induced stomatitis".<br><br>"The evidence emerging from this systematic review is encouraging but not convincing. Further research should attempt to answer the many open questions related to homeopathy". |
| | | | | | Mean time to worsening of symptoms | Statistically significant difference between groups favouring homeopathy. Homeopathy group: 6.9 days; placebo group: 4.3 days; p<0.001 | |
| | | | | | Median time to worsening in those patients whose symptoms worsened | Homeopathy group: 4.7 days; placebo group: 4.0 days. p-value not specified | |
| | | | | | Severity score (subgroup analysis of patients aged less than 15 years) | Significant difference between treatment groups favouring homeopathy. Homeopathy group: 11; placebo group: 25.9; p<0.01 | |

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | Oral pain and discomfort | Patients in the intervention group experienced a reduction (no p-values provided) | |
| | | | | | Dryness of mouth and tongue | Patients in the intervention group experienced a reduction (no p-values provided) | |
| | | | | | Difficulty to swallow | Patients in the intervention group experienced a reduction (no p-values provided) | |
| | | | | | Dysphagia | Patients in the intervention group experienced a reduction (no p-values provided) | |
| | | | | | Adverse events: (i) Graft vs. host disease, (ii) Sepsis, (iii) GI complications, (iv) VOD, (v) Pneumonitis | In homeopathy and placebo groups respectively: (i) n=3, n=6; (ii) n=3, n=8; (iii) n=0, n=5; (iv) n=4, n=0; (v) n=4, n=0 | |
| | Oberbaum (1998) [Level III-2] | Children and teenagers with leukemia | TraumeelS®[g] | Randomly chosen controls from the same age group with | Symptom duration | Statistical difference between groups NR. Homeopathy group: 6 days; controls: 13 days | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | Jadad score 0[f]<br>N=27 | | | similar stages of cancer, who received no treatments for stomatitis | Use of opiates | Non-significant trend suggesting less patients in the intervention group required opiates compared to the control group (p=0.09) | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; AUC, area under the curve; NR, not reported; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality assessed using the Delphi List and Cochrane Collaboration tool for assessing bias.

[e] TraumeelS is a proprietary complex homeopathic medicine. Each 2.2ml ampoule contains: *Arnica montana* D2 (2.2mg), *calendula officianalis* D2 (2.2mg), *Achillea millefolium* D3 (2.2mg), *Matricharia chamomilla* D2 (2.2mg), *Symphytum officinale* D6 (2.2mg), Atropa *belladonna* D2 (2.2mg), *Aconitum napelus* D2 (1.32mg), *Bellis perenis* D2 (1.1mg), *Hypericum perfoliatum* D2 (0.66mg), *Echinacea angustifolia* D2 (2.2mg), *Echinacea purpurea* D2 (2.2mg), *Hammamelis virginica* D1 (0.22mg), *Mercurius solubilis* D1 (1.1mg), and *Hepar sulphuris* D6 (2.2mg).

[f] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

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

### 4.17.4 Hot flushes in women with a history of breast cancer

The effectiveness of homeopathy for the treatment of women with hot flushes and a history of breast cancer was assessed in three systematic reviews (Kassab et al, 2011; Milazzo et al, 2006; Rada et al, 2010) as summarised in Table 88 and Table 89.

**Table 88 Matrix indicating the studies that were included in the systematic reviews of hot flushes**

| | | Systematic review | | |
|---|---|---|---|---|
| | | **Kassab et al (2011) [Level I]** | **Milazzo et al (2006) [Level I/III]** | **Rada et al (2010) [Level I]** |
| **Study ID** | **Jacobs et al (2005) [Level II]** | ✓ | ✓ | ✓ |
| | **Thompson et al (2005) [Level II]** | ✓ | ✓ | ✓ |

Rada et al (2010) (AMSTAR score 8/10) conducted a Cochrane review that aimed to assess the efficacy of non-hormonal therapies for reducing hot flushes in women with a history of breast cancer. The authors identified two Level II studies (Jacobs et al, 2005; Thompson et al, 2005) that compared homeopathy with placebo. Rada et al (2010) assessed the risk of bias in the included studies using the criteria established in the Cochrane Handbook for Systematic Reviews of Interventions. No overall quality ratings were provided, however, both of the studies scored well according to the majority of the quality criteria, indicating a low overall risk of bias. Jacobs et al (2005) was a Level II study that compared two forms of homeopathy (single or combination therapy) with placebo in women with a history of breast cancer and at least three episodes of hot flushes per day for at least one month. There were no statistically significant differences among comparisons for the frequency or severity score of hot flushes. There was, however, a significant improvement in quality of life scores in women who used single or combination homeopathy (p-value not reported).

Thompson et al (2005) examined the effect of a tailored homeopathic prescription or placebo in women with non-metastatic breast cancer who experienced more than three hot flushes per day. The study reported that no significant effects were observed in a four-item profile score that included two self-rated symptom items, an activity of daily living item and a general feeling of well-being item (mean difference -0.10; 95% CI -4.86, 4.66).

Rada et al (2010) noted that the major limitation of the two included studies was loss to follow up. The authors concluded that “the available evidence suggests that homeopathy provides no significant benefit compared to placebo” and “even though the studies had limited power to show an effect, none of them showed significant benefit or supported the use of homeopathy”.

Kassab et al (2011) (AMSTAR score 9/10) conducted a Cochrane review that focused specifically on homeopathy for the treatment of adverse effects of cancer treatments. The same two studies included in Rada et al (2010) (Jacobs et al, 2005; Thompson et al, 2005). The studies were both assessed to be of “high quality and low risk of bias” by Kassab et al (2011). Kassab et al (2011) reported that the primary outcome investigated by Jacobs et al (2005) was hot flush severity score, which was not associated with a significant difference between the intervention group (single and combination homeopathic remedies) and placebo. However a post hoc, subgroup analysis indicated that patients not receiving tamoxifen that were randomised to combination homeopathic medicine

(Hyland's menopause) had significantly higher hot flush severity scores and total number of hot flushes than the single remedy and placebo groups. Thompson et al (2005) was reported as finding no statistically significant differences between individualised homeopathy and placebo, based on symptom and mood disturbances or other self-reported outcomes. Overall, Kassab et al (2011) concluded that there was "no convincing evidence" for the efficacy of homeopathy in the treatment of hot flushes in women with a history of breast cancer.

Finally, Milazzo et al (2006) (AMSTAR score 7/10) carried out a systematic review that assessed the efficacy of homeopathic therapy in cancer treatment. The authors identified the same two Level II studies (Jacobs et al, 2005; Thompson et al, 2005), and gave them both Jadad scores of 5. Milazzo et al (2006) reported that the study by Jacobs et al (2005) found that homeopathy resulted in an improvement in general health score compared with placebo ($p<0.03$ and $p=0.02$ in the combination and single remedies, respectively). In addition, Jacobs et al (2005) was reported to have found that the whole combination therapy group had statistically significantly higher rates of headaches than those in the other treatment arms ($p=0.03$). Consistent with the other systematic reviews, Milazzo et al (2006) reported that Thompson et al (2005) found no statistically significant differences between individualised homeopathy and placebo. Milazzo et al (2006) stated that even though the trials received a Jadad score of 5 they were not devoid of flaws, particularly small sample sizes that precluded definitive conclusions. Overall, the Milazzo et al (2006) concluded that there is "insufficient evidence to support clinical efficacy" of homeopathy in cancer care.

*Reviewer comments*

*There was substantial heterogeneity between the trials, particularly in terms of the homeopathic remedies prescribed. Thirty five different homeopathic medicines were prescribed in Jacobs et al (2005) and 71 different homeopathic medicines were prescribed in Thompson et al (2005). Only two of the five most commonly prescribed remedies were common to both studies. The trials by Jacobs et al (2005) and Thompson et al (2005) also adopted considerably different primary outcomes; menopausal symptoms and a patient-reported outcome (Measure Your Medical Outcome Profile), respectively.*

*Evidence statement*

Three systematic reviews of medium to good quality identified two randomised controlled trials (good quality; 53 and 83 participants) that compared homeopathy with placebo for the treatment of hot flushes in women with a history of breast cancer.

These studies are of insufficient size to warrant further consideration of their findings. LOC: Low.

Based on the body of evidence evaluated in this review there is no reliable evidence that homeopathy is more effective than placebo for the treatment of hot flushes in women with a history of breast cancer.

