HOMEOPATHY FOR PREVENTING AND TREATING HEALTH CONDITIONS

Evidence Evaluation Report

prepared by
HTANALYSTS

for
National Health and Medical Research Council

NHMRC | Natural Therapies Working Committee
Canberra ACT 2601

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Dates

This evidence evaluation report and accompanying technical reports received approval from the NHMRC Natural Therapies Working Committee (NTWC) on 16 AUG 2024.

The protocol for the evidence evaluation received approval from the NHMRC NTWC on 13 July 2022 (PROSPERO: CRD42022346433).

History

NHMRC has been engaged by the Department of Health and Aged Care (formerly Department of Health; Department) to update the evidence underpinning the *2015 Review of the Australian Government Rebate on Natural Therapies for Private Health Insurance* (2015 Review) (1). The natural therapies to be reviewed are Alexander technique, aromatherapy, Bowen therapy, Buteyko, Feldenkrais, homeopathy, iridology, kinesiology, naturopathy, Pilates, reflexology, Rolfing, shiatsu, Tai Chi, Western herbalism and yoga. These therapies are among those excluded from the private health insurance rebate as of 1 April 2019.

To support NHMRC in their evidence review, Health Technology Analysts (**HT**ANALYSTS) was engaged to conduct a systematic review of the evidence of clinical effectiveness of homeopathy. Eligible studies received from the Department's public call for evidence, the Natural Therapies Review Expert Advisory Panel (NTREAP) and the NTWC were also included in the evidence evaluation.

This evidence evaluation report has been developed by **HT**ANALYSTS in conjunction with NHMRC, the NTWC, and the NTREAP. It describes the main body of evidence related to the effect of homeopathy for preventing and treating health conditions. Supplementary data are provided in Appendices A to H. All associated materials have been developed in a robust and transparent manner in accordance with relevant best practice standards (2-5).

Funding

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Acknowledgments

Thanks to the members of the Department of Health's NTREAP and the National Health and Medical Research Council's NTWC for their advice and comments throughout the creation of this document. PRACI data was provided by Dr Amie Steel at UTS.

Membership and other details of the Panel and Committee can be found at:

https://www.health.gov.au/committees-and-groups/natural-therapies-review-expert-advisory-panel

https://www.nhmrc.gov.au/about-us/leadership-and-governance/committees/natural-therapies-working-committee

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List of abbreviations

AMED	Allied and Complementary Medicine Database
BRISA	Regional Base of Health Technology Assessment Reports of the Americas
CENTRAL	Cochrane Controlled Register of Trials
CH	Centesimal dilutions using Hahnemann's dilution method
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COMET	Core Outcome Measures in Effectiveness Trials
D	Decimal dilutions
DSM	Diagnostic and Statistical Manual of Mental Disorders
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ITT	Intent-to-treat
M	millesimal dilutions
MCID	minimal clinically important differences
MeSH	Medical Subject Headings
MD	mean difference
MID	minimal important difference
NHMRC	National Health and Medical Research Council
NRSI	Nonrandomised study of an intervention
NTREAP	Natural Therapies Review Expert Advisory Panel
NTWC	Natural Therapies Working Committee
OR	Odds ratios
PAHO VHL	Pan American Health Organization Virtual Health Library
PICO	Population, Intervention, Comparator, Outcome
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RoB	Risk of bias
RR	Risk ratios
SD	Standard deviation
SMD	Standardised mean difference
SR	Systematic review
TIDIER	Template for Intervention Description and Replication
X	Decimal dilutions

Plain language summary

What was the aim of this review?

The aim of this review was to identify eligible studies and assess whether they demonstrate that homeopathy is effective in preventing and/or treating certain injuries, diseases, medical conditions or pre-clinical conditions relevant to the Australian population.

Homeopathy is an alternative medical system based on the premise that if a substance causes similar symptoms in a healthy person, that same substance in a highly diluted dose can treat a disease with similar symptoms. Individualised (or 'classical) homeopathy typically involves the prescription of a single medicinal product, based on the holistic assessment of mental, emotional and/or physical symptoms. In non-individualised (or 'fixed') homeopathy, a specific homeopathic medicinal product is employed (with or without a consultation) for a specific condition.

This review was targeted for the Australian Government Department of Health and Aged Care (Department) to assist in their Natural Therapies Review, which was designed to determine whether certain natural therapies, including homeopathy, have enough evidence of effectiveness to be considered re-eligible for private health insurance rebates. This review was not designed to be a complete review of all studies published for homeopathy, nor was it intended to inform decisions about whether an individual or practitioner should use homeopathy.

Key messages

For the populations (or conditions) assessed, homeopathy appears to provide little to no benefit when compared with placebo (i.e. something that looks identical to the intervention, but is designed to have no therapeutic effect) for most of the priority outcomes for which there is evidence available. Similar results were seen in the few studies that compared homeopathy to inactive control (e.g. waitlist). The evidence assessed in this review was rated as moderate to very low certainty. The results of this review are consistent with other systematic reviews of homeopathy, in the populations considered in this review, published up to November 2023.

What was studied in this review?

This review identified studies using a planned literature search, with no limit on publication date. To ensure the review was manageable, the review only assessed studies for certain conditions or groups of people. These priority conditions and groups were decided based on Australian survey information and from seeking expert advice about the reasons why people in Australia commonly use homeopathy and the types of conditions seen by homeopaths. Decisions about which groups to include were made before looking at the results of the studies found. The primary comparison was with studies comparing the results of people who used homeopathy to a group of people who received a placebo. This is considered as the gold-standard methodology to establish the efficacy of a treatment. For completeness, studies that compared people who used homeopathy to a group of people who did not take another intervention ('inactive control') were included as a secondary comparison. This 'inactive control' may include people continuing their usual care (i.e. their usual medication or practices). Studies comparing people who use homeopathy to a different form of treatment ('active control') were included in an appendix. These were not included in the main analysis because different studies used different comparators and outcome measures, which did not meet the criteria planned in the protocol. The review focused on evidence reported in eligible randomised control trials (RCTs) or quasi RCTs, as RCTs are considered to be the strongest study type. Assessment of cost effectiveness, safety and studies of healthy populations were not included in this review.

Studies published in languages other than English were listed, but not included in the assessment.

Studies were assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. GRADE is a method to assess how confident (or certain) systematic review authors can be that the estimates of effect (reported in studies) are accurate. The assessment made by the reviewer is then described as either:

- high certainty – meaning the authors have a lot of confidence that the true effect is similar to the estimated effect,
- moderate certainty – meaning the true effect is probably close to the estimated effect,
- low certainty – meaning the true effect may be markedly different from the estimated effect,
- very low certainty – meaning the true effect is probably markedly different from the estimated effect. Reviewers' confidence was so limited that interpretation was not provided.

What studies did we identify in the review?

Using a planned approach, 5565 citations from 9 databases were collected and examined, including 584 studies submitted by the public via the Department's public call for evidence.

Out of 5565 citations identified, 93 studies covering 20 prioritised conditions were assessed in the evidence evaluation and are included in the results. Of the 93 included studies, 67 included a placebo group (72%), 14 had an inactive control group (15%) and 14 were compared against other controls (15%). Homeopathy reported in eligible studies was generally consistent with how homeopathy is practised in Australia, inclusive of individualised homeopathy (after a detailed consultation) and prescription of non-individualised 'fixed' medicinal products targeting the conventional medical diagnosis of the patient. The treatment provider was almost always an experienced homeopath. Most studies evaluated homeopathy administered orally (or under the tongue), delivered as a liquid, granule or tablet. In some instances, topical gels or nasal sprays were applied. Treatment duration varied from administration of a single dose, through to daily use of an intervention for up to 12 months. In some instances, the intervention was modified during the course of the study, after consultation with the homeopath.

At the time of the literature search, a further 41 studies had been presented at conferences, but data were incomplete; 89 studies were not in English; 16 studies could not be retrieved; and 4 studies were published after the search date. In addition, 192 studies had been registered but were not complete at the time of the search. Of these ongoing studies, 74 were in conditions prioritised in this review.

What were the main results of the review?

For the primary comparison, the evidence provides low certainty that homeopathy may be more effective than placebo for two conditions. The evidence also provides low certainty that homeopathy may be no more effective than placebo for many of the conditions and outcomes considered critical or important in this review. There are also many conditions and outcomes assessed in this review where the effect of homeopathy compared to placebo is uncertain (very low certainty) or unknown.

The evidence provides low certainty that homeopathy may be effective compared to placebo in:

- reducing medication use (1 RCT, 108 participants) in people with allergic rhinitis
- reducing disease severity (3 RCTs, 172 participants) in people with atopic dermatitis.

The evidence provides low certainty that homeopathy may have little (to no) effect compared to placebo in:

- improving quality of life (2 RCTs, 106 participants) in people with atopic dermatitis
- reducing infection frequency (1 RCT, 96 participants) in people with recurrent otitis media
- improving quality of life (1 RCT, 170 participants) or reducing medication use (2 RCTs, 377 participants) in people with recurrent upper respiratory tract infections
- reducing anxiety (3 RCTs, 150 participants), depression (1 RCT, 44 participants), or emotional functioning (1 RCT, 44 participants) in people with anxiety
- reducing insomnia severity, sleep quality or sleep onset latency (1 RCT, 60 participants) in people with insomnia
- improving quality of life (2 RCTs, 291 participants) or reducing medication use (1 RCT, 89 participants) in people with asthma
- reducing symptom severity (1 RCT, 292 participants) or symptom duration (3 RCTs, 448 participants) in people with diarrhoea
- reducing disease severity (1 RCT, 200 participants) in people with psoriasis
- reducing pain intensity (1 RCT, 134 participants), stiffness (1 RCT, 134 participants) or improving quality of life (1 RCT, 134 participants) in people with back or neck pain
- improving quality of life (1 RCT, 108 participants) in people with menopausal symptoms or complaints
- reducing fatigue (1 RCT, 86 participants) or improving quality of life (1 RCT, 86 participants) in people with chronic fatigue conditions.

Similarly, in the secondary comparison (inactive control), the evidence provides moderate to low certainty that homeopathy (in some cases plus usual care) is probably or may be more effective than not using homeopathy for three conditions and outcomes considered critical or important for this review. The evidence also provides moderate to low certainty that using homeopathy (in some cases plus usual care) is probably or may be no more effective than not using homeopathy for many conditions and outcomes considered critical or important in this review. For most of the conditions and outcomes assessed in this review the effect of homeopathy compared to inactive control is uncertain (very low certainty) or unknown.

The evidence provides moderate certainty that homeopathy is probably more effective than no intervention in:

- reducing infection frequency (1 RCT, 256 participants) in people with recurrent upper respiratory tract infections.

(The evidence from the primary comparison with placebo (1 RCT, 40 participants), was very uncertain about the effect of homeopathy on infection frequency in people with recurrent upper respiratory tract infections.)

The evidence provides low certainty that homeopathy may be more effective than no intervention in:

- reducing antibiotic use (2 RCTs, 306 participants) in people with recurrent upper respiratory tract infections
- reducing symptom severity (1 RCT, 60 participants) in people with menstrual disorders.

(The evidence from the primary comparison with placebo showed low certainty that homeopathy may have little to no effect on antibiotic use (2 RCTs, 377 participants). The evidence from the primary comparison with placebo was very uncertain about the effect of homeopathy on symptom severity (2 RCTs, 211 participants) for menstrual disorders.)

The evidence provides moderate certainty that homeopathy probably has little (to no) effect compared to no intervention in:

- reducing depression severity (1 RCT, 566 participants) in people with depression.

(The evidence for this outcome in the primary comparison was very uncertain about the effect of homeopathy on depression severity (1 RCT, 44 participants) in people with depression).

The evidence provides low certainty that homeopathy may have little (to no) effect compared to no intervention on:

- symptom severity (1 RCT, 210 participants) in children with recurrent otitis media
- symptom severity (2 RCTs, 86 participants), health-related quality of life (2 RCTs, 86 participants), hospitalisation (1 RCT, 35 participants) or medication use (1 RCT, 35 participants) in people with asthma
- symptom severity (1 RCT, 76 participants) or health-related quality of life (1 RCT, 76 participants) in people with irritable bowel syndrome
- pain (1 RCT, 36 participants), fatigue (1 RCT, 36 participants), health-related quality of life (1 RCT, 36 participants), or emotional wellbeing (1 RCT, 36 participants) in people with fibromyalgia.

(These results are generally consistent with those from the primary comparison with placebo, although sometimes the level of certainty differs.)

The planned subgroup analysis comparing individualised and non-individualised homeopathy could not be completed because of the small number of studies in each condition.

Implications for health policy and research

This review assesses the evidence for certain conditions and groups of people to inform the Australian Government about health policy decisions for private health insurance rebates. The review does not cover all the reasons that people use homeopathy, or the reasons practitioners prescribe homeopathic medicines and is not intended to inform individual choices about using homeopathy.

The results of this review indicate that homeopathy may improve some conditions and outcomes prioritised and have little to no effect for many other conditions and outcomes prioritised. There were many conditions and outcomes assessed in this review where the effect of homeopathy was uncertain (very low certainty) or unknown. Many of the studies where evidence was available compared homeopathy to placebo (the gold-standard). For completeness, homeopathy versus inactive control (no intervention, waitlist, or usual care if considered inactive) was included as a secondary comparator. In some of the studies compared to inactive control, the inactive control was "usual care". This means participants were encouraged to continue any usual medication or practices, but these can vary from person to person, and it is not always known or reported what they are. Therefore, where usual care is included, it is often not possible to tell the effects of homeopathy alone, and instead the results show the effect of homeopathy and usual care together.

Studies published in a language other than English were listed, but not included in the assessment. Including these studies would likely not have affected the overall conclusions of the review but could have increased the certainty of evidence across some outcomes. The review listed, but did not assess homeopathy versus other interventions, so no comment can be made on whether homeopathy is better or worse than other interventions.

Future research about the effectiveness of homeopathy could be improved by addressing preventable limitations in the conduct and reporting of trials. For example, using well established outcome measures and reporting all the outcomes which were tested with sufficient detail. Studies of homeopathy in conditions for which there is little (or no) evidence, and differentiating areas of care for which individualised or non-individualised homeopathy may also be important.

How up to date is this review?

Searches were conducted from the earliest date included in the databases until 15 July 2022. Studies published after this date are not included in this review. A search for recent systematic reviews was conducted up to November 2023 and results of this review were compared (where applicable) for completeness.

Executive summary

Background

Homeopathy is used in Australia by individuals who typically have a lower health-related quality of life due to chronic diseases or co-morbidities (6-8). Published reports indicate homeopathy is used to treat or alleviate symptoms associated with a range of chronic conditions such as allergic rhinitis, asthma, depression, rheumatoid arthritis, and irritable bowel syndrome (9-13), often when established treatments are not satisfactory, or when individuals are seeking to improve overall well-being (14, 15). Homeopathic medicinal products are also often used to prevent or treat side effects associated with cancer (16-18). In other cases, homeopathy is used by individuals seeking a more holistic lifestyle to treat infertility, or to prevent recurrent infections (19, 20).

Homeopathy is an alternative medical system that is based on the premise of similitude, that is, if a substance causes similar symptoms in a healthy person that same substance in a highly diluted dose can treat a disease with similar symptoms (21). Homeopathy can be broadly categorised into two main types: individualised, where patients are treated based on the totality of symptoms after a detailed consultation, and non-individualised (or 'fixed') homeopathy, where a specific homeopathic medicinal product is employed (with or without a consultation) for a specific condition (22). Both single homeopathic medicinal products or 'complex' medicinal products can be prescribed, with complex medicinal products containing a fixed combination of multiple homeopathic ingredients (23). They can be prepared as a liquid, powder, granules or tablets (24) and are administered orally or externally (25). Alternatively, allergens or causative infectious or toxic agents, including the patient's own bodily secretions (e.g. sputum or urine), are used to prepare the homeopathic medicinal product (23, 26).

In 2013, an overview of systematic reviews conducted for the Australian Government found that there was no reliable evidence about the health effects of homeopathy for any of the reported clinical conditions. This was due to the lack of studies for some clinical conditions, and inadequate reporting of information in the included systematic reviews (about the primary studies included in the eligible systematic reviews). In contrast, this systematic review has targeted analysis to primary studies assessing the effectiveness of homeopathy for conditions commonly seen and treated by homeopaths in Australia.

Objectives

The objective of this review was to evaluate the effectiveness of homeopathy in individuals with a described injury, disease, medical condition, or preclinical condition (including primary prevention) in at-risk individuals, on outcomes that align with the reasons why people commonly use homeopathy in Australia. This information will be used by the Australian Government in deciding whether to reinclude homeopathy as eligible for private health insurance rebates, after homeopathy was excluded in 2019. This review was not designed to assess all the reasons that people use homeopathy, or the reasons practitioners prescribe homeopathy, and is not intended to inform individual choices about using homeopathic products.

Search methods

Literature searches were conducted in Embase, MEDLINE, Emcare, PsycINFO, AMED, CINAHL, CENTRAL, PubMed and PAHO VHL to identify relevant studies published from database inception to 15 July 2022. The public was also invited by the Department of Health and Aged Care to submit references for published research evidence. There were no limits on language of publication or date of publication in the search.

Selection criteria

Randomised controlled trials (RCTs) that examined homeopathy compared to placebo or control (inclusive of no intervention, waitlist or usual care if considered inactive) or another intervention (active control) were eligible, including quasi-randomised studies, cluster-randomised and crossover trials. Any form of homeopathy was eligible for inclusion, including simple homeopathic medicinal products involving single substances, and complex medicinal products involving more than one substance. The treatment could be individualised (i.e. prescribed by a homeopath according to the person's presenting symptoms after a consultation) or non-individualised (i.e. where the same homeopathic medicinal product is given to all patients with the same condition, with or without a consultation). The homeopathic medicinal product had to be administered orally or externally (i.e. topical, oral, nasal, rectal, vaginal, ocular or auricular use). Preparations could be liquid, sublingual pellets, ointments, gels, drops, creams, sprays, or tablets. Homeopathic products delivered via injection were not eligible for inclusion, as this is not consistent with Australian practice of homeopathy.

The search was not restricted by comparators, however the primary comparator of interest for this review was homeopathy versus placebo because it is considered the gold-standard methodology to establish the efficacy of a treatment. For completeness, homeopathy versus inactive control (no intervention, waitlist, or usual care if considered inactive) was included as a secondary comparator, and homeopathy versus another comparator (including usual care if considered active) as a tertiary comparator. Outcomes were not part of the eligibility criteria and were not included in the search terms but were prioritised as described below. Studies were not excluded based on country of origin, however studies published in a language other than English were not translated and were not included in the synthesis. These studies were listed in an inventory for completeness.

Data collection and analysis

After the initial searching and screening process, but before data extraction, a list of conditions (and at-risk populations) in the eligible studies was collated. Priority conditions were then nominated by the National Health and Medical Research Council (NHMRC) Natural Therapies Working Committee (NTWC) for inclusion in the evidence synthesis. In determining the priority populations, the NTWC were guided by relevant Australian survey data and expert advice from the Department's Natural Therapies Review Expert Advisory Panel (NTREAP). After this, a blinded outcome prioritisation process was undertaken that included all prespecified outcome domains and measures in each eligible RCT, supplemented with outcome domains or measures derived from core outcome sets (where available) or recent Cochrane reviews for that condition. NTWC (with advice from NTREAP) was asked to specify up to seven 'critical' or 'important' outcome domains for inclusion in the analysis and synthesis of the review. Where a study did not report a prioritised outcome for that population or condition, this was noted as an evidence gap in the review. For outcome domains, NTWC applied the GRADE scoring of 0 (of limited importance for decision making) to 9 (critical for decision making). Harms and cost effectiveness measures were out of scope.

For each included study, data collection was performed by two researchers, the first collected data using data extraction forms and the second checked the forms for completeness and accuracy. Risk of Bias of the eligible studies was conducted using the RoB 2 tool, the revised Cochrane risk of bias tool for randomised trials.

In the data analysis and synthesis for each prioritised population, the overall certainty of evidence for a maximum of seven critical or important outcomes were reported in GRADE summary of findings tables, with corresponding evidence statements assigned to each outcome based on a pre-specified list of statements. Reported outcomes were assessed at 'end of treatment' and were judged based on reported minimal clinically important differences (MCID) or minimal important difference (MID) (where available). In instances where MCID were unavailable, effect estimates were assessed using ranges of (1) small (Mean difference [MD] <10% of the scale), (2) moderate (MD between 10% to 20% of the scale), or (3) large (MD more than 20% of the scale). If the effect was quantified using a standardised mean difference (SMD), we used Cohen's guidance for interpreting the magnitude of the SMD, where 0.2 represents a small difference, 0.5 is moderate, and 0.8 is large.

Main results

A total of 254 studies were identified as eligible for inclusion in this review. Of these, 93 studies covering 20 prioritised conditions were considered in the evidence evaluation and are included in the results. For the synthesis, 67 studies (72%) compared homeopathy with placebo and 14 studies (15%) compared homeopathy with an inactive control (no intervention, wait list or usual care if considered inactive). Results for the remaining 14 studies of prioritised conditions with active comparators (including usual care where active) are presented in Appendix F2, but not in the synthesis, as the wide range of comparators and outcomes did not allow for synthesis as planned in the protocol.

At the time of the search, an additional 150 studies were awaiting classification, and an additional 192 studies were recorded as ongoing (registered but not published at the time of the search). Of the studies awaiting classification, 41 were conference abstracts, 89 were not published in English and 16 studies were not able to be retrieved and therefore not assessed. The remaining 4 studies were published after the search date. Of the ongoing studies, at the time of search 50 studies were not yet recruiting participants, 59 studies were recruiting participants, 8 studies had recruited participants but not collected data, 36 studies were complete, but data were not yet available, and 5 studies completed data analysis but had not reported any results at the time of the search. The status of 19 studies was unknown. Results for approximately 29 of the ongoing studies, that were complete but not yet available for full text review, may have been eligible for inclusion for conditions prioritised in this review, and may have reported on some of the outcomes considered critical or important by NTWC.

Evidence was available for all 20 prioritised conditions. Summary of findings tables were restricted to outcomes rated as critical and important by NTWC, study results for outcomes not considered critical or important were not included in the synthesis.

All included studies examined homeopathy that could be applicable to the Australian context, inclusive of individualised and non-individualised prescriptions, accompanied by consultations with a homeopath. Most studies evaluated homeopathic products that were administered orally (either as tablet or pellet), but some were topically applied or administered via a nasal spray.

Studies were assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. GRADE combines information to assess overall how certain systematic review authors can be that the estimates of the effect (reported across a study/s for each critical or important outcome) are correct. High certainty means the authors have a lot of confidence that the true effect is similar to the estimated effect. Moderate certainty means the true effect is probably close to the estimated effect. Low certainty means the true effect might be markedly different from the estimated effect. Very low certainty means the true effect is probably markedly different from the estimated effect.[1]

This review evaluated 20 prioritised conditions for which there was evidence about the effect of homeopathy on an outcome considered critical or important by NTWC.

For the primary comparison (vs placebo) the evidence provides:

- low certainty that, compared to placebo, homeopathy may result in:
    - a moderate reduction in medication use (1 RCT, 108 participants) in people with allergic rhinitis
    - a small reduction in disease severity (3 RCTs, 172 participants) in people with atopic dermatitis.