**Table 89 Evidence summary table: the effectiveness of homeopathy for the treatment of hot flushes in women with a history of breast cancer**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Kassab et al (2011)<br>[Level I]<br>AMSTAR: 9/10<br><br>SR of homeopathy for adverse effects of cancer treatments | Jacobs et al (2005)<br>[Level II]<br>Low risk of bias[d]<br>N=83 | Women with a history of carcinoma in situ or Stage I to III breast cancer<br>• who had completed all surgery, chemotherapy and radiotherapy<br>• with hot flushes for at least one month, with an average of at least three hot flushes per day in the week prior to beginning treatment<br>• mean age: 55.5 years | Individualised homeopathy – unrestricted remedy choice and unrestricted ability to change remedy (single medicine given once monthly or bimonthly); or Hyland's Menopause[e] (given 3 times a day) | Placebo | Hot flush severity score | Positive trend towards an improvement in the single remedy group during the first three months of the study, however the trend was not significant (p=0.1) | In general there were mixed findings or unclear risk of bias.<br><br>Overall the authors concluded that there is no evidence to support the efficacy of homeopathic medicines for adverse effects of cancer treatments (other than preliminary data to support the use of Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis). |
| | | | | | General health score (SF-36) at 1 year | Statistically significant improvement in both homeopathy groups (p<0.05) | |
| | | | | | General health score (SF-36) compared with placebo | Significantly increase in both homeopathy groups compared with placebo (p=NR) | |
| | | | | | Hot flush severity score (post hoc subgroup analysis defined by use of tamoxifen) | Highly statistically significant increase in the combination homeopathic group (subgroup of patients not receiving tamoxifen) | |
| | Thompson et al (2005)<br>[Level II]<br>Low risk of bias[d]<br>N=53 | Women treated for breast cancer<br>• more than three hot flushes per day<br>• no metastatic disease<br>• not on any other treatment for hot flushes<br>• not undergoing, or about the receive, any adjuvant chemotherapy<br>• mean age: 52.7 years | Individualised homeopathy – unrestricted remedy choice and unrestricted ability to change remedy | Placebo | Symptoms and mood disturbances | Clinically relevant improvements for both groups. Inter-group differences not reported | |
| | | | | | MYMOP activity score | No evidence of a difference between groups (adjusted difference: -0.4, 95% CI -0.9, 0.1, p=0.13) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Rada et al (2010)<br>[Level I]<br>AMSTAR: 8/10<br><br>SR of CAM for hot flushes | Jacobs (2005)<br>[Level II]<br>Quality not specified<br>N=83 | Women (mean age 55.5 years) with a history of breast cancer (carcinoma *in situ* and stages I to III)<br>• at least 3 episodes of hot flushes per day for at least one month<br>• 58% on tamoxifen<br>• 65% taking unspecified hormones | Single or combination (Hyland's menopause) homeopathic remedies | Placebo | SF-36 | Significant improvement in QoL scores in women using single or combination homeopathy (p=NR) | The available evidence suggests that homeopathy provides no significant benefit compared to placebo<br><br>Even though the studies had limited power to show an effect, none of them reported significant benefit or supported the use of homeopathy |
| | | | | | Total number of hot flushes | No significant difference | |
| | | | | | Hot flush severity score | No significant difference | |
| | | | | | Kupperman Menopausal Index | No significant difference | |
| | Thompson (2005)<br>[Level II]<br>Quality not specified<br>N=53 | Women (mean age 52 years) with non-metastatic breast cancer<br>• more than 3 hot flushes per day<br>• 80% on tamoxifen<br>• baseline hot flush frequency of 7.5 per day | Individualised homeopathy | Placebo | MYMOP activity score | No significant difference<br>Mean difference: -0.10 (95% CI -4.86, 4.66) | |
| | | | | | Daily living disruption and general well-being | No significant difference | |
| | | | | | Frequency and severity of hot flushes | No significant difference | |
| | | | | | QoL (EORTC QLQ-C30) | No significant difference | |
| | | | | | HADS | No significant difference | |
| | | | | | Overall satisfaction with homeopathy (measure not specified) | No significant difference | |
| | | | | | Impact on daily living | No significant difference | |
| | | | | | Side-effects | No significant difference | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Milazzo et al (2006)<br>[Level I]<br>AMSTAR: 7/10<br><br>SR of homeopathy for cancer treatment | Jacobs et al (2005)<br>[Level II]<br>Jadad score 5[f]<br>N=83 | Breast cancer survivors | Verum single remedy[g] plus placebo, or a verum combination medicine (Hyland's menopause)[h] plus a verum single remedy | Placebo | General health score (SF-36) compared with placebo | Significant improvement in both homeopathy groups compared to placebo (p<0.03, combination; p=0.02, single) | There is insufficient evidence to support clinical efficacy of homeopathic therapy in cancer care. |
| | | | | | Hot flush severity score (subgroup not receiving tamoxifen) | Statistically significantly higher in combination group than single remedy (p<0.001; 95% CI -51.9, 15.0). Statistically significantly higher in combination homeopathy group than placebo (p=0.01; 95% CI 6.2, 47.1) | |
| | | | | | Total number of hot flushes (subgroup not receiving tamoxifen) | Statistically significantly higher in combination group than single remedy (p=0.002). Statistically significantly higher in combination homeopathy group than placebo (p=0.006) | |
| | | | | | Headaches | Statistically significant increase in headaches in the combination group (p=0.03) | |
| | Thompson et al (2005) | Breast cancer survivors with oestrogen withdrawal symptoms | 71 different remedies (tablets, liquid, or granules) | Placebo | MYMOP activity score | No significant difference between treatment groups (p=0.17; 95% CI -1.0, 0.2) | |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | [Level II]<br>Jadad score 5[f]<br>N=53 | • no more than three hot flushes per day<br>• without metastatic disease<br>• no concurrent treatment for hot flushes<br>• not undergoing chemotherapy | | | MYMOP overall profile score | No significant difference between treatment groups (p=0.13; 95% CI -0.9, 0.1) | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; MYMOP, Measure Your Medical Outcome Profile; NR, not reported; QoL, quality of life; SF-36, Short Form-36; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality assessed using the Delphi List and Cochrane Collaboration tool for assessing bias.

[e] Hyland's Menopause is a proprietary combination homeopathic medicine of Amyl Nitrate 3x, Sanguinaria Canadensis 3x and Lachesis 12x.

[f] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

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

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

### 4.17.5 Radiodermatitis in breast cancer patients undergoing radiotherapy

The effectiveness of homeopathy for the treatment of radiodermatitis in breast cancer patients undergoing radiotherapy was assessed in three systematic reviews (Kassab et al, 2011; Milazzo et al, 2006; Simonart et al, 2011) as summarised in Table 90. In total, the systematic reviews identified one Level II study (Balzarini et al, 2000) that specifically examined homeopathy for the treatment of radiodermatitis in breast cancer patients.

Kassab et al (2011) (AMSTAR score 9/10) was a Cochrane review that examined homeopathic therapies for the treatment of adverse effects of a variety of cancer treatments. Although Kassab et al (2011) identified the Level II study by Balzarini et al (2000) for inclusion in their review, it was not clear whether the remedy (homeopathic *Belladonna* 7c and X-ray 15c) was used for preventative or therapeutic purposes. The findings of the study reported in Kassab et al (2011) were that there was no significant difference in the total severity of skin reactions during radiotherapy, but there was a significant reduction in severity in the homeopathy group during recovery (p=0.05), compared to placebo. The assessment of total severity of skin reaction was assessed by physicians based on skin colour, heat to touch, hyperpigmentation and oedema.

Kassab et al (2011) reported that the Level II study by Balzarini et al (2000) had an "unclear risk of bias" and concluded that "there is no evidence to support the efficacy" of homeopathic *Belladonna* 7c and X-ray 15c for the treatment of radiodermatitis in women undergoing radiotherapy for breast cancer.

Milazzo et al (2006) (AMSTAR score 7/10) carried out a systematic review that assessed the efficacy of homeopathic therapy as a sole or additional therapy in cancer care. The authors reported that the Level II study by Balzarini et al (2000; Jadad score 4) found transient benefits in the homeopathy group based on hyperpigmentation and skin heat that were no longer statistically significant by the 10-week follow-up. Milazzo et al (2006) concluded that there is "insufficient evidence to support clinical efficacy of homeopathic therapy in cancer care".

Simonart et al (2011) (AMSTAR score 8/10) conducted a systematic review that examined the effectiveness of homeopathy in treating a variety of dermatological conditions. The authors of the systematic review reported that the Level II study by Balzarini et al (2000) found no significant differences between homeopathy and placebo across four outcomes. Simonart et al (2011) did not discuss the quality of Balzarini et al (2000), but concluded that "the hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".

*Evidence statement*

Three systematic reviews of medium to good quality identified one small randomised controlled trial (medium quality; 66 participants) that compared homeopathy (*Belladona*) with placebo for the treatment of radiodermatitis in women with breast cancer undergoing radiotherapy. LOC: Very low - low.

Based on only one small study there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy compared to placebo for the treatment of radiodermatitis in women with breast cancer undergoing radiotherapy.

**Table 90 Evidence summary table: the effectiveness of homeopathy for the treatment of radiodermatitis in patients undergoing radiotherapy**

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Simonart et al (2011) [Level I] AMSTAR: 8/10<br><br>SR of homeopathy for multiple conditions | Balzarini et al (2000) [Level II] Quality not specified N=66 | Breast cancer patients aged 28-70 years with radiodermatitis and who are undergoing radiotherapy | *Belladona* 7 cH and X-ray 15 cH for 10 weeks | Placebo | Breast skin colour score | No significant difference | "The hypothesis that any dermatological condition responds convincingly better to homeopathic treatment than to placebo or other control interventions is not supported by evidence".<br><br>(Note: this conclusion refers to all clinical conditions and is not specific to skin reactions during radiotherapy) |
| | | | | | Warmth score | No significant difference | |
| | | | | | Swelling score | No significant difference | |
| | | | | | Pigmentation score | No significant difference | |
| Kassab et al (2011) [Level I] AMSTAR: 9/10<br><br>SR of homeopathy for adverse | Balzarini et al (2000) [Level II] Unclear risk of bias[d] N=66 | Women who had undergone conservative surgery for breast cancer and were being treated with radiotherapy<br>• mean age: 52.7 years, range: 28.3 to 70 years | *Belladonna* 7cH – three granules twice daily and X-ray 15cH three granules once daily | Placebo | Total severity of skin reactions during radiotherapy (based on skin colour, heat to touch, hyperpigmentation and oedema) | No significant difference between groups | In general there were mixed findings or unclear risk of bias.<br><br>There is preliminary data to support the efficacy of Traumeel S mouthwash in the treatment of |

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| effects of cancer treatments | | | | | Total severity of skin reactions during recovery (based on skin colour, heat to touch, oedema and hyperpigmentation) | Statistically significant reduction in homeopathy-treated patients (p=0.05) | chemotherapy-induced stomatitis, but there is no evidence to support the efficacy of homeopathic medicines for other adverse effects of cancer treatments. |
| Milazzo et al (2006) [Level I/III] AMSTAR: 7/10<br><br>SR of homeopathy for cancer treatment | Balzarini et al (2000) [Level II] Jadad score 4[e] N=61 | Breast cancer patients undergoing radiotherapy | *Belladonna* 7cH (three granules, twice a day) and X-ray 15cH (once a day) | Placebo | Hyperpigmentation | Significantly less hyperpigmentation in the homeopathy group at Week 5 (p=0.050); the difference was no longer statistically significant by the end of the 10-week follow-up (p=0.060) | There is insufficient evidence to support clinical efficacy of homeopathic therapy in cancer care. |
| | | | | | Skin heat | Significant decrease in the homeopathy group compared to placebo at Week 8 (p=0.011). However the benefit was transient as the difference was no longer significant at the 10-week follow-up (p=0.250) | |
| | | | | | Total severity score | More favourable in the intervention group during radiotherapy and | |

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| | | | | | | recovery. Statistically significant in recovery only (p=0.05) | |
| | | | | | Frequency of oedema | Higher frequency in the intervention group - statistically significant difference at Weeks 5 and 6 (p=0.025) | |
| | | | | | Adverse event – hot flushes, perspiration and migraine | Statistical difference between groups NR. Homeopathy group: n=1; placebo group: n=0 | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; cH, Hahnemannian centesimal scale; NR, not reported; SR, systematic review.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Quality assessed using the Delphi List and Cochrane Collaboration tool for assessing bias.

[e] The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding and the flow of patients. The range of possible scores is zero (bad quality) to 5 (good quality).

# 4.18 Pain

## 4.18.1 Chronic facial pain

The effectiveness of homeopathy for the treatment of patients with chronic facial pain was assessed in one systematic review (Myers et al, 2002). Myers et al (2002) (AMSTAR score 3/5) was a systematic review of complementary and alternative medicines used to treat chronic facial pain, which failed to identify any Level II studies that tested the effects of homeopathy.

*Evidence statement*

One systematic review (2002) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy in people with chronic facial pain.

### 4.18.2 Lower back pain

The effectiveness of homeopathy for the treatment of patients with lower back pain was assessed in one systematic review (Quinn et al, 2006; AMSTAR score 5/10), as summarised in Table 91.

Quinn et al (2006) examined the effectiveness of complementary and alternative medicine for the management of lower back pain. The systematic review did not identify any Level II, Level III-1 or Level III-2 studies that compared homeopathy to placebo. However, one high-quality Level II study (Stam et al, 2001) was identified which assessed the effect of a homeopathic gel in patients with lower back pain in comparison to a 'standard' capsicum-based product. The study reported that "both products (were) equally effective but homeopathic gel had less adverse effects". Overall, Quinn et al (2006) concluded that "while RCTs for those therapies which were investigated produced encouraging results, small sample sizes and the low number of trials investigating individual therapies prevents definite conclusions being drawn".

*Reviewer comments*

*Although Quinn et al (2006) indicated that the study by Stam et al (2001) was of high methodological quality, the effectiveness of the comparator (capsicum-based product, Cremor Capsici Compositus) is unclear and thus the finding of "equal effectiveness" should be interpreted with caution. Consequently, it is difficult to draw a conclusion about the effectiveness of homeopathy for lower back pain without a randomised, placebo-controlled trial.*

*Evidence statement*

One systematic review (2006) did not identify any prospectively designed and controlled studies that assessed the effectiveness of homeopathy compared with placebo for the treatment of people with lower back pain.

One systematic review of poor quality identified one medium-sized randomised controlled trial (good quality; 161 participants) that compared homeopathy (*Spiroflor SRL*) with Cremor Capsici Compositus for the treatment of people with lower back pain.

This study did not detect a difference between homeopathy and Cremor Capsici Compositus in the treatment of people with lower back pain and concluded that the products were equally effective. LOC: Low - moderate.

Based on one medium-sized good quality study there is some evidence that homeopathy is as effective as Cremor Capsici Compositus (a capsicum based product) for the treatment of people with lower back pain.

However, the effectiveness of Cremor Capsici Compositus for the treatment of people with lower back pain is unclear, and it is likely that the study was not sufficiently large to demonstrate 'equal effectiveness'. In addition, no placebo controlled studies were identified. Further, the findings of this study have not been confirmed by other good quality, sufficiently sized studies.

Based on the body of evidence evaluated in this review there is no reliable evidence on which to draw a conclusion about the effectiveness of homeopathy for the treatment of people with lower back pain.

**Table 91 Evidence summary table: the effectiveness of homeopathy for the treatment of lower back pain**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Quinn et al (2006)<br>[Level I]<br>AMSTAR: 5/10<br><br>SR of CAM for pain | Stam et al (2001)<br>[Level II]<br>Quality: high[d]<br>N=161 | Not reported. Assumed to be patients with lower back pain | Homeopathic gel (Spiroflor SRL) | Standard Capsicum-based product (*Cremor Capsici Compositus*) | VAS for pain<br>Paracetamol use<br>Sleep disturbance<br>Absence from work<br>Patient and general practitioner satisfaction<br>Presence of adverse effects | "Both products equally effective but homeopathic gel had less adverse effects". | "While RCTs for those therapies which were investigated produced encouraging results, including yoga, homeopathy, herbal therapies, and hypnotherapy, small sample sizes and the low number of trials investigating individual therapies prevents definite conclusions being drawn." |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; SR, systematic review; SRL, undefined. This is the name of the homeopathic gel; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Study quality as assessed using the van Tulder methodological quality criterion.

### 4.18.3 Pain in dental practice

The effectiveness of homeopathy for the treatment of patients with pain in dental practice was assessed in two systematic reviews (Linde and Melchart, 1998; Raak et al, 2012). In total, the systematic reviews included five Level II studies as summarised in Table 92 and Table 93.

**Table 92 Matrix indicating the studies that were included in the systematic reviews of pain in dental practice**

| | | Systematic review | |
|---|---|---|---|
| | | **Raak et al (2012) [Level I]** | **Linde and Melchart (1998) [Level I]** |
| **Study ID** | **Sardella (2008) [Level II]** | ✓ | |
| | **Rafai (2004) [Level II]** | ✓ | |
| | **Lökken et al (1995) [Level II]** | ✓ | ✓ |
| | **Albertini (1984) [Level II]** | ✓ | |
| | **Bendre (1980) [Level II]** | ✓ | |

Raak et al (2012) (AMSTAR score of 7/11) performed a systematic review of the literature on the use of homeopathic *Hypericum perforatum* (St John's Wort) for pain conditions in dental practice. The results of five Level II studies were included in their analysis, many of which examined the use of *Hypericum perforatum* in combination with homeopathic *Arnica*. Three studies were rated as weak in quality (Albertini, 1984; Bendre, 1980; Lökken et al, 1995), one was rated as strong in quality (Rafai, 2004) and the quality of one Level II study was not specified (Sardella, 2008). Raak et al (2012) noted that a major limitation of the included studies was that they were "highly likely" to be confounded, mostly by the use of *Arnica*.

Sardella (2008) was a Level II study that examined the effect of homeopathic *Hypericum perforatum* in patients with burning mouth syndrome. The study reported no significant difference in pain relief between the homeopathy and placebo groups; however, the number of sites with reported burning sensation was "reduced significantly". It was unclear from the systematic review whether the reduction referred to a significant difference in the homeopathy group compared to placebo or baseline. Rafai (2004) was a study of homeopathic *Hypericum perforatum* with *Arnica* in patients with trismus and postoperative pain after third molar surgery. Lökken et al (1995) examined the effect of homeopathic treatment (homeopathic *Hypericum perforatum* with *Arnica*) in patients with postoperative pain and other inflammatory events after bilateral oral surgery. Neither of the Level II studies reported a significant difference between homeopathy and placebo for any of the primary outcomes. Lökken et al (1995) noted, however, that treatment "tended to improve ability to open mouth". Albertini (1984) reported "significant improvements (in pain reduction) after Day 2" in patients with dental neuropathic pain. Similarly, Bendre (1980) observed that 93% of patients with pain following tooth extraction showed significant improvements in pain relief and swelling after 48

hours. In both Level II studies, it was unclear if the significant effect was in favour of homeopathic *Hypericum perforatum* and *Arnica* or placebo.

Raak et al (2012) conducted a meta-analysis of the results from four of the included Level II studies (Albertini, 1984; Bendre, 1980; Lökken et al, 1995; Rafai, 2004). The study found no statistically significant difference in dental pain between homeopathic *Hypericum perforatum* and placebo, but the effect slightly favoured homeopathy (RR 0.24; 95% CI 0.06, 1.03). The authors also noted that the meta-analysis was highly heterogeneous ($I^2$=0.89). Importantly, at the time of the systematic review there were no properly conducted Level II studies that had tested the effect of *Hypericum perforatum* alone. In addition to the studies discussed above, Raak et al (2012) examined case reports that suggested a therapeutic effect of *Hypericum perforatum*; however, the results were usually confounded by *Arnica*. Overall, the authors concluded that "evidence from RCTs does not support the use of *Hypericum perforatum* alone, for pain conditions in dental care". In addition, "the use of *Hypericum perforatum* is currently not adequately supported by properly conducted clinical trials with *Hypericum perforatum* alone".

Linde and Melchart (1998) (AMSTAR score 8/11) also conducted a systematic review of the efficacy of individualised homeopathy across a range of clinical conditions, including pain after oral surgery. The same Level II study by Lökken et al (1995) was identified that compared treatment preference, pain, swelling and bleeding in patients treated with homeopathy and placebo in a cross-over design. Although swelling favoured homeopathy, treatment preference favoured placebo. None of the differences were reported to be statistically significant. Linde and Melchart (1998) stated that the trial was rigorous in terms of methodology; however, it was thought to have an "artificial study model" due to an unusually high frequency of remedy application. Overall, the authors of the systematic review concluded that, across all clinical conditions, any evidence suggesting that homeopathy has an effect over placebo is "not convincing because of methodological shortcomings and inconsistencies".

*Evidence statement*

Two systematic reviews of medium quality identified five randomised controlled trials (poor to good quality; total of 364 participants, range: 24-200) that compared homeopathy with placebo for the treatment of people with pain in dental practice. LOC: Very low - low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with pain in dental practice.

**Table 93 Evidence summary table: the effectiveness of homeopathy for the treatment of pain in dental practice**

| Study ID Level of evidence[a] Quality[b] | Included study Level of evidence[a] Quality[c] Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Raak et al (2012) [Level I] AMSTAR: 7/11<br><br>SR of homeopathy for pain | Sardella (2008) [Level II] Quality not specified N=39 | Patients with burning mouth syndrome | 300mg capsules containing *H. perforatum* extract (hypericin 0.31% and hyperforin 3.0%) three times a day for 12 weeks | Placebo | Pain relief | No significant results | "The use of *Hypericum perforatum* is currently not adequately supported by properly conducted clinical trials with *Hypericum perforatum* alone" |
| | | | | | Number of sites with reported burning sensation | "Reduced significantly" (unclear whether vs placebo or baseline) | |
| | Rafai (2004) [Level II] Quality: strong N=41 | Patients with trismus and postoperative pain after third molar surgery | 3+3 globuli of *Arnica/Hypericum* D30 before surgery and continued for 5 postoperative days | Placebo | Reduction of trismus | No significant results | |
| | | | | | Pain relief | No significant results | |
| | Lökken et al (1995) [Level II] Quality: weak N=24 | Patients with postoperative pain and other inflammatory events after bilateral oral surgery | 3 globuli of *Arnica/Hypericum* D30, 3 hours after tooth extraction and 2 doses before bedtime and the morning after | Placebo | Pain relief | No significant results | |
| | | | | | Swelling | No significant results, but treatment tended to improve ability to open mouth | |
| | | | | | Postoperative bleeding | No significant results | |
| | Albertini (1984) [Level II] Quality: weak N=60 | Patients with dental neuropathic pain | 4+4 granula of *Arnica/Hypericum* directly after the visit and for 2 days | Placebo | Pain reduction | "Significant improvements after Day 2" | |
| | Bendre (1980) [Level II] Quality: weak N=200 | Patients with post extraction pain and swelling | 4 globuli of *Arnica/Hypericum* directly after tooth extraction and 15 minutes later | Placebo | Pain relief and swelling (not reported separately) | "93% of patients showed significant improvements in pain relief and swelling after 48 hours" | |
| Linde and | Lökken et al | Patients with pain after | Best-fitting simillimum | Placebo | Treatment | "No significant differences". | "Rigorous trial; |

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Melchart (1998)<br>[Level I]<br>AMSTAR: 8/11<br><br>SR of homeopathy for multiple conditions | (1995)[d]<br>[Level II]<br>Quality: 5, 5.5[e]<br>N=24 | oral surgery (83% female; age 19 to 28 years) | from 6 predefined remedies in D30 given according to a fixed scheme (highly repetitive) | | preference (cross-over design) | 11 patients preferred homeopathy; 13 preferred placebo.<br>Rate ratio (95% CI): 0.85 (0.48, 1.50) | uncommonly high frequency of remedy application; rather artificial study model" |
| | | | | | Pain | "Pain similar in both groups" | |
| | | | | | Bleeding | "Bleeding similar in both groups" | |
| | | | | | Swelling | "Less swelling in homeopathy group" | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; D, decimal; SR, systematic review; SRL, undefined. This is the name of the homeopathic gel; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] The date of the publication was reported as 1994 in the systematic review by Linde and Melchart (1998); however the evidence reviewer believes that it was a typing error and has referred to the study as "Lökken et al (1995)".

[e] Quality was assessed using two measures: (i) Jadad score, out of five; (ii) internal validity score, out of six.

### 4.18.4 Pain following orthopaedic surgery

The effectiveness of homeopathy for the treatment of patients with pain was assessed in one systematic review (Roberts et al, 2012; AMSTAR score 7/10), as summarised in Table 94.