- low certainty that, compared to placebo, homeopathy may result in little (to no) benefit in:
    - improving quality of life (2 RCTs, 106 participants) in people with atopic dermatitis
    - reducing infection frequency (1 RCT, 96 participants) in people with recurrent otitis media
    - improving quality of life (1 RCT, 170 participants) or reducing medication use (2 RCTs, 377 participants) in people with recurrent upper respiratory tract infections
    - reducing anxiety (3 RCTs, 150 participants), depression (1 RCT, 44 participants), or emotional functioning (1 RCT, 44 participants) in people with anxiety
    - reducing insomnia severity, sleep quality or sleep onset latency (1 RCT, 60 participants) in people with insomnia
    - improving quality of life (2 RCTs, 291 participants) or reducing medication use (1 RCT, 89 participants) in people with asthma
    - reducing symptom severity (1 RCT, 292 participants) or symptom duration (3 RCTs, 448 participants) in people with diarrhoea
    - reducing disease severity (1 RCT, 200 participants) in people with psoriasis
    - reducing pain intensity (1 RCT, 134 participants), stiffness (1 RCT, 134 participants) or improving quality of life (1 RCT, 134 participants) in people with back or neck pain
    - improving quality of life (1 RCT, 108 participants) in people with menopausal symptoms or complaints
    - reducing fatigue (1 RCT, 86 participants) or improving quality of life (1 RCT, 86 participants) in people with chronic fatigue conditions.

[1] The estimated effect could suggest either that the therapy in question has an effect (e.g. works better than placebo) or that it has little to no effect. The result for each outcome for a condition is described both in terms of the certainty and the direction of effect. For example, “the evidence provides low certainty that homeopathy may have little (to no) effect compared to placebo on [outcome x] in [condition y]” means that the evidence suggests the effect does not differ from the placebo, but the certainty is low so the true result may be different.

The evidence is very uncertain of the effect of homeopathy compared with placebo for 39 out of the 94 critical or important outcomes prioritised for analysis in this review. There were no results reported across 32 out of 94 critical or important outcomes prioritised in this review, and therefore the effect of homeopathy on these outcomes is unknown. In total, the evidence was very uncertain or there were no results reported compared with placebo for 71 out of 94 critical or important outcomes prioritised in this review. For 8 populations, including depression, neurodevelopmental disorders, headache disorders, digestive complaints, irritable bowel syndrome, arthropathies, menstrual disorders and fibromyalgia there was not enough evidence to assess the role of homeopathy.

For the secondary comparison (vs inactive control), the evidence provides:

- moderate certainty that, compared with inactive control, homeopathy probably results in:
    - a moderate reduction in infection frequency (1 RCT, 256 participants) in people with recurrent upper respiratory tract infections.[2]

- low certainty that, compared with inactive control, homeopathy may result in:
    - a slight reduction in antibiotic use (2 RCTs, 306 participants) in people with recurrent upper respiratory tract infections[3]
    - a reduction in symptom severity in people with menstrual disorders (1 RCT, 60 participants).[4]

- moderate certainty that, compared with inactive control, homeopathy probably has little (to no) effect in:
    - reducing depressive symptoms (1 RCT, 566 participants) in people with depression.[5]

- low certainty that, compared with inactive control, homeopathy may have little (to no) effect in:
    - reducing symptom severity (1 RCT, 210 participants) in children with recurrent otitis media
    - reducing symptom severity (2 RCTs, 86 participants), health-related quality of life (2 RCTs, 86 participants), hospitalisation (1 RCT, 35 participants), or medication use (1 RCT, 35 participants) in people with asthma
    - reducing symptom severity (1 RCT, 76 participants) or health-related quality of life (1 RCT, 76 participants) in people with irritable bowel syndrome
    - reducing pain, fatigue, health-related quality of life or emotional wellbeing (1 RCT, 36 participants) in people with fibromyalgia.

(These results suggesting low certainty of little, to no difference are generally consistent with those from the primary comparison with placebo, although sometimes the level of certainty differs.)

[2] In the primary comparison, the evidence provided very low certainty (1 RCT, 40 participants) about the effect of homeopathy on infection frequency in people with recurrent upper respiratory tract infections.

[3] In the primary comparison, the evidence provided low certainty that homeopathy may have little to no effect on antibiotic use (2 RCTs, 377 participants) in people with recurrent upper respiratory tract infections.

[4] In the primary comparison, the evidence was very uncertain about the effect of homeopathy on symptom severity for menstrual disorders (2 RCTs, 211 participants)

[5] In the primary comparison, the evidence provided very low certainty (1 RCT, 44 participants) about the effect of homeopathy on depression severity in people with depression.

The evidence is very uncertain of the effect of homeopathy compared with inactive control for 12 out of the 94 critical or important outcomes prioritised for analysis in this review. For these 12 outcomes, confidence in the effect estimate is very uncertain and a clinically important difference was not observed (this may relate to study design or duration of the study). A further 67 outcomes (out of 94) prioritised as critical or important in this review were not addressed by any studies compared to inactive control, and therefore the effect of homeopathy on these 67 outcomes compared with no intervention is unknown.

The planned subgroup analysis between individualised and non-individualised homeopathy could not be completed because of the small number of studies in each condition.

A summary of harms of homeopathy was not possible, as it as it was out of scope of this review to assess adverse effects of homeopathy.

Limitations

This review is limited to analysis of conditions prioritised by NTWC, who were guided by relevant patient and/or practitioner reported Australian survey data (where available) and expert advice from NTREAP during the prioritisation process, therefore, this report does not cover all the reasons people use homeopathy. The outcomes assessed in this review were limited to those deemed critical or important by NTWC for each priority condition. Most conditions had evidence available for 3 or 4 critical or important outcomes.

Many of the studies where evidence was available were compared to placebo (the gold-standard methodology to establish the efficacy of a treatment). For completeness, homeopathy versus inactive control (no intervention, waitlist, or usual care if considered inactive) was included as a secondary comparator. In some of the studies compared to inactive control, the inactive control was “usual care”. This means participants were encouraged to continue any usual medication or practices, but it is not always known or reported what those are and they can vary from person to person. Therefore, where usual care is included, it is often not possible to tell the effects of homeopathy alone, and instead the results show the effect of homeopathy as an adjunct to usual care.

There were a large number of studies that remained ongoing or were unpublished at the time of the search. Results of these studies may (or may not) support the use of homeopathy. It is therefore unknown whether the results of these studies would impact the overall conclusions of this review.

An examination of the effectiveness of homeopathy compared with other interventions was not conducted.

Conclusions

For the primary comparison, the evidence provides low certainty that homeopathy may be more effective than placebo for two of the prioritised conditions and outcomes assessed in this review. However, the evidence also provides low certainty that homeopathy may have little (to no) benefit for many of the prioritised conditions and outcomes assessed in this review, where evidence was available. For many of the prioritised outcomes there was no evidence available.

For the secondary comparison, the evidence provides moderate to low certainty that using homeopathy probably or may be more effective than inactive control for some prioritised conditions and outcomes assessed in this review. However, the evidence also provides moderate to low certainty that homeopathy probably or may have little (to no) benefit for many of the prioritised conditions and outcomes assessed in this review, where evidence was available. For many of the prioritised outcomes there was no evidence available.

The results of this review are generally consistent with systematic reviews of homeopathy published on included conditions up until November 2023. These systematic reviews conclude that there is little to no evidence of benefit for homeopathy to improve outcomes for examined health conditions due to poor methodological quality of included studies, which limits interpretation of the results.

There are many trials on the effectiveness of homeopathy compared with placebo or an inactive control. To ensure that future research is able to answer questions about the effectiveness of homeopathy it is important that trials are well conducted (e.g. including outcomes and measures defined in core outcome sets, focus on greater retention or follow-up of participants in trials) and that reporting is comprehensive (e.g. including standard deviations or confidence intervals, providing end of treatment score, reporting both total scores and sub scores of outcome measures). A focus on priority populations relevant to Australia for which there is an absence of evidence would also be of benefit.

1 Background

In 2015, a review of homeopathy found no reliable evidence demonstrating its efficacy in treating any clinical condition (27). The 2015 review was underpinned by an Overview of systematic reviews (SRs) that focused solely on homeopathy and were published in the English language between 2007 and January 2013 (28, 29). Prospectively designed and controlled studies (i.e. randomised controlled trials [RCTs], quasi-randomised controlled trials, non-randomised controlled trials or prospective cohort studies) that were reported within included SRs and assessed homeopathy delivered to treat any clinical condition were included, with outcomes selected according to predefined criteria. The 2013 Overview informed the *2015 Review of the Australian Government Rebate on Private Health Insurance for Natural Therapies*, which resulted in homeopathy and 15 other natural therapies being excluded from private health insurance rebates[6].

NHMRC was engaged by the Department of Health and Aged Care to update the evidence for the effectiveness of homeopathy. This review was not limited by publication date and was focused on evidence reported in eligible RCTs or quasi RCTs. The review focused on evaluating the evidence for populations and conditions commonly seen and treated by homeopaths in Australia.

The process for conducting the review was built upon the following framework:

1. source the clinical evidence by performing a systematic literature search,
2. identify the best available evidence published in English and indexed in English language databases,
3. incorporate additional literature identified through non-database sources received from the Department's public call for evidence, NTREAP and NTWC,
4. critically appraise and present the evidence, and
5. determine the certainty in the evidence base for each question, using a structured assessment of the body of evidence in accordance with GRADE methodology (5).

1.1 Description of the condition and setting

Homeopathy has a long history in Australia, with the first practitioner having arrived in the 1840s followed by the establishment of the first of several homeopathic hospitals in 1876 (30). By the late 1920s, homeopathic hospitals ceased operation, primarily due to advances in medical practice such as the development of antibiotics. Nevertheless, over the last 50 years, homeopathy has experienced a revival, largely fuelled by changes in public perceptions regarding health (30, 31), with homeopathy typically used in Australia as an alternative to, or in conjunction with traditional medicine (6-8, 32-34).

Studies exploring reasons why people in Australia use homeopathy are lacking, however individuals who typically seek out and use complementary medicines (CMs) are reported to be individuals who have a lower health-related quality of life due to chronic diseases or co-morbidities (6-8). CM product use in Australia is also reported to be higher among females, in full-time employment, and with a higher level of education (6-8). A 2002 study that assessed changes in the usage patterns and expenditure of alternative therapies in Australia found there was no difference in use of homeopathy between 1993 and 2000 (4.4% vs 4.3%) and no difference between the proportion of Australians who had visited a homeopath (1.2% for both surveys) (35, 36). More recent studies also suggest a continuing use of homeopathy in Australia (6-8).

[6] https://www.health.gov.au/resources/publications/private-health-insurance-reforms-changing-coverage-for-some-natural-therapies

Published reports indicate homeopathy is used to treat or alleviate symptoms associated with a range of chronic conditions such as allergic rhinitis, asthma, depression, rheumatoid arthritis, and irritable bowel syndrome (9-13), often when established treatments are not satisfactory, or when individuals are seeking to improve overall well-being (14, 15). Homeopathic medicinal products are also often used to prevent or treat side effects associated with cancer (16-18). In other cases, homeopathy is used by individuals seeking a more holistic lifestyle to treat infertility, or to prevent recurrent infections (19, 20).

Given the breadth of the review and variety of potential populations and conditions for which homeopathy is used, a concise description of each condition addressed in the review is provided before each results section (see Results). Appendix A6 provides information on how populations were prioritised for inclusion in the review.

Homeopathy can be practised in a range of settings (e.g. primary, acute, palliative care) (see Description of the intervention) and as such this review was not limited by type of setting.

1.2 Description of the intervention

Homeopathy is an alternative medical system that was first developed approximately 200 years ago by the German pharmacist Samuel Hahnemann (37). It is based on the premise “treat likes by likes”, that is, if a substance causes similar symptoms in a healthy person that same substance in a highly diluted dose can treat a disease with similar symptoms (21). The homeopathic system of treatment allocation and the recognition of clinical patterns of signs and symptoms differ from those of conventional medicine (38).

Patients seeking homeopathic treatment are likely to encounter various approaches depending on their homeopathy practitioner’s philosophy and training (39). Homeopathy can be broadly categorised into two main types: individualised and non-individualised.