The aim of the systematic review by Roberts et al (2012) was "to determine which analgesic modalities used following discharge, have the greatest efficacy in reducing postoperative pain after elective non-axial orthopaedic surgery". Three good-quality Level II studies examining the effect of homeopathic *Arnica* in patients undergoing either knee procedures or carpal tunnel release procedures were identified (Brinkhaus et al, 2006; Jeffrey and Belcher 2002; Stevinson et al, 2003). None of the Level II studies reported a significant difference between homeopathy and placebo for the primary outcomes. However, Jeffrey and Belcher (2002) reported "reduced hand discomfort during Week 2 despite the use of higher potency *Arnica* and preoperative medication". Roberts et al (2012) concluded that "homeopathy is not an effective analgesic modality".

*Evidence statement*

One systematic review of medium quality identified three randomised controlled trials (good quality; total of 181 participants, range: 37-82) that compared homeopathy (*Arnica*) with placebo for the treatment of people with pain following orthopaedic surgery. LOC: Low.

Based on the body of evidence evaluated in this review homeopathy is not more effective than placebo for the treatment of people with pain following orthopaedic surgery.

**Table 94 Evidence summary table: the effectiveness of homeopathy for the treatment of pain following orthopaedic surgery**

| Study ID<br>Level of evidence[a]<br>Quality[b] | Included study<br>Level of evidence[a]<br>Quality[c]<br>Sample size | Patient population | Intervention | Comparator | Outcome | Results as reported in the systematic review | Systematic review interpretation |
|---|---|---|---|---|---|---|---|
| Roberts et al (2012)<br>[Level I]<br>AMSTAR: 7/10<br><br>SR of CAM for pain | Brinkhaus et al (2006)<br>[Level II]<br>Quality: 5/5[d]<br>N=82 | Patients undergoing knee procedures (cruciate ligament, or knee arthroscopy) | Homeopathic *Arnica* following knee surgery (cruciate ligament repair or knee arthroplasty) | Placebo | Pain reduction | No difference between the intervention and placebo groups | "Homeopathy is not an effective analgesic modality" |
| | Stevinson et al (2003)<br>[Level II]<br>Quality: 5/5[d]<br>N=62 | Patients undergoing carpal tunnel release procedures | *Arnica* 30C or *Arnica* 6C following elective carpal tunnel surgery, three times per day | Placebo | Pain reduction | No significant differences between intervention and placebo groups, although placebo group had less pain on Day 9 | |
| | Jeffrey and Belcher (2002)<br>[Level II]<br>Quality: 5/5[d]<br>N=37 | Patients undergoing carpal tunnel release procedures | *Arnica* D6 tablets and ointment following endoscopic carpal tunnel release (bilateral), three times per day | Placebo | Level of pain | "Reduced hand discomfort during Week 2 despite the use of higher potency *Arnica* and preoperative medication" | |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CAM, complementary and alternative medicines; C, centesimal; D, decimal; SR, systematic review; SRL, undefined. This is the name of the homeopathic gel; VAS, visual analogue scale.

[a] Level of evidence as assessed by the evidence reviewer.

[b] Study quality as assessed by the evidence reviewer using the AMSTAR measurement toolkit.

[c] Study quality as reported in the systematic review.

[d] Study quality as assessed using the Oxford Quality Score. The higher the quality score out of 5, the higher the quality of the study.

# 5 Discussion

## 5.1 Summary of main results

The 57 systematic reviews included for assessment in this Overview Report examined the evidence on homeopathy for a total of 68 clinical conditions. The relevant reviews tended to have one of three main objectives (i) to review a variety of CAM, including homeopathy, for the treatment of a particular clinical condition or specific clinical area; (ii) to review homeopathy for the treatment of one clinical condition; or (iii) to review homeopathy for the treatment of a variety of clinical conditions. Of the 68 clinical conditions included in this overview, seven were the subject of systematic reviews that identified no relevant primary studies (glaucoma, children with constipation, nocturnal enuresis, men with lower urinary tract symptoms, personality disorder, dementia and chronic facial pain). Consequently, no concluding statement about the efficacy of homeopathy for these specific conditions could be made.

For the remaining 61 clinical conditions, the evidence-base concerning the efficacy of homeopathy comes from many poorly designed, conducted, and reported primary studies. Importantly, for 31 clinical conditions, the evidence base consists of only one Level II or Level III-2 study. In 36 of the 61 conditions, the total number of participants included in the trial(s) was less than 150; therefore, the evidence base for the majority of clinical conditions was considered of insufficient size to enable clear conclusions on the efficacy of homeopathy to be drawn. Of the remaining 25 clinical conditions, there were 15 conditions for which the total number of participants included in the trial(s) was between 150 and 499, and 10 conditions for which the evidence base collectively comprised 500 or more participants.

The paucity of good quality primary studies, the preponderance of studies with small sample size and insufficient power, and the lack of replication of results in multiple studies made the interpretation of apparent ‘significant’ differences in favour of homeopathy over placebo difficult. Many studies also failed to use (or report) appropriate comparators, blinding, or randomization, all of which would be necessary to permit a high level of confidence in the outcomes reported. Accordingly, in rating the body of evidence, the overall shortcomings of the primary evidence limited the ability of the evidence review team to draw conclusions as to the efficacy of homeopathy for many of the clinical conditions included in this overview.

## 5.2 Overall completeness and quality of evidence

All of the systematic reviews included in this overview contained limitations that affected the ability of the evidence reviewer to evaluate the evidence. These limitations stemmed from the variable quality of the primary study data as well as the quality of the systematic reviews themselves. In general, the evidence base for homeopathy is not of high quality. Many of the individual studies were poorly designed, conducted and reported. In addition, most of the individual studies were small in size and likely to be insufficiently powered to detect a statistically significant outcome.

In primary studies that examined the effectiveness of homeopathy compared to non-placebo comparators, the small number of participants included in the trials is of particular concern. A number of the studies interpreted a lack of difference between the two treatment arms as “equivalence” between homeopathy and the non-placebo comparator, or stated that homeopathy was “as effective” as the other therapy. It is highly likely that the studies were underpowered and

could not have demonstrated “equivalence” between treatments. As a result, claims of equivalence must be interpreted with caution. Because of the shortcomings within the primary studies, the overall completeness and quality of the systematic reviews was also limited.

Several systematic reviews were identified that examined the effectiveness of homeopathy for multiple clinical conditions as described in Section 4.2. In some of these reviews, an overall conclusion was often drawn instead of specific conclusions for each clinical condition. Other systematic reviews were broad reviews of various CAM, including homeopathy, for the treatment of a particular clinical condition or specific clinical area. In these cases, the level of detail provided on the homeopathy studies was often limited. Some systematic reviews (Cucherat et al 2000; Linde et al 1997; Linde and Melchart 1998) also performed a ‘mega’ meta-analysis of the effectiveness of homeopathy across clinical conditions, often without separate presentation of the meta-analysed results for the individual clinical conditions. The appropriateness of these meta-analyses is questionable as the included studies were highly heterogeneous in terms of the investigated clinical condition, study design, intervention, comparator, outcomes reported and overall quality.

Publication bias may also have impacted the findings of the evidence review. Although many of the systematic review authors acknowledged the risk of publication bias, very few attempted to quantify the likelihood that publication bias affected the overall evidence base (using graphical aids or statistical tests). Publication bias is a complex issue, particularly for therapies such as homeopathy. Journals of complementary and alternative medicines may be more likely to publish trials with positive findings, despite significant methodological flaws; whereas mainstream medical journals may tend to publish more rigorous trials with negative results. There is also the possibility that the mainstream journals would not publish homeopathy trials with negative results, as the publication of such trials could be perceived to be of little relevance or interest for the mainstream on the basis that the field of homeopathy as a whole has already been deemed to be inefficacious and unscientific (Barnes et al 1997). Indeed, in an investigation of 110 homeopathy trials, Shang et al (2005) noted that sources of heterogeneity included the language of publication (more beneficial effects in trials published in languages other than English), indexing in MEDLINE (more beneficial effects in trials not indexed in MEDLINE) and indicators of trial quality (more beneficial effects in trials of lower quality). Importantly, smaller trials and those of lower quality showed more beneficial treatment effect of homeopathy than larger and higher quality trials (Shang et al, 2005).

## 5.3 Limitations

Although the approach adopted in this overview of systematic reviews guarantees that the widest possible range of high-quality evidence is identified and included, it is limited by the quality of the included systematic reviews. Many of the systematic reviews inadequately reported the included trials and it was often difficult to ascertain details as to the length of follow up, the outcomes examined, and the statistical and clinical significance of the results. Indeed, the authors of the reviews often commented on the poor reporting and serious methodological flaws of the included studies. The quality assessment of included primary trials sometimes differed between systematic reviews making it difficult to determine if the apparent inadequacies of the systematic reviews were, in fact, shortcomings of the included trials or of the reviews themselves.

The evidence reviewer would argue that the overview process was limited by elements of poor reporting and flawed methodology in the primary studies, exacerbated by incomplete reporting in the systematic reviews. The classification of primary studies as Level II or Level III-2 studies also relied

on information reported in the systematic reviews. As a result of these limitations, the evidence reviewers did not place a "high" level of confidence in the evidence base for *any* clinical condition, and the majority of conditions were associated with "low" or "very low" levels of confidence.

The evidence reviewers acknowledge that a limitation to this overview was the assessment of 'effectiveness' based on statistical significance and not clinical significance. This was, however, necessary due to the poor reporting and lack of analyses by the included systematic reviews and primary studies. Without the reporting of intervention effects, decisions could not be made about the clinical importance of the intervention.

Another limitation was the process by which outcomes were aggregated in order to determine the overall effectiveness of homeopathy for each clinical condition. Ideally, the overview would have included one evidence statement for each outcome within each clinical condition. However, this was not possible due to the large number of outcomes and variable reporting of those outcomes between the different systematic reviews. As a result, outcomes were aggregated in order to formulate one evidence statement per clinical condition. It was also not possible to create a hierarchy of clinically relevant outcomes prior to conducting the overview because the clinical conditions that would ultimately be included in the Overview Report were not known. Although it would have been possible to prioritise outcomes post hoc, such a process would have been subject to bias and was therefore avoided. Consequently, all outcomes reported in the systematic reviews were taken into account when the evidence statements were formulated unless the HWC determined that a particular outcome had no clinical relevance.

Additionally, it was difficult for the evidence reviewer to compare the quality of primary studies that had been examined in different systematic reviews. This limitation stemmed from the fact that the systematic reviewers often used different scoring systems to rate the quality of the individual studies (e.g. risk of bias assessments vs Jadad scores). The various scoring systems are inherently different and likening a 'poor' quality trial based on one scoring system to a 'poor' quality trial based on another system is problematic. Nevertheless, the evidence reviewer felt that it was necessary to comment on the quality of the individual studies in the evidence statements and, as a result, various scoring systems have been used for the comparison of study quality.

A further limitation of the overview process is that no attempt was made to systematically identify any recent Level II studies that may not have been included in a systematic review, but met the inclusion criteria described in the primary clinical research question. An additional report was produced by the evidence reviewer that accompanies this Overview Report that considers the evidence from literature submitted to NHMRC in 2011 by the Australian Homoeopathy Association, the Australian Medical Fellowship of Homeopathy and members of the public that was not otherwise considered in the Overview Report. The 'Review of Submitted Literature' identified eight Level II studies and one Level III-2 study that were not included in the Overview Report. However, these studies remain a self-selected sample and other literature concerning the effectiveness of homeopathy for a specific clinical condition has not been systematically retrieved.

Due to the broad scope of the overview and the large number of clinical conditions identified, it was not possible to separate evidence for the different types of homeopathic regimens (clinical or individualized, practitioner-prescribed or self-prescribed) utilized in the primary studies. Details regarding the homeopathic interventions under investigation were often lacking in the systematic reviews. Similarly, comparators were generally not well described. Many primary studies investigated individualised homeopathy as the intervention. Whilst individualisation of therapy allows

homeopathy to be practiced in its traditional fashion, this increases the complexity of comparing outcomes and determining the efficacy of specific homeopathic regimens. Importantly, information regarding the nature of the consultation between patients and homeopaths (if any) was rarely provided. This is important as there is evidence for the therapeutic benefits of the consultation process on health outcomes in both conventional medicine and CAM (Brien et al 2011; Di Blasi et al 2002; Walach 2003), which draws into question the effectiveness of the homeopathic medicine *per se* as opposed to the interaction between patients and homeopaths.

Finally, the systematic reviews did not discuss the use of active comparators or provide a critique of whether or not the authors of the studies had chosen appropriate or clinically effective 'active' comparators. For example, homeopathy was compared with diazepam (Valium) as a treatment for depression (Heulluy 1985 in Pilkington et al 2005), 'standard care' included antibiotics and nasal sprays as a treatment of children with otitis media (Kruse 1998 in Bellavite et al 2011) and homeopathy was compared with chloroquine for the treatment of malaria (van Erp and Brands 1996 in Linde and Melchart 1998). A discussion regarding the appropriateness of these and other active comparators within the systematic reviews would have been beneficial in order to put the results for homeopathy in context.

## 5.4 Research Gaps

A major challenge in assessing the evidence and interpreting the results for this overview has been the paucity of good-quality primary studies that are of sufficient size to demonstrate the effectiveness of homeopathy for specific clinical conditions in humans.

If further primary research is conducted, investigators should endeavour to:

- Recruit substantially larger samples of patients and include statistical tests to demonstrate the significance of results
- Utilise blinding/double blinding methodology and randomised assignment of subjects to treatment groups
- Improve trial reporting and follow up (e.g. reporting of drop outs)
- Improve reporting of conflicts of interest
- Provide more detailed descriptions of interventions (including doses, dilutions), better descriptions of outcomes and how they were measured, and better discussion of potential confounders or bias
- Justify the use of active comparators and comment on the effectiveness of those comparators compared to placebo
- Use a methodological approach that can differentiate between the effect of homeopathic medicines and treatment by a homeopath (i.e. interaction at a consultation)

In addition, systematic reviewers should:

- Justify the pooling of results in meta-analyses and provide a detailed discussion of heterogeneity between the primary studies
- Adequately and accurately report study details including treatment regimens, length of follow up, outcomes studied and the clinical and statistical significance of results

# 6 Conclusion

There is a paucity of good-quality studies of sufficient size that examine the effectiveness of homeopathy as a treatment for any clinical condition in humans. The available evidence is not compelling and fails to demonstrate that homeopathy is an effective treatment for any of the reported clinical conditions in humans.

# 7 References

## 7.1 References – Systematic Reviews

### 7.1.1 Included reviews

Alraek T, Lee MS, Choi TY, Cao H, Liu J (2011) Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review. BMC Complement Altern Med 11:87.

Altunc U, Pittler MH, Ernst E (2007) Homeopathy for childhood and adolescence ailments: Systematic review of randomized clinical trials. Mayo Clin Proc 82(1):69-75.

Baranowsky J, Klose P, Musial F, Haeuser W, Dobos G, Langhorst J (2009) Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia. Rheumatol Int 30(1):1-21.

Barnes J, Resch KL, Ernst E (1997) Homeopathy for postoperative ileus?: A meta-analysis. J Clin Gastroenterol 25(4):628-33.

Bellavite P, Marzotto M, Chirumbolo S, Conforti A (2011) Advances in homeopathy and immunology: a review of clinical research. Front Biosci (Schol Ed) 3:1363-89.

Cooper KL, Relton C (2010) Homeopathy for insomnia: A systematic review of research evidence. Sleep Med Rev 14(5):329-37.

Cucherat M, Haugh MC, Gooch M, Boissel JP (2000) Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials. Eur J Clin Pharmacol 56(1):27-33.

Davidson JRT, Crawford C, Ives JA, Jonas WB (2011) Homeopathic treatments in psychiatry: A systematic review of randomized placebo-controlled studies. J Clin Psychiatry 72(6):795-805.

De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (2010) Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: A systematic review. Rheumatology (UK) 49(6):1063-8.

De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (2011) Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: A systematic review. Rheumatology (UK) 50(5):911-20.

Ernst E, Barnes J (1998) Are homoeopathic remedies effective for delayed-onset muscle soreness: a systematic review of placebo-controlled trials. Perfusion 11:4-8.

Ernst E, Pittler MH (1998) Efficacy of homeopathic Arnica: A systematic review of placebo- controlled clinical trials. Arch Surg 133(11):1187-90.

Ernst E (2011) Homeopathic Galphimia glauca for hay fever: A systematic review of randomised clinical trials and a critique of a published meta-analysis. Focus Altern Complement Ther 16(3):200-3.

Ernst E (2012) Homeopathy for eczema: A systematic review of controlled clinical trials. Br J Dermatol 166(6):1170-2.

Ernst E (2011) Homeopathy for insomnia and sleep-related disorders: A systematic review of randomised controlled trials. Focus Altern Complement Ther 16(3):195-9.

Heirs M, Dean ME (2007) Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane Database Syst Rev.

Holdcraft LC, Assefi N, Buchwald D (2003) Complementary and alternative medicine in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 17(4):667-83.

Huang T, Shu X, Huang YS, Cheuk DK (2011) Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 12:CD005230.

Kassab S, Cummings M, Berkovitz S, Van Haselen R, Fisher P (2011) Homeopathic medicines for adverse effects of cancer treatments. Cochrane Database Syst Rev(2).

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

Linde K (1998) Erratum. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 351(9097):220.

Linde K, Melchart D (1998) Randomized controlled trials of individualized homeopathy: a state-of-the-art review. J Altern Complement Med 4(4):371-88.

Long L, Ernst E (2001) Homeopathic remedies for the treatment of osteoarthritis: A systematic review. Br Homeopath J 90(1):37-43.

Loo SK, Tang WY (2009) Warts (non-genital). Clin Evid (Online) 2009.

Macfarlane GJ, El-Metwally A, De Silva V, Ernst E, Dowds GL, Moots RJ (2011) Evidence for the efficacy of complementary and alternative medicines in the management of rheumatoid arthritis: A systematic review. Rheumatology (UK) 50(9):1672-83.

Mathie RT, Frye J, Fisher P (2012) Homeopathic Oscillococcinum((R)) for preventing and treating influenza and influenza-like illness. Cochrane Database Syst Rev 12:CD001957.

McCarney R, Warner J, Fisher P, Van Haselen R (2009) Homeopathy for dementia. Cochrane Database Syst Rev(1):CD003803.

McCarney RW, Linde K, Lasserson TJ (2008) Homeopathy for chronic asthma. Cochrane Database Syst Rev(1):CD000353.

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

Mills E, Wu P, Ernst E (2005) Complementary therapies for the treatment of HIV: In search of the evidence. Int J STD AIDS 16(6):395-402.

Myers CD, White BA, Heft MW (2002) A review of complementary and alternative medicine use for treating chronic facial pain. J Am Dent Assoc 133(9):1189-96.

National Clinical Guideline Centre (UK). The management of lower urinary tract symptoms in men. London: Royal College of Physicians; 2010. (NICE Clinical Guidelines, No. 97).

National Collaborating Centre for Acute Care (UK). Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension. London: National Collaborating Centre for Acute Care; 2009 Apr. (NICE Clinical Guidelines, No. 85).

National Collaborating Centre for Mental Health (UK). Borderline personality disorder: treatment and management. Leicester: British Psychological Society; 2009. (NICE Clinical Guidelines, No. 78).

National Collaborating Centre for Nursing and Supportive Care (UK). Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. London: Royal College of Nursing; 2008 Feb. (NICE Clinical Guidelines, No. 61).

National Collaborating Centre for Women's and Children's Health (UK). Constipation in children and young people: diagnosis and management of idiopathic childhood constipation in primary and secondary care. London: RCOG Press; 2010. (NICE Clinical Guidelines, No. 99).

National Collaborating Centre for Women's and Children's Health (UK). Diarrhoea and Vomiting Caused by Gastroenteritis: Diagnosis, Assessment and Management in Children Younger than 5 Years. London: RCOG Press; 2009 Apr. (NICE Clinical Guidelines, No. 84).

National Collaborating Centre for Women's and Children's Health (UK). Surgical management of otitis media with effusion in children. London: RCOG Press; 2008 Feb. (NICE Clinical Guidelines, No. 60).

Oladapo OT, Fawole B (2012) Treatments for suppression of lactation. Cochrane Database Syst Rev.

Owen JM, Green BN (2004) Homeopathic treatment of headaches: a systematic review of the literature. J Chiropr Med 3(2):45-52.

Passalacqua G, Bousquet PJ, Carlsen KH, Kemp J, Lockey RF, Niggemann B, Pawankar R, Price D, Bousquet J (2006) ARIA update: I--Systematic review of complementary and alternative medicine for rhinitis and asthma. J Allergy Clin Immunol 117(5):1054-62.

Perry R, Terry R, Ernst E (2010) A systematic review of homoeopathy for the treatment of fibromyalgia. Clin Rheumatol 29(5):457-64.

Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J (2006) Homeopathy for anxiety and anxiety disorders: A systematic review of the research. Homeopathy 95(3):151-62.

Pilkington K, Kirkwood G, Rampes H, Fisher P, Richardson J (2005) Homeopathy for depression: A systematic review of the research evidence. Homeopathy 94(3):153-63.

Porter NS, Jason LA, Boulton A, Bothne N, Coleman B (2010) Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. J Altern Complement Med 16(3):235-49.

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

Raak C, Bussing A, Gassmann G, Boehm K, Ostermann T (2012) A systematic review and meta-analysis on the use of Hypericum perforatum (St. John's Wort) for pain conditions in dental practice. Homeopathy 101(4):204-10.

Rada G, Capurro D, Pantoja T, Corbalan J, Moreno G, Letelier LM, Vera C (2010) Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev 9:CD004923.

Reid S, Chalder T, Cleare A, Hotopf M, Wessely S (2011) Chronic fatigue syndrome. Clin Evid (Online) 2011 pii:1101.

Roberts M, Brodribb W, Mitchell G (2012) Reducing the Pain: A Systematic Review of Postdischarge Analgesia Following Elective Orthopedic Surgery. Pain Med 13(5):711-27.