In individualised homeopathy, patients are treated based on the totality of symptoms, with the most common form, known as ‘Classical Homeopathy’ involving the prescription of a single medicinal product, based on the holistic assessment of mental, emotional and/or physical symptoms (39). Following a detailed consultation, medicinal products are prescribed by a trained practitioner, matching a patient’s symptoms with symptoms produced by these medicinal products in healthy individuals (23).

In non-individualised (or ‘fixed’) homeopathy, a specific homeopathic medicinal product is employed (with or without a consultation) for a specific condition, such that the same homeopathic medicinal product can be given to all patients with the same condition (22). For example, all patients who have asthma would be give the same remedy (23). In addition, both single homeopathic medicinal products or ‘complex’ medicinal products can be prescribed, with complex medicinal products containing a fixed combination of multiple homeopathic ingredients (23). The most common forms of non-individualised homeopathy include ‘Clinical homeopathy’ and ‘Isopathy’. In clinical homeopathy, complex medicinal products or single homeopathic remedies are prescribed based on the conventional medical diagnosis of the patient (40). In isopathy, allergens or causative infectious or toxic agents, including the patient’s own bodily secretions (e.g. sputum or urine), are used to prepare the homeopathic medicinal product (23, 26).

Homeopathic medicinal products are prepared according to homeopathic pharmacopoeia and are created from a wide variety of substances such as plants, animals, minerals, or chemicals (38). To reduce toxicity and increase the effectiveness of homeopathic medicinal products, substances are serially diluted and vigorously shaken or agitated between each dilution (39). This process is called ‘potentisation’ (32).

Homeopathic medicinal products can be prepared as a liquid, powder (e.g. teething powder), granules or tablets (e.g. sugar pellets) (24) and are administered orally or externally (25).

Overview of the regulation of listed medicines and registered complementary medicines outlines the regulation of listed medicines and registered complementary medicines in Australia, including homeopathic preparations (41).

The *Therapeutic Goods Regulations 1990*[7] include the following definition for 'homoeopathic preparations':

> **homoeopathic preparation** means a preparation:
>
> a. formulated for use on the principle that it is capable of producing symptoms in a healthy person similar to those which it is administered to alleviate; and
>
> b. prepared according to the practices of homoeopathic pharmacy using the methods of:
> (i) serial dilution and succussion of a mother tincture in water, ethanol, aqueous ethanol or glycerol; or
> (ii) serial trituration in lactose.

Most homeopathic medicinal products that are sufficiently diluted do not require listing in the Australian Register of Therapeutic Goods (provided they meet the requirements for exemption in Item 8 of Schedule 5 of the *Therapeutic Goods Regulations 1990*). However, they must still comply with other requirements under the *Therapeutic Goods Act 1989* and the *Therapeutic Goods Regulations 1990* (41). A homeopathic medicinal product prepared for a particular patient following a consultation (extemporaneous compounding) or to fill a prescription for that patient (dispensing) is also exempt from the requirement for Australian Register of Therapeutic Goods listing.

Homeopaths are designated unregistered healthcare practitioners in Australia and are not required to be registered under legislation. Homeopaths have established their own registration body which sets educational standards according to Government guidelines (40). The National Competency Standards in Homeopathy were established in 1999 to ensure practitioners of homeopathy are appropriately qualified and work within appropriate standards of ethical and professional behaviour to safeguard customers (42). The Australian Register of Homoeopaths (ARoH), also established in 1999, is the national registration board and self-regulation body for homeopaths (43). Certain criteria must be met to retain registration as a professional homeopathic practitioner with the ARoH including maintaining professional registration annually, meeting continuing professional development (CPD) requirements, and maintaining indemnity insurance (43). Prior to 2019, health fund rebates for homeopathic services were provided only to those who sought advice from practitioners who were registered with ARoH or members of certain associations (44).

Regulation of unregistered health practitioners (including homeopaths) varies across jurisdictions in Australia (45). In 2014, the Australian Health Ministers' Advisory Council published the National Code of Conduct for health care workers, a set of recommended provisions for health care complaints and enforcement powers (45). To date, New South Wales, Queensland, South Australia and Victoria have enacted legislation to implement the National Code (46). These regulatory regimes have been described as 'negative licensing', as they do not restrict who can provide health services (e.g. based on minimum qualifications) but enable disciplinary action to be taken against practitioners that fail to comply with minimum standards (46). Disciplinary action can include imposing fines and issuing orders that prohibit or set conditions on practice. Some states or territories that have not yet enacted the National Code have provisions in existing legislation enabling complaints to be made about various unregistered health practitioners including homeopaths (for example, Tasmania) (45).

[7] Available from: https://www.legislation.gov.au/Details/F2021C00839

In Australia homeopaths are mostly self-employed in private, clinical practice in major towns and cities (42). As primary health care providers, homeopaths can offer a unique, specialised and holistic approach to health and preventive healthcare (42). Members of the public may choose to consult with homeopaths in conjunction with conventional healthcare providers. In addition to prescribing homeopathic medicinal products, homeopaths can also integrate several other techniques to facilitate the homeopathic therapeutic approach, such as nutritional guidance, personal hygiene, and counselling (42). Generally, homeopaths require long consultations, usually at least an hour, whereby all aspects of a patient's illness and life are considered, and then treatment is chosen based on the patient as a whole and not on the illness or symptoms alone (47). Homeopathic treatment is also employed as a therapy of trade by a range of non-homeopathic practitioners, for example naturopaths (48).

1.3 How the intervention might work

Homeopathy is based on the core tenet of similitude ("treat likes by likes" or "like cures like"). The principle of 'similars' is based on the idea that substances which can elicit specific symptoms in healthy individuals, can be used to treat patients and/or diseases with similar symptoms. Homeopathic medicinal products are created by a series of dilutions (usually 1:10 or 1:100 diluent: volume ratio) with agitation between each dilution, called "succussions" (49). Succussion is believed to render highly diluted solutions biologically active (50). Serial dilutions may occur more than 30 times before the final homeopathic medicinal product is produced. Established potency scales can be the centesimal or "C scale", the decimal or "D scale", or the quintamillesimal or "Q/LM scales". The serial kinetic dilution is called "potentisation". Both high potency (higher dilution) and low potency (lower dilution) homeopathic medicinal products are commonly used (51).

The scientific basis for homeopathy is subject to substantial debate, and the mechanism of action of homeopathic medicinal products has not been established. In some cases substances are diluted beyond the limit of Avogadro's number, such that it is unlikely even one molecule of the original substance is present (39). Various explanations have been proposed for how highly diluted solutions may be biologically active after succussion (52-54). For example, water clusters or clathrates may form around the original molecules and remain even after those molecules are removed (55). These are then hypothesised to be recognised within the body to elicit a response. Alternatively, it has been suggested that nanoparticles of the original material may remain and cause a response (56).

Individualised prescribing introduces unique requirements when designing and conducting clinical research in homeopathy, given that patients with the same diagnosis are treated with different homeopathic medicinal products based on their characteristic symptoms.

1.4 Why it is important to do this review

In Australia, natural therapies, including homeopathy, are most often used in conjunction with conventional medicine and other strategies for supporting good health and wellness. Homeopathy is a popular CM in Australia, with a 2005 survey reporting 6% of respondents had used homeopathy and, of those 6%, 47.7% had visited a homeopathic practitioner in the last 12 months (7). To enable consumers, health care providers and policy makers to make informed decisions about care, the Australian Government will use this review to assist in deciding whether to reinclude homeopathy as eligible for private health insurance rebates.

The 2013 Overview of systematic reviews (sometimes called an Umbrella review) identified 57 systematic reviews published in the English language between 2007 and January 2013. The Overview concluded that there was no reliable evidence that homeopathy is an effective treatment for any of the reported clinical conditions (28, 29). Overviews or Umbrella reviews are an efficient way to collect and evaluate evidence. However, they are dependent on the quality and completeness of the included systematic reviews and may be less comprehensive than systematic reviews of primary literature.

This systematic review will evaluate primary studies (e.g. RCTs) relating to the effectiveness of homeopathy for conditions commonly seen and treated by homeopaths in Australia. There will be no limit on publication date. The rationale for conducting this review is to inform the Australian Government's Natural Therapies Review, which is evaluating evidence of the clinical effectiveness of 16 therapies (including homeopathy).

2 Objectives

To evaluate the effectiveness of homeopathy in preventing and/or treating injury, disease, medical conditions, or pre-clinical conditions.

The questions for the review were as follows:

1. What is the effectiveness of homeopathy compared to placebo on outcomes considered critical or important among individuals with any condition, pre-condition, injury or risk factor?
2. What is the effectiveness of homeopathy compared to an inactive control (no intervention, waitlist or usual care [if considered inactive]) on outcomes considered critical or important among individuals with any condition, pre-condition, injury or risk factor?
3. What evidence exists examining the effectiveness of homeopathy compared to active comparators (including usual care if considered active) on outcomes considered critical or important among individuals with any condition, pre-condition, injury or risk factor?

The intent was to evaluate the evidence representative of the evidence for populations and outcomes commonly seen and treated by homeopaths in Australia, to inform the Australian Government Natural Therapies Review of the Private Health Insurance rebate. It was out of scope to evaluate harms or cost-effectiveness of homeopathy.

Table 1 lists the populations/conditions identified and considered for this review and specifies whether these studies were in priority populations that assessed homeopathy versus placebo (primary comparison) or an inactive control (secondary comparison). A prespecified prioritisation process aimed at making best use of the available evidence is described in Appendix A6.

Populations/conditions in order of priority are listed below:

1. Anxiety
2. Atopic conditions (allergies, hay fever, eczema)
3. Headache/migraine
4. Digestive disorders (infantile colic)
5. Digestive disorders (infantile diarrhea)
6. Irritable bowel syndrome
7. Recurrent infections (childhood otitis media)
8. Recurrent infections (upper respiratory tract)
9. Insomnia/sleep disorders
10. Fatigue conditions (e.g. post viral fatigue)
11. Depressive/mood disorders
12. Fibromyalgia
13. Arthritis
14. Asthma (prevention of)
15. Recurrent infections (urinary tract)
16. Psoriasis
17. Neurodevelopmental (attention deficit /autism/ learning difficulties)
18. Menopausal symptoms
19. Menstrual disorders
20. Back pain/ neck pain

3 Methods

Methods reported in this systematic review are based on that described in the *Cochrane Handbook for Systematic Reviews of Interventions* (57). Covidence (www.covidence.org), a web-based platform for producing SRs, was used for screening citations and recording decisions made. Covidence is compatible with EndNote and Microsoft Excel, which were used for managing citations and data extraction, respectively. Where appropriate, RevMan (58) was used for the main analyses and GRADEpro GDT software (www.gradepro.org) was used to record decisions and derive an overall assessment of the certainty of evidence for each outcome guided by GRADE methodology (5).

Eligible studies were assigned to an appropriate *International Classification of Disease* (ICD-11) category based on the primary clinical condition reported in the study, such that each study only contributed data to one population (see Appendix A5.4). Results are presented in ICD-11 order.

Populations and up to 7 critical or important outcomes were prioritised to inform the data synthesis (see Appendix A6). Throughout the population and outcome prioritisation exercise, the NTWC remained blinded to the screening results (i.e. number of studies identified) and characteristics of included studies (e.g. study design, size, quality) to prevent any influence on decision-making. For prioritised conditions, risk of bias was assessed, appropriate data was extracted into data extraction tables, and the results summarised into appropriate categories according to identified populations, conditions and comparators.

Summary of Findings tables (see Appendix B4) were developed for studies that compared homeopathy to placebo (primary comparison) or an inactive control (secondary comparison) and which reported on outcomes rated as critical or important by NTWC. The Summary of Findings tables included up to 7 critical and important outcomes prioritised by NTWC who were guided by the GRADE framework (see Appendix A6.2).

The final approved review protocol was registered on the international prospective register of SRs (PROSPERO: CRD42022346433).