Sarris J, Byrne GJ (2011) A systematic review of insomnia and complementary medicine. Sleep Med Rev 15(2):99-106.

Simonart T, Kabagabo C, De Maertelaer V (2011) Homoeopathic remedies in dermatology: A systematic review of controlled clinical trials . Br J Dermatol 165(4):897-905.

Simonart T, De Maertelaer V (2012) Systemic treatments for cutaneous warts: A systematic review. J Dermatol Treat 23(1):72-7.

Smith CA (2010) Homoeopathy for induction of labour. Cochrane Database Syst Rev(4):CD003399.

Stevinson C, Ernst E (2001) Complementary/alternative therapies for premenstrual syndrome: A systematic review of randomized controlled trials. Am J Obstet Gynecol 185(1):227-35.

Tabbers MM, Boluyt N, Berger MY, Benninga MA (2011) Nonpharmacologic treatments for childhood constipation: Systematic review. Pediatrics 128(4):753-61.

Turnbull N, Shaw EJ, Baker R, Dunsdon S, Costin N, Britton G, Kuntze S, Norman R (2007). Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children. London: Royal College of General Practitioners.

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(3):142-55.

### 7.1.2 Excluded reviews

Barnes J (1998) Complementary medicine homoeopathy. Pharm J 260(6988):492-7.
Notes: Full text review. Excluded. Wrong publication type

Becker C, Gottschling S, Graf N, Ludtke R (2007) Homeopathic remedies for preventing recurrent acute respiratory tract infections in children. Cochrane Database Syst Rev(1).
Notes: Full text review. Excluded. Wrong publication type

Bellavite P, Ortolani R, Pontarollo F, Piasere V, Benato G, Conforti A (2006) Immunology and homeopathy. 4: Clinical studies - part 1 (Provisional abstract). Evidence Based Complementary and Alternative Medicine 3:293-301.
Notes: Full text review. Excluded. Superseded publication

Benveniste J (1998) Meta-analysis of homoeopathy trials. Lancet 351(9099):367.
Notes: Full text review. Excluded. Wrong publication type

Bloom BS, Retbi A, Dahan S, Jonsson E (2000) Evaluation of randomized controlled trials on complementary and alternative medicine. Int J Technol Assess Health Care 16(1):13-21.
Notes: Full text review. Excluded. Wrong intervention

Bobak M, Donald A (1998) Meta-analysis of homoeopathy trials. Lancet 351(9099):368.
Notes: Full text review. Excluded. Wrong publication type

Bornhoft G, Wolf U, Von Ammon K, Righetti M, Maxion-Bergemann S, Baumgartner S, Thurneysen A, Matthiessen PF (2006) Effectiveness, safety and cost-effectiveness of homeopathy in general practice - Summarized health technology assessment. Forsch Komplementarmed 13(SUPPL. 2):19-29.
Notes: Full text review. Excluded. Wrong publication type

Carpenter JS, Neal JG (2005) Other complementary and alternative medicine modalities: acupuncture, magnets, reflexology, and homeopathy. Am J Med 118 Suppl 12B:109-17.
Notes: Full text review. Excluded. Wrong publication type

Caulfield T, DeBow S (2008) Erratum: A systematic review of how homeopathy is represented in conventional and CAM peer reviewed journals (BMC Complementary and Alternative Medicine). BMC Complement Altern Med 8.
Notes: Full text review. Excluded. Wrong outcomes

Centre for Public Health Excellence at NICE (UK). Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children. London: National Institute for Health and Clinical Excellence; 2006 Dec. (NICE Clinical Guidelines, No. 43).
Notes: Full text review. Excluded. Wrong publication type

Coulter MK, Dean ME (2007) Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. Cochrane Database Syst Rev(4):CD005648.
Notes: Full text review. Excluded. Superseded publication

Dalacorte RR, Rigo JC, Dalacorte A (2011) Pain management in the elderly at the end of life. North Am J Med Sci 3(8):348-54.
Notes: Full text review. Excluded. Wrong intervention

Daniele C, Mazzanti G, Pittler MH, Ernst E (2006) Adverse event profile of Crataegus spp.: A systematic review. Drug Saf 29(6):523-35.
Notes: Full text review. Excluded. Wrong intervention

Dantas F, Fisher P, Walach H, Wieland F, Rastogi DP, Teixeira H, Koster D, Jansen JP, Eizayaga J, Alvarez MEP, Marim M, Belon P, Weckx LLM (2007) A systematic review of the quality of homeopathic pathogenetic trials published from 1945 to 1995. Homeopathy 96(1):4-16.
Notes: Full text review. Excluded. Wrong outcomes

Dantas F, Rampes H (2000) Do homeopathic medicines provoke adverse effects? A systematic review. Br Homeopath J 89(SUPPL. 1):S35-S38.
Notes: Full text review. Excluded. Wrong publication type

Ernst E (2002) A systematic review of systematic reviews of homeopathy. Br J Clin Pharmacol 54(6):577-82.
Notes: Full text review. Excluded. Wrong publication type

Ernst E (1999) Classical homoeopathy versus conventional treatments: a systematic review (Structured abstract). Perfusion 12:13-5.
Notes: Full text review. Excluded. Wrong publication type

Ernst E, Posadzki P, Lee MS (2011) Complementary and alternative medicine (CAM) for sexual dysfunction and erectile dysfunction in older men and women: An overview of systematic reviews. Maturitas 70(1):37-41.
Notes: Full text review. Excluded. Wrong publication type

Ernst E, Pittler MH, Stevinson C (2002) Complementary/alternative medicine in dermatology: Evidence-assessed efficacy of two diseases and two treatments. Am J Clin Dermatol 3(5):341-8.
Notes: Full text review. Excluded. Wrong publication type

Ernst E (1999) Homeopathic prophylaxis of headaches and migraine? A systematic review. J Pain Symptom Manage 18(5):353-7.
Notes: Full text review. Excluded. Wrong outcomes

Ernst E (2010) Homeopathy: What does the "best" evidence tell us? Med J Aust 192(8):458-60.
Notes: Full text review. Excluded. Wrong publication type

Ernst E, Schmidt K (2004) Homotoxicology - A review of randomised clinical trials. Eur J Clin Pharmacol 60(5):299-306.
Notes: Full text review. Excluded. Wrong intervention

Ernst E, Pittler MH (2000) Re-analysis of previous meta-analysis of clinical trials of homeopathy. J Clin Epidemiol 53(11):1188.
Notes: Full text review. Excluded. Wrong publication type

Ernst E (2003) Serious adverse effects of unconventional therapies for children and adolescents: A systematic review of recent evidence. Eur J Pediatr 162(2):72-80.
Notes: Full text review. Excluded. Wrong publication type

Ernst E (2010) Systematic reviews of RCTs in homeopathy: Systematic reviews conclusively show that homeopathic remedies are placebos. Focus Altern Complement Ther 15(2):107-8.
Notes: Full text review. Excluded. Wrong publication type

Ernst E (2000) The usage of complementary therapies by dermatological patients: A systematic review. Br J Dermatol 142(5):857-61.
Notes: Full text review. Excluded. Wrong publication type

Fisher P, Berman B, Davidson J, Reilly D, Thompson T (2005) Are the clinical effects of homoeopathy placebo effects? Lancet 366(9503):2082-3.
Notes: Full text review. Excluded. Wrong publication type

Fisher P (2008) Meta-analyses of homoeopathy trials. Lancet 371(9617):985.
Notes: Full text review. Excluded. Wrong publication type

Fritts M, Crawford CC, Quibell D, Gupta A, Jonas WB, Coulter I, Andrade SA (2008) Traditional Indian medicine and homeopathy for HIV/AIDS: a review of the literature. AIDS Res Ther 5:25.
Notes: Full text review. Excluded. Wrong publication type

Gagnier JJ, Van Tulder MW, Berman B, Bombardier C (2007) Herbal medicine for low back pain: A cochrane review. Spine 32(1):82-92.
Notes: Full text review. Excluded. Wrong intervention

Glazener CM, Evans JH, Cheuk DK (2005) Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database Syst Rev(2):CD005230.
Notes: Full text review. Excluded. Superseded publication

Grabia S, Ernst E (2003) Homeopathic aggravations: A systematic review of randomised, placebo-controlled clinical trials. Homeopathy 92(2):92-8.
Notes: Full text review. Excluded. Wrong outcomes

Gyorik SA, Brutsche MH (2004) Complementary and alternative medicine for bronchial asthma: Is there new evidence? Curr Opin Pulm Med 10(1):37-43.
Notes: Full text review. Excluded. Wrong publication type

Hayes M, Buckley D, Judkins DZ, Lo V (2007) Clinical inquiries. Are any alternative therapies effective in treating asthma? J Fam Pract 56(5):385-7.
Notes: Full text review. Excluded. Wrong publication type

Hoare C, Li Wan PA, Williams H (2000) Systematic review of treatments for atopic eczema. Health Technol Assess 4(37):1-191.
Notes: Full text review. Excluded. Wrong publication type

Hunt K, Ernst E (2011) The evidence-base for complementary medicine in children: A critical overview of systematic reviews. Arch Dis Child 96(8):769-76.
Notes: Full text review. Excluded. Wrong publication type

Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D (2003) Homeopathy for childhood diarrhea: Combined results and metaanalysis from three randomized, controlled clinical trials. Pediatr Infect Dis J 22(3):229-34.
Notes: Full text review. Excluded. Wrong publication type

Joos S (2011) Review on efficacy and health services research studies of complementary and alternative medicine in inflammatory bowel disease. Chin J Integr Med 17(6):403-9.
Notes: Full text review. Excluded. Wrong publication type

Jorm AF, Christensen H, Griffiths KM, Parslow RA, Rodgers B, Blewitt KA (2004) Effectiveness of complementary and self-help treatments for anxiety disorders. Med J Aust 181(7 SUPPL.):S29-S46.
Notes: Full text review. Excluded. Did not provide appraisal of primary studies (criterion 7 of AMSTAR)

Kahn MF (1998) Meta-analysis of homoeopathy trials. Lancet 351(9099):365-8.
Notes: Full text review. Excluded. Wrong publication type

Karkos PD, Leong SC, Arya AK, Papouliakos SM, Apostolidou MT, Issing WJ (2007) 'Complementary ENT': A systematic review of commonly used supplements. J Laryngol Otol 121(8):779-82.
Notes: Full text review. Excluded. Wrong intervention

Keen D, Hadijikoumi I (2008) ADHD in children and adolescents. Clin Evid (Online) 2008.
Notes: Full text review. Excluded. Superseded publication

Keen D, Hadijikoumi I (2011) ADHD in children and adolescents. Clin Evid (Online) 2011.
Notes: Full text review. Excluded. Wrong publication type

Koch A (1998) Meta-analysis of homoeopathy trials. Lancet 351(9099):366-7.
Notes: Full text review. Excluded. Wrong publication type

Kronenberg F, Fugh-Berman A (2002) Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann Intern Med 137(10):805-13.
Notes: Full text review. Excluded. Wrong intervention

Levin C, Maibach H (2002) Exploration of "alternative" and "natural" drugs in dermatology. Arch Dermatol 138(2):207-11.
Notes: Full text review. Excluded. Wrong publication type

Linde K, Jonas W (2005) Are the clinical effects of homoeopathy placebo effects? Lancet 366(9503):2081-2.
Notes: Full text review. Excluded. Wrong publication type

Linde K, Jobst KA (2000) Homeopathy for chronic asthma . Cochrane Database Syst Rev(2):CD000353.
Notes: Full text review. Excluded. Superseded publication

Linde K, Willich SN (2003) How objective are systematic reviews? Differences between reviews on complementary medicine. J R Soc Med 96(1):17-22.
Notes: Full text review. Excluded. Wrong outcomes

Linde K, Scholz M, Ramirez G, Clausius N, Melchart D, Jonas WB (1999) Impact of study quality on outcome in placebo-controlled trials of homeopathy. J Clin Epidemiol 52(7):631-6.
Notes: Full text review. Excluded. Wrong outcomes

Linde K (1999) Proof of the effectiveness of homeopathic drugs. Dtsch Med Wochenschr 124(41):1221-3.
Notes: Full text review. Excluded. Wrong publication type

Linde K, Hondras M, Vickers A, Ter Riet G, Melchart D (2001) Systematic reviews of complementary therapies - an annotated bibliography. Part 3: homeopathy. BMC Complement Altern Med 1:4.
Notes: Full text review. Excluded. Wrong publication type

Linde K (2006) Updating Systematic Reviews. Explor J Sci Heal 2(4):363-4.
Notes: Full text review. Excluded. Wrong publication type

Ludtke R, Rutten ALB (2008) The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. J Clin Epidemiol 61(12):1197-204.
Notes: Full text review. Excluded. Wrong publication type

Maclennan AH (2009) Evidence-based review of therapies at the menopause. Int J Evid Based Healthc 7(2):112-23.
Notes: Full text review. Excluded. Wrong publication type

Mascarenhas AR, Seebold JA, Cundy WJ, McGuire T, van-Driel ML (2011) Homeopathic remedies for preventing and treating acute respiratory tract infections in children. Cochrane Database Syst Rev.
Notes: Full text review. Excluded. Wrong publication type

Mathie RT (2003) The research evidence base for homeopathy: a fresh assessment of the literature. Homeopathy 92(2):84-91.
Notes: Full text review. Excluded. Did not provide appraisal of primary studies (criterion 7 of AMSTAR)

Mathie RT, Fisher P (2007) Homeopathy is safe and does not lack positive evidence in clinical trials. Br J Clin Pharmacol 64(3):396-7.
Notes: Full text review. Excluded. Wrong publication type

Mathie RT (2010) Systematic reviews of RCTs in homeopathy A focused appraisal. Focus Altern Complement Ther 15(2):104-6.
Notes: Full text review. Excluded. Wrong publication type

McCarney RW, Lasserson TJ, Linde K, Brinkhaus B (2004) An overview of two Cochrane systematic reviews of complementary treatments for chronic asthma: Acupuncture and homeopathy. Respir Med 98(8):687-96.
Notes: Full text review. Excluded. Wrong publication type

McConeghy KW, Mikolich DJ, LaPlante KL (2009) Agents for the decolonization of methicillin-resistant Staphylococcus aureus. Pharmacotherapy 29(3):263-80.
Notes: Full text review. Excluded. Wrong intervention

Munar A, Gamboa OA, Ortiz NI (2007) Homeopathy for osteoarthritis. Cochrane Database Syst Rev(1).
Notes: Full text review. Excluded. Wrong publication type

Nai-Ming L, Yuk-Ming WT (2007) Warts (non-genital). Clin Evid (Online) 2007.
Notes: Full text review. Excluded. Superseded publication

National Clinical Guideline Centre (UK). Nocturnal enuresis. London: Royal College of Physicians; 2010. (NICE Clinical Guidelines, No. 111).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Cancer (UK). Advanced breast cancer: diagnosis and treatment. Cardiff (UK): National Collaborating Centre for Cancer; 2009 Feb. (NICE Clinical Guidelines, No. 81).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Cancer (UK). Early and locally advanced breast cancer: diagnosis and treatment. Cardiff (UK): National Collaborating Centre for Cancer; 2009 Feb. (NICE Clinical Guidelines, No. 80).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Chronic Conditions (UK). Chronic heart failure. London: Royal College of Physicians; 2003. (NICE Clinical Guidelines, No. 5).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Chronic Conditions (UK). Multiple sclerosis. London: Royal College of Physicians; 2004. (NICE Clinical Guidelines, No. 8).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Chronic Conditions (UK). Rheumatoid arthritis: national clinical guideline for management and treatment in adults. London: Royal College of Physicians; 2009 Feb. (NICE Clinical Guidelines, No. 79).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Mental Health (UK). Generalised anxiety disorder in adults: management in primary, secondary and community care. Leicester (UK): British Psychological Society; 2011. (NICE Clinical Guidelines, No. 113).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Mental Health (UK). Obsessive-compulsive disorder: core intervention in the treatment of obsessive compulsive disorder and body dysmorphic disorder. Leicester (UK): British Psychological Society; 2006. (NICE Clinical Guidelines, No. 31).
Notes: Full text review. Excluded. Wrong publication type

National Collaborating Centre for Mental Health (UK). Psychosis with coexisting substance misuse. Leicester (UK): British Psychological Society; 2011. (NICE Clinical Guidelines, No. 120).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Primary Care (UK). Postnatal care: routine postnatal care of women and their babies. London: Royal College of General Practitioners; 2006 Jul. (NICE Clinical Guidelines, No. 37).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Women's and Children's Health (UK). Antenatal care. London: Royal College of Obstetricians and Gynaecologists Press; 2008 Mar. (NICE Clinical Guidelines, No. 62).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Women's and Children's Health (UK). Atopic eczema in children. London: Royal College of Obstetricians and Gynaecologists Press; 2007 Dec. (NICE Clinical Guidelines, No. 57).
Notes: Full text review. Excluded. Wrong publication type

National Collaborating Centre for Women's and Children's Health (UK). Caesarean section. London: Royal College of Obstetricians and Gynaecologists Press; 2011 Nov. (NICE Clinical Guidelines, No. 132).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Women's and Children's Health (UK). Fertility: assessment and treatment for people with fertility problems. London: Royal College of Obstetricians and Gynaecologists Press; 2004 Feb. (NICE Clinical Guidelines, No. 11).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Women's and Children's Health (UK). Induction of labour. London: Royal College of Obstetricians and Gynaecologists Press; 2008 Jul. (NICE Clinical Guidelines, No. 70). Notes: Full text review. Excluded. Wrong publication type

National Collaborating Centre for Women's and Children's Health (UK). Intrapartum care: care of healthy women and their babies during childbirth. London: Royal College of Obstetricians and Gynaecologists Press; 2007 Sept. (NICE Clinical Guidelines, No. 55).
Notes: Full text review. Excluded. Wrong intervention

National Collaborating Centre for Women's and Children's Health (UK). Neonatal jaundice. London: Royal College of Obstetricians and Gynaecologists Press; 2010 May. (NICE Clinical Guidelines, No. 98).
Notes: Full text review. Excluded. Wrong publication type

Paterson C (1998) Meta-analysis of homoeopathy trials. Lancet 351(9099):365-6.
Notes: Full text review. Excluded. Wrong publication type

Peckham EJ, -Nelson-E-Andrea, Greenhalgh J, Cooper K, Roberts ER, Agrawal A (2012) Homeopathy for treatment of irritable bowel syndrome. Cochrane Database Syst Rev.
Notes: Full text review. Excluded. Wrong publication type

Pilkington K (2007) Searching for CAM evidence: An evaluation of therapy-specific search strategies. J Altern Complement Med 13(4):451-9.
Notes: Full text review. Excluded. Wrong outcomes

Pittler MH, Ernst E (2005) Complementary therapies for reducing body weight: A systematic review. Int J Obes 29(9):1030-8.
Notes: Full text review. Excluded. Wrong outcomes

Posadzki P, Alotaibi A, Ernst E (2012) Adverse effects of homeopathy: A systematic review of published case reports and case series. Int J Clin Pract 66(12):1178-88.
Notes: Full text review. Excluded. Wrong publication type

Posadzki P, Lee MS, Ernst E (2012) Complementary and alternative medicine for diabetes mellitus: An overview of systematic reviews. Focus Altern Complement Ther 17(3):142-8.
Notes: Full text review. Excluded. Wrong publication type

Rao AM, Fitzgerald-James EF, Ahmed I (2011) Role of homeopathic medicines in prevention and treatment of paralytic ileus. Cochrane Database Syst Rev.
Notes: Full text review. Excluded. Wrong publication type

Reid SF, Chalder T, Cleare A, Hotopf M, Wessely S (2008) Chronic fatigue syndrome. Clin Evid (Online) 2008.
Notes: Full text review. Excluded. Superseded publication

Reznik M, Ozuah PO (2005) CAM in the treatment of paediatric asthma. Focus Altern Complement Ther 10(3):177-80.
Notes: Full text review. Excluded. Wrong publication type

Robinson L, Hutchings D, Dickinson HO, Corner L, Beyer F, Finch T, Hughes J, Vanoli A, Ballard C, Bond J (2007) Effectiveness and acceptability of non-pharmacological interventions to reduce wandering in dementia: A systematic review. Int J Geriatr Psychiatry 22(1):9-22.
Notes: Full text review. Excluded. Wrong intervention

Rodriguez-Caballero A, Torres-Lagares D, Robles-Garcia M, Pachon-Ibanez J, Gonzalez-Padilla D, Gutierrez-Perez JL (2012) Cancer treatment-induced oral mucositis: a critical review. Int J Oral Maxillofac Surg 41(2):225-38.
Notes: Full text review. Excluded. Wrong publication type

Rutten ALB, Stolper CF (2008) The 2005 meta-analysis of homeopathy: the importance of post-publication data. Homeopathy 97(4):169-77.
Notes: Full text review. Excluded. Wrong publication type

Sarris J, Moylan S, Camfield DA, Pase MP, Mischoulon D, Berk M, Jacka FN, Schweitzer I (2012) Complementary medicine, exercise, meditation, diet, and lifestyle modification for anxiety disorders: A review of current evidence. Evid -Based Complement Altern Med 2012.
Notes: Full text review. Excluded. Wrong publication type

Schafer T (2010) Complementary alternative medicine (CAM) and atopic eczema. Allergologie 33(4):180-9.
Notes: Full text review. Excluded. Wrong publication type

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. Arzneim -Forsch Drug Res 55(1):23-9.
Notes: Full text review. Excluded. Wrong publication type

Searight HR, Robertson K, Smith T, Searight BK (2011) A qualitative systematic review of complementary and alternative therapies for childhood attention deficit hyperactivity disorder: Botanicals, diet, minerals, and homeopathy. Fam Med Prim Care Rev 13(4):798-803.
Notes: Full text review. Excluded. Wrong intervention

Seidl MM, Stewart DE (1998) Alternative treatments for menopausal symptoms. Systematic review of scientific and lay literature. Can Fam Physician 44:1299-308.
Notes: Full text review. Excluded. Did not provide appraisal of primary studies (criterion 7 of AMSTAR)