Further details on the methods and approach used to conduct the evidence evaluation are provided in Appendix A and Appendix B of the Technical Report, which outline the following:

- Appendix A1 search methods
- Appendix A2 search strategy
- Appendix A3 search results
- Appendix A4 study selection criteria
- Appendix A5 selection of studies (inclusion decisions)
- Appendix A6 refining the research questions
- Appendix A7 summary screening results
- Appendix B1 risk of bias process
- Appendix B2 data extraction process
- Appendix B3 data analysis and synthesis
- Appendix B4 evidence statements

4 Results

4.1 Description of studies

4.1.1 Flow of studies

The literature was searched on 15 July 2022 to identify relevant studies published from database inception to the literature search date. The results of the literature search and the application of the study selection criteria are provided in Appendix A1 – A5 and Appendix C1 and C2.

A PRISMA flow diagram summarising the search and screening results is provided in Figure 1. The PRISMA flow diagram shows the number of studies at each stage of the search and screening process, including: the initial search, studies considered irrelevant based on the title and/or abstract, studies found not to be relevant when reviewed at full text, studies that met the eligibility criteria for inclusion in the review and the number of studies that were considered in the analysis for prioritised conditions.

The search retrieved 427 citations corresponding to 208 studies that were eligible for inclusion. There were 46 additional studies (not retrieved in the search) that were identified and included from the Department's public call for evidence (see Included studies). The remaining studies provided from the Department's call were already identified in the search (see Appendix C2). A further 150 studies are awaiting classification, and 192 studies are recorded as ongoing.

4.1.2 Excluded studies

There were 1188 citations screened at full text that were excluded for not meeting the prespecified eligibility criteria. Of these, 338 had a study design out of scope for the intended analysis (e.g. systematic review), 318 were of a publication type out of scope (e.g. opinion piece, grey literature), 258 studied an intervention out of scope (not homeopathy or unable to assess effects of homeopathy independent of other interventions), 103 had a comparator out of scope (e.g. studies comparing different homeopathic products), 81 studied a population out of scope (e.g. healthy population not at risk), 70 studies were not in humans, 10 studied an outcome out of scope (e.g. adverse events), and 10 citations were associated with 2 studies that had been retracted.

Citation details of the excluded studies can be found in Appendix C1. Note that some studies may have been out of scope for more than one reason, but only one reason is listed for each.

4.1.3 Studies awaiting classification

Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data to make a judgment about eligibility for inclusion are listed in Appendix C4 (*Citation details of studies awaiting classification*). This includes 41 conference abstracts (54 citations) with incomplete information about the study (Appendix C4.1), 89 studies published in languages other than English (114 citations) that are possibly eligible for inclusion (pending translation into English; Appendix C4.2), 16 studies (20 citations) for which publications were not able to be retrieved (Appendix C4.3) and 4 studies that were published after the literature search date (Appendix C4.5). There were also 93 studies that were unable to be translated or interpreted at the title/abstract stage (Appendix C4.4).

Among the 150 studies awaiting classification, 61 were conducted in a priority population[8], with 48 of those comparing homeopathy either with placebo or an inactive control[9]. The studies appeared to be comparable to those included in the evidence synthesis in terms of sample size, study duration and outcomes measured. Among those published in a language other than English, many had been conducted in the same (non-English) countries to those identified and included in the review (i.e. Italy, Germany, Russia, France, Iran, Spain).

4.1.4 Ongoing studies

Ongoing studies that do not have published results at the time of search are listed in the *Characteristics of ongoing studies* table (see Appendix C5). Of the 192 ongoing studies, there were 50 studies 'not yet recruiting', 60 studies currently 'recruiting,' 2 studies that were 'active but not recruiting' and 6 studies that had completed recruitment. A further 36 studies were complete, but the study data were not yet available, and 5 studies had completed data synthesis, but results were not yet published. The status of 18 studies is unknown, and 15 other studies had been marked as suspended, terminated or withdrawn, usually for slow enrolment or an inability to recruit participants.

Among the 192 ongoing studies, 72 were conducted in a priority population and 69 of those compared homeopathy either with placebo (68 studies) or an inactive control (1 study). The ongoing studies appeared to be comparable to those included in the evidence synthesis in terms of sample size, study duration and outcomes measured. Many ongoing studies were found on clinical trial registries of countries corresponding those identified and included in the review (i.e. India, Germany, Russia).

4.1.5 Included studies

There were 254 RCTs identified as eligible for inclusion in the review (see Figure 1). After prioritisation of the populations (or conditions) considered most relevant to the practise of homeopathy in Australia (see Appendix A6.1), 93 studies were considered in the evidence evaluation (qualitative synthesis). Those that included NTWC prioritised critical and important outcome domains and measures (see Appendix A6.2), were included in the final analysis.

An overview of the conditions identified and included in this review is provided in provided in Table 1. For the primary comparison (homeopathy versus placebo), 67 studies were considered for quantitative synthesis. For the secondary comparison (homeopathy versus inactive control), 14 studies were considered for quantitative synthesis. Studies comparing homeopathy with other active comparators are included in qualitative descriptions in the report, and results are listed in Appendix F2.

There were 137 studies that met the eligibility criteria for the review but were not included in the evidence evaluation. This is because they were conducted in populations (or conditions) not prioritised by NTWC for analysis or synthesis. These studies are listed in an inventory titled *Citation details of studies from non-priority populations* (Appendix C3).

Appendix D provides detailed descriptions of the included studies, including an overview of the PICO criteria, a summary of the risk of bias assessment and results of the data synthesis for the main comparison. Descriptions of the included studies can be found in Appendix F1 (see *'Characteristics of included studies'*).

[8] 37 of these studies were published in a language other than English.

[9] 29 of these studies were published in a language other than English.

Figure 1 Literature screening results: Homeopathy, randomised controlled trials

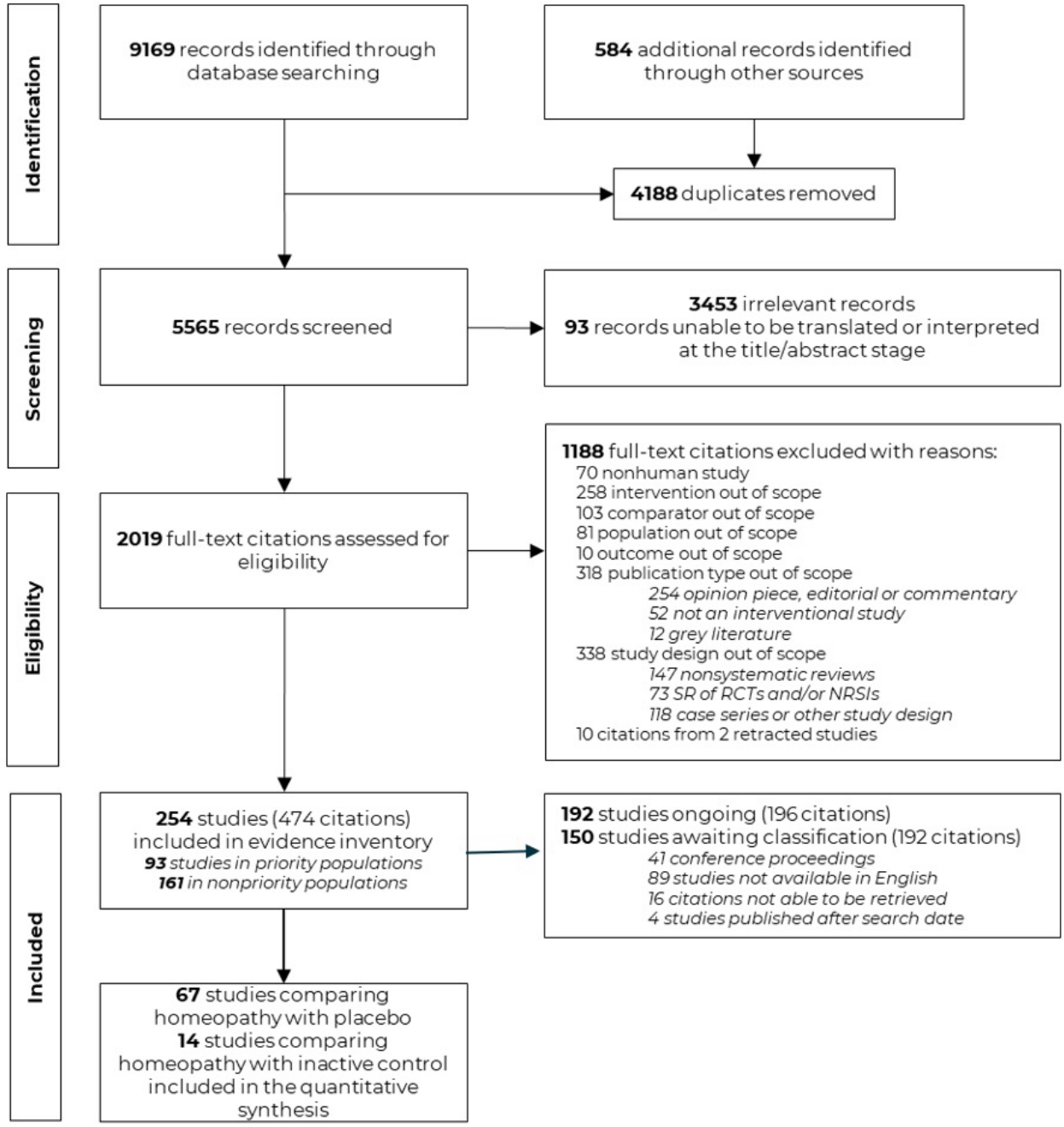


Table 1 List of conditions and population groups identified and considered in this review

ICD-11	Condition	No. of RCTs	Priority population	Included in primary or secondary comparison
01 Certain infectious and parasitic diseases		**23**		
	Acute Encephalitis Syndrome (infants & children)	1	No	--
	Calicivirus, acute (treatment)	1	No	--
	Chikungunya (prophylaxis)	1	No	--
	Cholera	1	No	--
	Dengue fever	1	No	--
	Herpes simplex, genital (recurrent)	2	No	--
	Human immunodeficiency virus	1	No	--
	Human papilloma virus	1	No	--
	Leprosy, paucibacillary	1	No	--
	Leprosy, posttreatment (with trophic ulcer, peripheral anaesthesia)	1	No	--
	Lymphatic filariasis, with acute adenolymphangitis	1	No	--
	Malaria	2	No	--
	Scabies	1	No	--
	Severe sepsis	1	No	--
	Tuberculosis, multi-drug-resistant	1	No	--
	Varicella zoster, acute (treatment) (chicken pox)	1	No	--
	Viral conjunctivitis (prophylaxis)	1	No	--
	Warts, common cutaneous or plantar	4	No	--
02 Neoplasms		**12**		
	Cancer, any	1	No	--
	Cancer, breast (survivors and/or undergoing treatment)	7	No	--
	Cancer, non-small cell lung	1	No	--
	Fibroadenoma, breast	1	No	--
	Undergoing stem cell transplant (autologous or allogeneic)	2	No	--
03 Diseases of the blood or blood-forming organs		**2**		
	Anaemia, iron-deficiency	1	No	--
	Thalassemia	1	No	--
04 Diseases of the immune system		**21**		
	Hay fever (allergic rhinitis)	9	Yes	9
	Recurrent infection, URTI (incl. otitis media, strep infection, tonsillitis, sinusitis)	10	Yes	5
	Recurrent infection, UTI	2	Yes	1
05 Endocrine, nutritional and metabolic diseases		**12**		
	Diabetes, type 1	1	No	--
	Diabetes, type 2	6	No	--
	Dyslipidaemia	2	No	--
	Overweight & obese	1	No	--
	Polycystic ovary syndrome (with persistent amenorrhea)	1	No	--
	Undernutrition (children 1-19 yrs)	1	No	--

ICD-11	Condition	No. of RCTs	Priority population	Included in primary or secondary comparison
06 Mental and behavioural disorders		**25**		
	Acute Anxiety (pre-dental, pre-test)	3	Yes	3
	Attention deficit disorder (with hyperactivity)	6	Yes	6
	Depression	4	Yes	3
	Generalised Anxiety Disorder	2	Yes	2
	Learning disabilities (dyslexia and dysgraphia)	1	Yes	1
	Neurotic disorder secondary to perinatal trauma (children)	1	No	--
	Nocturnal enuresis	1	No	--
	Schizophrenia	1	No	--
	Stress	1	No	--
	Substance use or addictive behaviour (alcohol, cocaine, opiates)	5	No	--
07 Sleep-wake disorders		**5**		
	Insomnia (chronic)	3	Yes	3
	Nocturnal bruxism	1	No	--
	Sleep problems (infants and children up to 6 years)	1	Yes	0
08 Diseases of the nervous system		**7**		
	Cerebral palsy	1	No	--
	Diabetic distal symmetric polyneuropathy	1	No	--
	Headache disorder	3	Yes	3
	Peripheral neuropathy (plantar cutaneous pain)	1	No	--
	Stroke recovery, hemiparesis	1	No	--
09 Disease of the visual system		**1**		
	Myopia	1	No	--
10 Diseases of the ear or mastoid process		**1**		
	Tinnitus	1	No	--
11 Diseases of the circulatory system		**9**		
	Hypertensive heart disease	7	No	--
	Varicose leg ulcer	1	No	--
	Varicose veins	1	No	--
12 Diseases of the respiratory system		**25**		
	Adenoid vegetations	1	No	--
	Asthma (allergic)	2	Yes	2
	Asthma, bronchial	4	Yes	4
	COPD (with acute exacerbations or acute respiratory failure)	2	No	--
	COVID-19, acute (mild [treatment])	1	No	--
	COVID-19, acute (treatment [hospitalised])	1	No	--
	Rhinitis (non-allergic)	1	No	--
	Rhinosinusitis, chronic	2	No	--
	Sinusitis, acute maxillary	1	No	--
	URTI, acute (cold symptoms, influenza-like illness)	6	No	--

ICD-11	Condition	No. of RCTs	Priority population	Included in primary or secondary comparison
	URTI, acute (cough [dry or productive])	2	No	--
	URTI, acute (influenza A or B)	1	No	--
	URTI, acute (viral tonsilitis)	1	No	--
13 Diseases of the digestive system		**18**		
	Aphthous ulcer	1	No	--
	Dentin hypersensitivity	1	No	--
	Diarrhea, acute childhood	4	Yes	4
	Digestive disorder (functional dyspepsia)	1	Yes	1
	Digestive disorder (gastroesophageal reflux disease)	1	Yes	1
	Digestive disorder (infantile colic)	1	Yes	0
	Gum disease (plaque-induced gingivitis and/or periodontitis)	5	No	--
	Haemorrhoids	1	No	--
	Irritable bowel syndrome	1	Yes	1
	Peptic ulcer disease (H. pylori)	1	No	--
	Xerostomia (dry mouth)	1	No	--
14 Diseases of the skin		**12**		
	Cutaneous insect bite reactions (mosquito)	2	No	--
	Dermatitis, atopic	2	Yes	2
	Dermatitis, irritant (diaper) (3 to 24 months)	1	No	--
	Dermatitis, seborrheic	1	No	--
	Eczema, chronic	1	Yes	1
	Lichen planus, oral	1	No	--
	Psoriasis	2	Yes	2
	Vitiligo	2	No	--
15 Diseases of the musculoskeletal system or connective tissue		**14**		
	Arthropathies, osteoarthritis (hand, hip or knee)	7	Yes	3
	Arthropathies, periarthritis of the shoulder joint	1	Yes	0
	Arthropathies, rheumatoid arthritis	2	Yes	2
	Low back pain, acute	1	Yes	0
	Low back pain, chronic (secondary to osteoarthritis)	1	Yes	1
	Plantar fasciitis	1	No	--
	Spondylosis, cervical (mechanical neck pain)	1	Yes	1
16 Diseases of the genitourinary system		**22**		
	21 Chronic complaints, females (anxiety, joint problems, headache, dizziness, hypertension)	1	Yes	1
	21 Symptoms of menopause	6	Yes	6
	Chronic kidney disease (dialysis-dependent [with/without pruritis])	2	No	--
	Endometriosis	1	Yes	1
	Erectile dysfunction	2	No	--
	Lower urinary tract symptoms (benign prostate hyperplasia)	3	No	--

ICD-11	Condition	No. of RCTs	Priority population	Included in primary or secondary comparison
	Mastalgia, cyclic	1	No	--
	Menstrual disorder, primary dysmenorrhea	2	Yes	2
	Premenstrual disturbances	3	Yes	3
	Urolithiasis (kidney stones, radiographically confirmed)	1	No	--
18 Pregnancy, childbirth or the puerperium		**4**		
	Pregnant women, ≤ 28 wks. gestation (overweight & neurotic)	1	No	--
	Pregnant women, early labour (3-6 cm) (singleton)	1	No	--
	Pregnant women, primiparous (20 to 35 years) (prevention of PPH)	1	No	--
	Pregnant women, with uterine contractile function disturbances (high risk of hypotonic labour)	1	No	--
21 Symptoms, signs or clinical findings, not elsewhere classified		**9**		
	Chronic fatigue syndrome	1	Yes	1
	Fibromyalgia	3	Yes	3
	Sedentary adults	1	No	--
	Snoring (non-apnoea)	1	No	--
	Vertigo (vestibular, non-vestibular)	3	No	--
22 Injury, poisoning or certain other consequences of external causes		**9**		
	Ankle sprain (acute)	2	No	--
	Burns injury (minor)	1	No	--
	Harmful effect of vaccination (fever)	1	No	--
	Harmful effects of arsenic exposure	1	No	--
	Harmful effects of lead exposure	1	No	--
	Procedural pain (neonates, heel-stick for screening)	1	No	--
	Traumatic brain injury (mild)	1	No	--
	Whiplash injury (acute)	1	No	--
24 Factors influencing health status or contact with health services		**22**		
	Postoperative recovery (aortic valve replacement)	1	No	--
	Postoperative recovery (carpal tunnel syndrome)	2	No	--
	Postoperative recovery (dental procedures or oral surgery)	3	No	--
	Postoperative recovery (disc herniation)	1	No	--
	Postoperative recovery (face lift)	1	No	--
	Postoperative recovery (Hallux valgus [bunion])	2	No	--
	Postoperative recovery (knee, after arthroscopy, joint implantations, ligament reconstruction)	2	No	--
	Postoperative recovery (mastectomy)	1	No	--
	Postoperative recovery (removal of wisdom teeth, impacted)	1	No	--
	Postoperative recovery (rhinoplasty)	2	No	--
	Postoperative recovery (tonsillectomy)	1	No	--

ICD-11	Condition	No. of RCTs	Priority population	Included in primary or secondary comparison
	Postoperative recovery (total abdominal hysterectomy)	1	No	--
	Postoperative recovery (upper eyelid blepharoplasty)	2	No	--
	Postoperative recovery (varicose vein surgery)	1	No	--
	Postprocedural pain (orthodontic separators)	1	No	--
25 Prevention/ codes for special purposes		**1**		
	Homeopathy as practice (people presenting to homeopathy clinic)	1	No	--
Grand Total		**254**	**93**	**78**

4.2 Atopic conditions

4.2.1 Description of the condition

Atopic conditions include allergic and hypersensitivity disorders, characterised by an inappropriate or exaggerated immune system response to foreign antigens (59). The most common forms of atopy include allergic asthma, allergic rhinitis, and atopic dermatitis (59).

4.2.1.1 Allergic rhinitis

Allergic rhinitis is clinically defined as a symptomatic disorder induced by an IgE-mediated inflammation after allergen exposure of the membranous lining the nose (60). Common allergic triggers include house dust mites, pollens (from trees, grasses, shrubs and weeds), animal dander or fungi, which occur naturally in the environment. Allergic rhinitis can also be caused by triggers to which a person is exposed in the course of their work (occupational exposure)(61). These may include vegetable proteins, enzymes and chemicals. The condition can be subdivided into “intermittent” or “persistent” disease, which references the duration symptoms persist. Persistent allergic rhinitis is diagnosed when symptoms are present more frequently than four days per week and for at least four consecutive weeks (62).

Allergic rhinitis is characterised by nasal obstruction, rhinorrhoea (runny nose), sneezing, itching of the nose and/or post-nasal drainage. It is also often associated with ocular symptoms (62). Severe allergic rhinitis has been associated with significant impairments in quality of life, sleep and work performance (63). Based on self-reports, an estimated 19% of Australians had allergic rhinitis in 2017–18; or about 4.6 million people (64). It is most common among those aged 35–44 and more commonly reported by females than males.

Symptoms of allergic rhinitis may spontaneously resolve or can be alleviated with treatment. There are a number of options available to manage allergic rhinitis in the community, which typically focus on achieving symptom control. In addition to allergen avoidance and non-medicated options (such as saline spray), pharmacological interventions that include intranasal corticosteroids and intranasal or oral antihistamines are available. Immunotherapy is also an option for patients with moderate to severe persistent allergic rhinitis that cannot be managed using other available therapies (64).

4.2.1.2 Atopic dermatitis

Atopic dermatitis (eczema) is a chronic condition that causes dry, itchy and inflamed skin (65). When eczema worsens, it is called an eczema flare, which can be caused by a range of irritants (66). Atopic dermatitis usually affects young children but can affect people at any age (65). There is no cure for atopic dermatitis, however up to 70% of children with eczema grow out of it (65).

Atopic dermatitis is managed through maintaining and protecting the skin, avoiding known irritants, treating eczema flares, controlling itching, and preventing and treating infection (66). Eczema flares are often treated with topical corticosteroids or calcineurin inhibitors (66).

4.2.2 Description of the studies

There were 14 citations (67-80) corresponding to 10 RCTs (Aabel 2000a, Aabel 2000b, Aabel 2001, Dey 2022, Kim 2005, Liu 2013, Naidoo 2013, Reilly 1984, Taylor 2000, Vickers 2000) identified in the literature search. Two additional studies (81, 82) were identified in the Department’s public call for evidence (Carello 2017, Wiesenauer 1995). There were 11 ongoing studies, and 10 studies awaiting classification, including 9 studies not in English. An overview of the PICO criteria of included studies is provided in Appendix D1.1.1 (allergic rhinitis) and D1.2.1 (atopic dermatitis).

The studies were conducted in single- or multi-centre settings in Germany (Wiesenauer 1995), India (Dey 2022), Italy (Carello 2017), Norway (Aabel 2000a, Aabel 2000b, Aabel 2001), South Africa (Naidoo 2013), Taiwan (Liu 2013), the United Kingdom (Vickers 2000, Reilly 1984, Taylor 2000) or the United States (Kim 2005).

Nine studies (Aabel 2000a, Aabel 2000b, Aabel 2001, Kim 2005, Liu 2013, Naidoo 2013, Reilly 1984, Taylor 2000, Wiesenauer 1995) were in people with allergic rhinitis (total 690 participants). Aabel 2001 enrolled patients who had been included in previous studies conducted by the trialists (Aabel 2000a and Aabel 2000b). Three studies (Carello 2017, Dey 2022, Vickers 2000) were in people with atopic dermatitis (total 215 participants). Total sample size ranged from 30 to 164 participants.

All studies examined the effectiveness of homeopathy compared with placebo. Three studies used individualised homeopathy (Dey 2022, Liu 2013, Vickers 2000) and the remainder used non-individualised homeopathic products. Most studies had a 4-week intervention period, with the intervention period across all studies ranging from 2 weeks to 8 months.