Semple MG, Smyth RL (2003) Update on Cochrane data on paediatric respiratory diseases. Paediatr Respir Rev 4(3):250-66.
Notes: Full text review. Excluded. Wrong publication type

Shang A, Huwiler-Muntener K, Nartey L, Juni P, Dorig S, Sterne JA, Pewsner D, Egger M (2005) Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet 366(9487):726-32.
Notes: Full text review. Excluded. Wrong outcomes

Shekelle PG, Takata G, Newberry SJ, Coker T, Limbos M, Chan LS, Timmer M, Suttorp M, Carter J, Motala A, Valentine D, Johnsen B, Shanman R. Management of Acute Otitis Media: Update. Evidence Report/Technology Assessment No. 198. (Prepared by the RAND Evidence-Based Practice Center under Contract No. 290 2007 10056 I). Rockville, MD: Agency for Healthcare Research and Quality. November 2010.
Notes: Full text review. Excluded. Wrong intervention

Sherr J, Quirk T (2007) Systematic review of homeopathic pathogenetic trials: an excess of rigour? Homeopathy 96(4):273-5.
Notes: Full text review. Excluded. Wrong publication type

Soeken KL (2004) Selected CAM Therapies for Arthritis-Related Pain: The Evidence from Systematic Reviews. Clin J Pain 20(1):13-8.
Notes: Full text review. Excluded. Wrong publication type

Steurer-Stey C, Russi EW, Steurer J (2002) Complementary and alternative medicine in asthma: do they work? Swiss Med Wkly 132(25-26):338-44.
Notes: Full text review. Excluded. Wrong publication type

Strauss JL, Coeytaux R, McDuffie J, Nagi A, Williams JW Jr. Efficacy of Complementary and Alternative Therapies for Posttraumatic Stress Disorder. VA-ESP Project #09-010; 2011.
Notes: Full text review. Excluded. Wrong intervention

Struijs P, Kerkhoffs G (2007) Ankle sprain. Clin Evid (Online) 2007.
Notes: Full text review. Excluded. Superseded publication

Struijs PA, Kerkhoffs GM (2010) Ankle sprain. Clin Evid (Online) 2010.
Notes: Full text review. Excluded. Wrong publication type

Stub T, Musial F, Alraek T (2012) Adverse effects of homeopathy, what do we know? A systematic review. BMC Complement Altern Med 12.
Notes: Full text review. Excluded. Wrong publication type

Terry R, Perry R, Ernst E (2012) An overview of systematic reviews of complementary and alternative medicine for fibromyalgia. Clin Rheumatol 31(1):55-66.
Notes: Full text review. Excluded. Wrong publication type

Thachil AF, Mohan R, Bhugra D (2007) The evidence base of complementary and alternative therapies in depression. J Affect Disord 97(1-3):23-35.
Notes: Full text review. Excluded. Wrong intervention

Ullman D (2003) Controlled clinical trials evaluating the homeopathic treatment of people with human immunodeficiency virus or acquired immune deficiency syndrome. J Altern Complement Med 9(1):133-41.
Notes: Full text review. Excluded. Wrong publication type

Vallance AK, Jobst KA (1998) Meta-analysis of homoeopathy trials. Lancet 351(9099):366-8.
Notes: Full text review. Excluded. Wrong publication type

Van Den Biggelaar FJHM, Smolders J, Jansen JFA (2010) Complementary and alternative medicine in alopecia areata. Am J Clin Dermatol 11(1):11-20.
Notes: Full text review. Excluded. Wrong intervention

van der Wouden JC, Menke J, Gajadin S, Koning S, Tasche MJ, van Suijlekom-Smit LW, Berger MY, Butler CC (2006) Interventions for cutaneous molluscum contagiosum. Cochrane Database Syst Rev(2):CD004767.
Notes: Full text review. Excluded. Superseded publication

van der Wouden JC, van der Sande R, van Suijlekom-Smit LW, Berger M, Butler C, Koning S (2009) Interventions for cutaneous molluscum contagiosum. Cochrane Database Syst Rev(4):CD004767.
Notes: Full text review. Excluded. Wrong intervention

Van Wijk R (2007) The in vitro evidence for an effect of high homeopathic potencies-A systematic review of the literature. Complement Ther Med 15(2):139-41.
Notes: Full text review. Excluded. Wrong publication type

Vickers AJ, Smith C (2000) Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database Syst Rev(2):CD001957.
Notes: Full text review. Excluded. Superseded publication

Vickers AJ, Smith C (2004) Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes. Cochrane Database Syst Rev(1):CD001957.
Notes: Full text review. Excluded. Superseded publication

Vickers AJ, Smith C (2006) Homoeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndromes (Review). Cochrane Database Syst Rev(3).
Notes: Full text review. Excluded. Superseded publication

Walach H (2002) Homeopathy in rheumatoid arthritis - No evidence for its superiority to placebo. Forsch Komplementarmed Klass Naturheilkd 9(6):363-5.
Notes: Full text review. Excluded. Wrong publication type

Warren Z, Veenstra-VanderWeele J, Stone W, Bruzek JL, Nahmias AS, Foss-Feig JH, Jerome RN, Krishnaswami S, Sathe NA, Glasser AM, Surawicz T, McPheeters ML. Therapies for Children With Autism Spectrum Disorders. Comparative Effectiveness Review No. 26. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 11-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.
Notes: Full text review. Excluded. Wrong intervention

Weiner DK, Ernst E (2004) Complementary and alternative approaches to the treatment of persistent musculoskeletal pain. Clin J Pain 20(4):244-55.
Notes: Full text review. Excluded. Wrong publication type

Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of Primary Care Interventions for Weight Management in Children and Adolescents: An Updated, Targeted Systematic Review for the USPSTF. Evidence synthesis No. 76. AHRQ Publication No. 10-05144-EF-1. Rockville, Maryland: Agency for Healthcare Research and Quality, January 2010.
Notes: Full text review. Excluded. Wrong intervention

Wiesenauer ML, Ludtke R (2000) A meta-analysis of the homeopathic treatment of pollinosis with Galphimia glauca. Br Homeopath J 89(SUPPL. 1):S52.
Notes: Full text review. Excluded. Wrong publication type

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. Complement Ther Med 15(2):128-38.
Notes: Full text review. Excluded. Wrong outcomes

Yaju Y, Kataoka Y, Eto H, Horiuchi S, Mori R (2011) Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period. Cochrane Database Syst Rev.
Notes: Full text review. Excluded. Wrong publication type

Zochling J (2004) Complementary and alternative medicines and arthritis. Med Today 5(9):63-6.
Notes: Full text review. Excluded. Wrong publication type

### 7.1.3 Studies not published in English

Bonard EC (1999) [Homeopathy]. *Rev Med Suisse Romande* 119(1):83-6.

Ernst E (1997) [For an evidence-based complementary medicine]. *Ann Med Interne* (Paris) 148(7):472-6.

Heine H (2008) Are homeopathic preparations of Rhus toxicodendron L. (Toxicodendron quercifolium Greene) suitable for adjuvant tumor therapy? A systematic review. *Schweiz Z GanzheitsMed* 20(1):35-40.

Langhorst J, Hauser 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.

Ludtke R, Wiesenauer M (1997) A meta-analysis of homeopathic treatment of pollinosis with Galphimia glauca. *Wien Med Wochenschr* 147(14):323-7.

Ludtke R, Hacke D (2005) On the effectiveness of the homeopathic remedy Arnica montana. *Wien Med Wochenschr* 155(21-22):482-90.

Scheen AJ (1997) Can positive results from a meta-analysis provide legitimacy for homeopathy? *REV MED LIEGE* 52(11):694-7.

Strubelt O, Claussen M (1999) On evaluating the efficacy of homoeopathic medications. *Deutsche Medizinische Wochenschrift* 124(9):261-6.

Winer N (2011) [Different methods for the induction of labour in postterm pregnancy]. *J Gynecol Obstet Biol Reprod* (Paris) 40(8):796-811.

Zimmer U (2005) Treatment of vertigo with Vertigoheel(R) - A meta-analysis. *Biol Med* 34(2):89.

## 7.2 References – Other


Barnes J, Resch KL, Ernst E (1997). Homeopathy for postoperative ileus?: A meta-analysis. *J Clin Gastroenterol* 25(4):628-33.

Bornhöft G, Matthiessen P, eds (2012). *Homeopathy in Healthcare: Effectiveness, Appropriateness, Safety, Costs: An HTA report on homeopathy as part of the Swiss Complementary Medicine Evaluation Programme.* Springer-Verlag, New York.

Brien S, Lachance L, Prescott P, McDermott C, Lewith G (2011). Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: a randomized controlled clinical trial. *Rheumatology* 50:1070-1082.

British Homeopathic Association (2010). The Science & Technology Select Committee Evidence Check on Homeopathy: British Homeopathic Association response to report. Available at: http://www.facultyofhomeopathy.org/export/sites/faculty_site/ST_parts_1-6.pdf.

Colquhoun D (1990). Re-analysis of clinical treatment of homeopathic treatment in fibrositis. *Lancet* 336:441-2.

Davidson JRT, Crawford C, Ives JA, Jonas WB (2011). Homeopathic treatments in psychiatry: A systematic review of randomized placebo-controlled studies. *J Clin Psychiatry* 72(6):795-805.

Di Basi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J (2002). Influence of context effects on health outcomes: a systematic review. *Lancet* 357:757.

Ernst E, Barnes J (1998). Are homoeopathic remedies effective for delayed-onset muscle soreness: a systematic review of placebo-controlled trials (Structured abstract). *Perfusion* 11:4-8.

GRADE Working Group (2004). Grading quality of evidence and strength of recommendations. *British Medical Journal* 328(7454):1490.

Higgins JPT, Green S, (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

House of Commons Science and Technology Committee (2009). *Evidence check 2: Homeopathy*. Available at: http://www.publications.parliament.uk/pa/cm200910/cmselect/cmsctech/45/45.pdf

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

Merlin T, Weston A, Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence' *BMC Medical Research Methodology* 9:34

NHMRC (2000). How to use the evidence: assessment and application of scientific evidence. National Health and Medical Research Council, Canberra ACT. Available at: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

NHMRC (2007). Standards and procedures for externally developed guidelines. National Health and Medical Research Council, Canberra ACT. Available at: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/nh56.pdf

NHMRC (2009). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. National Health and Medical Research Council, Canberra ACT. Available at: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf

Shang A, Huwiler-Muntener K, Nartey L, Juni P, Dorig S, Sterne JA, Pewsner D, Egger M (2005) Are the clinical effects of homoeopathy placebo effects? Comparative study of placebo-controlled trials of homoeopathy and allopathy. Lancet 366(9487):726-32.

Shaw D (2012). The Swiss report on homeopathy: a case study of research misconduct. *Swiss Med Wkly* 142:w13594.

Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM (2007). Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 7:10.

Walach H (2003). Placebo and placebo effects – a concise review. *Focus Altern Complement Ther* 8:178-187.

World Health Organization (2009). Safety issues in the preparation of homeopathic medicines. WHO Press, Geneva.