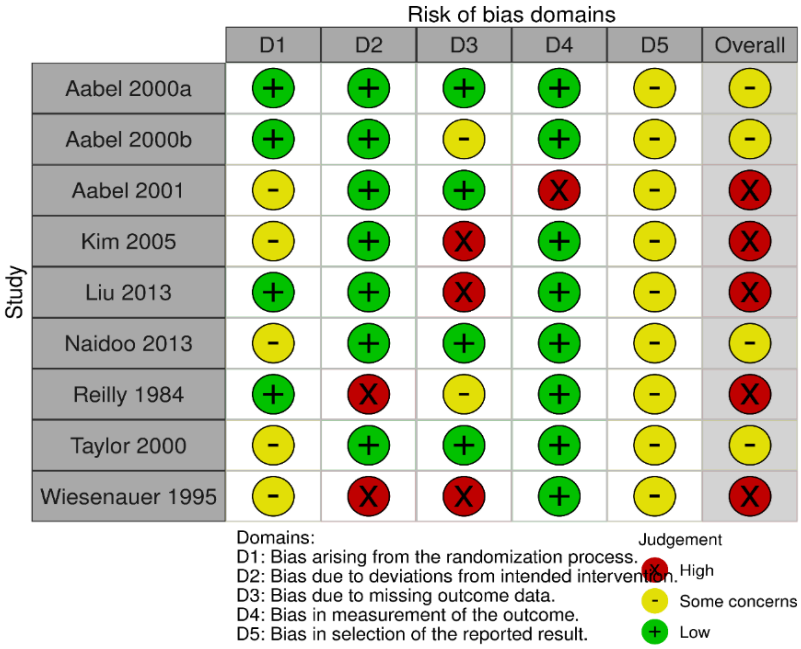
Results for the Primary Comparison: homeopathy versus placebo are provided in the Summary of Findings table (see section 4.2.4.1). There were no studies found for the Secondary Comparison: homeopathy versus inactive control (no intervention, waitlist or usual care) or Tertiary Comparison: homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.2.3 Risk of bias – summary assessment across studies

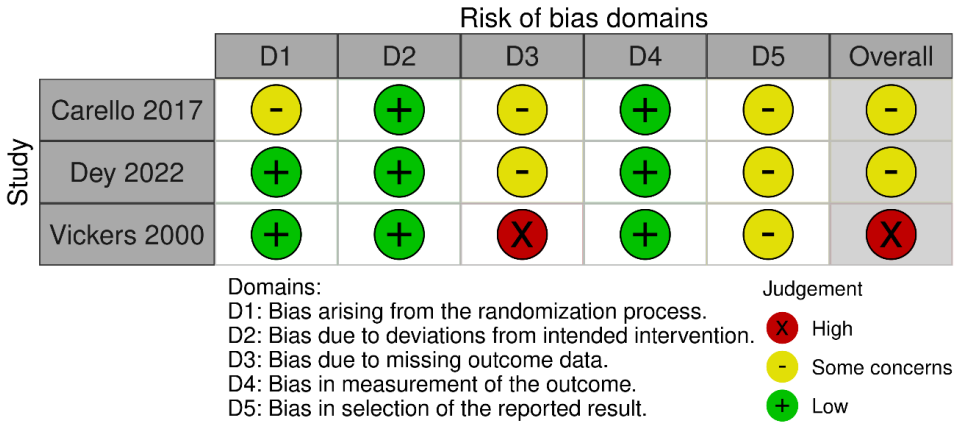
The risk of bias for each item in the included RCTs for atopic conditions (allergic rhinitis) is summarised in Figure 2. Details are provided in Appendix D1.1.2.

Figure 2 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Atopic conditions (allergic rhinitis)



The risk of bias for each item in the included RCTs for atopic conditions (dermatitis, eczema) is summarised in Figure 3. Details are provided in Appendix D1.2.2.

Figure 3 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Atopic conditions (dermatitis, eczema)



4.2.4 Summary of findings and evidence statements

4.2.4.1 Primary Comparison (vs placebo)

4.2.4.1.1 Allergic rhinitis

Homeopathy compared to placebo for Allergic rhinitis

Patient or population: Allergic rhinitis
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Symptom severity assessed with: VAS, NRS, TNSS follow-up: range 10 days to 3 months	-	SMD **0.32 SD lower** (0.6 lower to 0.03 lower)	-	194 (3 RCTs) †	⊕◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effect of homeopathy on symptom severity in people with allergic rhinitis **
Health-related quality of life assessed with: Rhinoconjunctivitis QLQ Scale from: 0 to 6 follow-up: 4 weeks	The mean QLQ score was **2.25**	MD **0.4 points lower** (1.1 lower to 0.3 higher)	-	34 (1 RCT)	⊕◯◯◯ VERY LOW [c,e,f,g,h]	The evidence is very uncertain about the effect of homeopathy on quality of life in people with allergic rhinitis ***

Homeopathy compared to placebo for Allergic rhinitis

Patient or population: Allergic rhinitis
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Medication use assessed with: Total number of antihistamine tablets taken follow-up: 5 weeks	The mean medication use was **19.7 tablets taken**	MD **8.5 fewer** (14.67 fewer to 2.33 fewer)	-	108 (1 RCT) ††	⊕⊕◯◯ LOW [c,f,h,i,j]	Homeopathy may reduce the number of antihistamine tablets taken in people with allergic rhinitis.**

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** As a rule of thumb, an SMD of 0.2 is considered a small difference, 0.5 is considered medium, and 0.8 is considered large (83).
*** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Missing data from 4 studies (310 participants) not able to be included in the meta-analysis due to the reporting format of the study authors. Results from all 4 studies suggest no important difference between homeopathy and placebo in symptom severity. Point estimates for measure of effect are not reported by the trialists. In one of these studies, homeopathy was shown to result in a significant improvement in ocular, but not nasal, symptoms.
†† Missing data from 4 RCTs (240 participants) that measured medication use but either did not report it in a format that could be extracted for meta-analysis (189 participants) or did not report it at all (51 participants). For studies that did not report results in an extractable format, the studies either did not report SD or only reported number of people using antihistamines but not the total volume of medication received. In one study that was not included in the meta-analysis, study authors report no important difference between homeopathy and placebo (p = 0.58). The remaining studies do not report estimates of effect.

CI: confidence interval; **MD:** mean difference; **QLQ:** Quality of Life Questionnaire; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. Two studies contributing over 70% of the data were at high risk of bias. In a sensitivity analysis examining the impact of these studies, the effect size decreased and show little to no effect. Certainty of evidence downgraded.

b. No serious inconsistency. Four studies (310 participants) reported data in a format that was not extractable for meta-analysis. These studies report no difference between homeopathy and placebo. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with allergic rhinitis and is applicable to the Australian population with some caveats. Many of the studies were conducted prior to 2005. It is unclear if changes in usual care or practice would influence the results. Certainty of evidence not downgraded.

d. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both important and no important benefit). Certainty of evidence downgraded.

e. Publication bias strongly suspected. Several studies ongoing and awaiting classification that could have contributed data to this outcome. Non-reporting is considered to be likely due to the p-value, direction or magnitude of effect. Certainty of evidence downgraded.

f. Serious risk of bias. One study contributing 100% of the data was considered at high risk of bias. Certainty of evidence downgraded.

g. Serious imprecision. One small study with wide confidence intervals (lower bounds overlap with both important and no important benefit). Certainty of evidence downgraded.

h. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

i. Publication bias strongly suspected. Several studies that measured this outcome did not report a result. Several studies ongoing and awaiting classification that could have contributed data to this outcome. Non-reporting is considered to be likely due to the p-value, direction or magnitude of effect. Certainty of evidence downgraded.

j. No serious imprecision. The upper and lower bounds of the 95% confidence interval suggest benefit (14.67 fewer to 2.33 fewer). In the absence of a CI that indicates important harm, a conservative judgement has been made. Certainty of evidence not downgraded.

4.2.4.1.2 Atopic dermatitis

Homeopathy compared to placebo for Atopic dermatitis

Patient or population: Atopic dermatitis
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Disease severity assessed with: SCORAD or VAS follow-up: range 3 months to 8 months	-	SMD **0.29 SD lower** (0.61 lower to 0.03 lower)	-	153 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may reduce disease severity slightly in people with atopic dermatitis.**
Quality of life assessed with: Dermatology Life Quality Index Scale from: 0 to 30 follow-up: mean 3 months		MD **0.55 points lower** (2.02 lower to 0.93 higher)	-	87 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c,e,i]	Homeopathy may result in little to no difference in health-related quality of life in people with atopic dermatitis. #
Medication use assessed with: Use of topical steroids follow-up: 12 weeks	-	SMD **0.23 SD lower** (0.53 lower to 0.99 higher)	-	46 (1 RCT)	⊕◯◯◯ VERY LOW [c,f,g,h,j]	The evidence is very uncertain about the effect of homeopathy on medication use in people with atopic dermatitis. ##
Itching – not reported	-	-	-	- ^	-	The effect of homeopathy on itching in people with atopic dermatitis is unknown.
Skin condition – not reported	-	-	-	- †	-	The effect of homeopathy on skin condition in people with atopic dermatitis is unknown.

Homeopathy compared to placebo for Atopic dermatitis

Patient or population: Atopic dermatitis
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				

*The **risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (83).

Studies assessing the MCID for the DLQI have varied from 3 to 5 points (84).
Results reported as SMD due to measure of effect used (clinical diary) which does not have a clear scale or MCID.

^ Results from 2 studies (90 participants) are not included in the meta-analysis as the study authors do not define outcome measure used, including the direction of effect, limiting interpretation of the results.
† Results from 1 study (46 participants) are not included in the meta-analysis as the study authors do not define outcome measure used, including the direction of effect, limiting interpretation of the results.

CI: confidence interval; **MD:** mean difference; **SMD**: standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. One study contributing data is at high risk of bias. In a sensitivity analysis examining the impact of this study, the result did not meaningfully change. Certainty of evidence not downgraded.

b. No serious inconsistency. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with atopic dermatitis and is directly applicable to the Australian health care context with few caveats. Certainty of evidence not downgraded.

d. Serious imprecision. The 95% confidence interval includes both benefit (SMD –0.61) and no important difference (SMD 0.03). Certainty of evidence downgraded.

e. Publication bias strongly suspected. One study awaiting classification and 2 ongoing studies that are complete with results not published (more than 140 total participants) could have contributed data to this comparison. Non-publication of results is considered likely to be due to the p-value, direction or magnitude of effect. Certainty of evidence downgraded.

f. Serious risk of bias. One study at high risk of bias contributing 100% of the data for this comparison. Certainty of evidence downgraded.

g. Very serious imprecision. One small study contributing data (sample size less than optimal). 95% confidence interval includes both important benefit and harm. Certainty of evidence downgraded 2 levels.

h. Publication bias not suspected. One study reported results that are not included in the meta-analysis due to incomplete reporting. Trialists report no difference between groups. Result is not considered likely to alter the interpretation of results. One study awaiting classification and 2 ongoing studies which are complete with results not published (over 140 participants total). It is unclear whether these studies could have contributed results to this comparison. Certainty of evidence not downgraded.

i. Serious imprecision. The 95% confidence interval is compatible with both benefit (MD –2.02) and harms (MD 0.93). Certainty of evidence downgraded.

j. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

4.2.4.2 Secondary Comparison (vs inactive control)

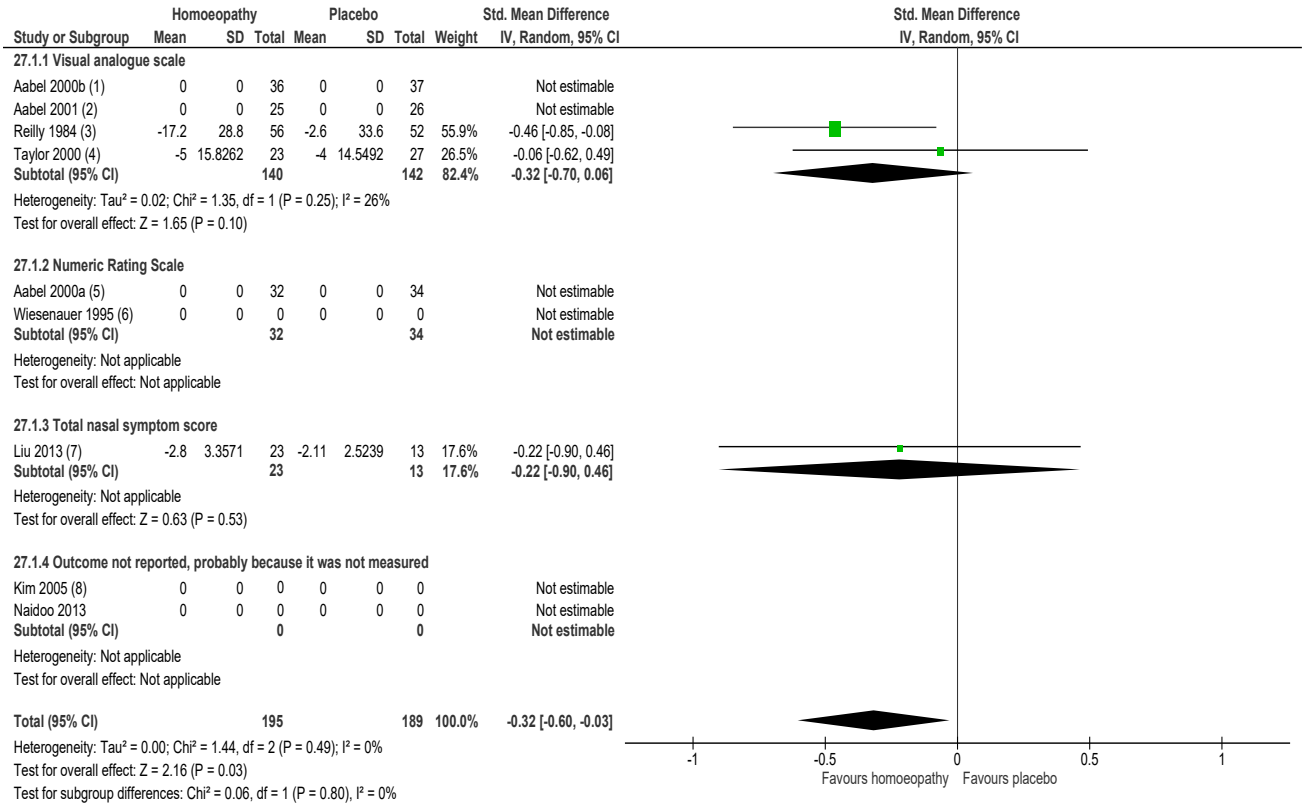
There were no studies identified that compared homeopathy to inactive control (no intervention, usual care or waitlist) in people with atopic conditions. The effect of homeopathy compared to inactive control is unknown.

4.2.5 Forest plots

4.2.5.1 Allergic rhinitis

Outcome results related to the primary comparison (homeopathy vs placebo) in people with allergic rhinitis are presented in Figure 4 (symptom severity), Figure 5 (quality of life), and Figure 6 (medication use).

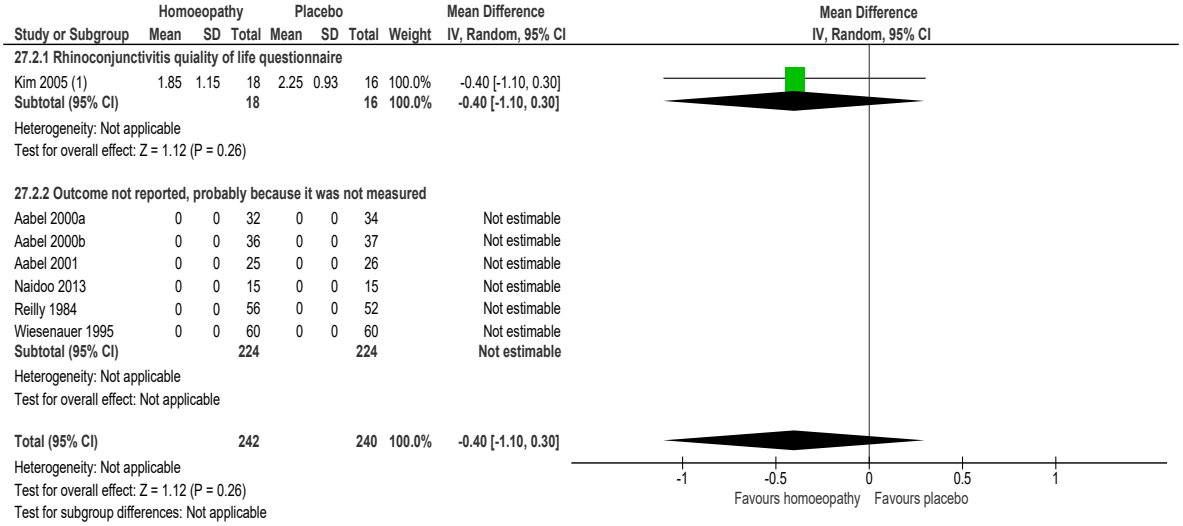
Figure 4 Forest plot of primary comparison: Homeopathy vs placebo: Allergic rhinitis – symptom severity



Footnotes

(1) Values reported graphically, not able to be extracted for analysis. Study authors report no significant difference between groups.
(2) Values not able to be extracted for analysis. Study authors report no significant difference between groups for most days.
(3) Mean change from baseline to 5 weeks, end of treatment (3 weeks) scores not reported.
(4) Authors report mean (SE). SD calculated as per protocol.
(5) Values reported graphically, not able to be extracted for analysis. Study authors report no significant difference between groups.
(6) Study authors report the proportion of participants with improved symptoms at 4 weeks. Authors report no difference in nasal symptoms and a significant improvement in occular symptoms for the homeopathy group.
(7) Change from baseline to end of treatment (week 4). Authors report mean (SE). SD calculated as per protocol.
(8) Symptom severity captured in the Rhinoconjunctivitis Quality of Life Questionnaire. Outcomes reported under quality of life.

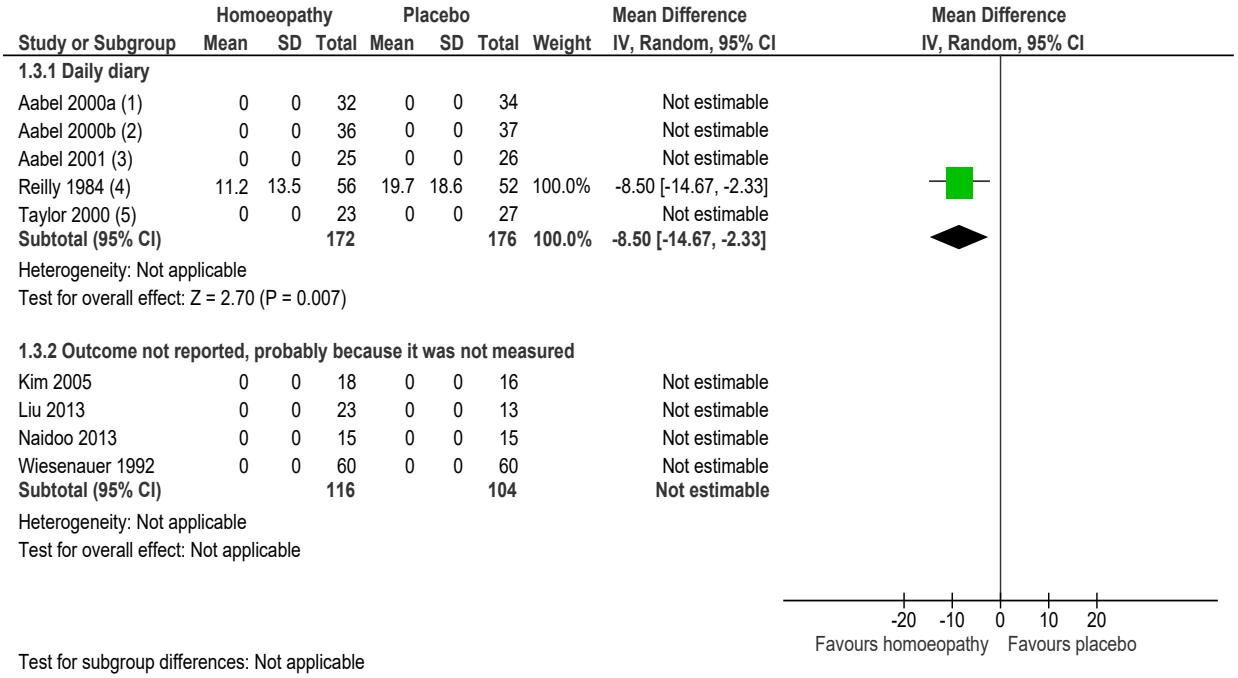
Figure 5 Forest plot of primary comparison: Homeopathy vs placebo: Allergic rhinitis – quality of life



Footnotes

(1) Study also measured quality of life using SF-36 but data were incomplete. RQLQ is the primary outcome and disease-specific quality of life measures were preferred where possible.

Figure 6 Forest plot of primary comparison: Homeopathy vs placebo: Allergic rhinitis – total medication use (see 2 forest plots below)



Test for subgroup differences: Not applicable

Footnotes

(1) Study authors do not report mean (SD), only total doses per group. Study data not able to be extracted for meta-analysis.

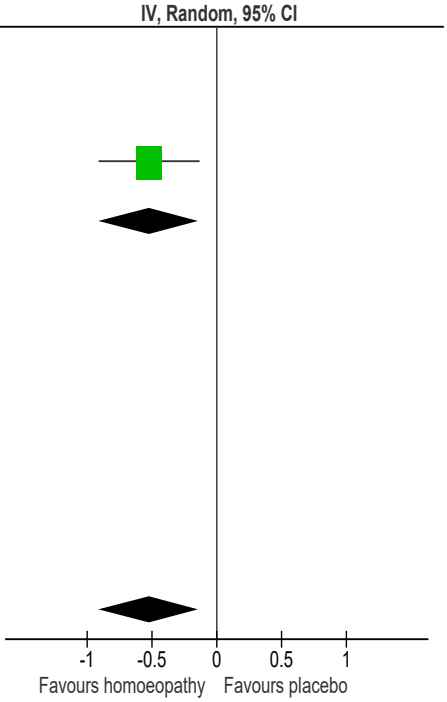
(2) Study authors do not report mean (SD), only total doses per group. Study data not able to be extracted for meta-analysis.

(3) Medication use was measured but not clearly reported by the study authors.

(4) Use of "escape" antihistamine. Mean change from baseline to 5 weeks, end of treatment (3 weeks) scores not reported.

(5) Medication use was measured but not adequately reported by the study authors.

Study or Subgroup	Homoeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 Diary								
Aabel 2000a (1)	0	0	32	0	0	34		Not estimable
Aabel 2000b (2)	0	0	36	0	0	37		Not estimable
Aabel 2001 (3)	0	0	25	0	0	26		Not estimable
Reilly 1984 (4)	11.2	13.5	56	19.7	18.6	52	100.0%	-0.52 [-0.91, -0.14]
Taylor 2000 (5)	0	0	23	0	0	27		Not estimable
Subtotal (95% CI)			**172**			**176**	**100.0%**	**-0.52 [-0.91, -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.67 (P = 0.008)								
1.3.2 Outcome not reported, probably because it was not measured								
Kim 2005	0	0	18	0	0	16		Not estimable
Liu 2013	0	0	23	0	0	13		Not estimable
Naidoo 2013	0	0	15	0	0	15		Not estimable
Wiesenauer 1995	0	0	60	0	0	60		Not estimable
Subtotal (95% CI)			**116**			**104**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**288**			**280**	**100.0%**	**-0.52 [-0.91, -0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.67 (P = 0.008)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Study authors do not report mean (SD), only total doses per group. Study data not able to be extracted for meta-analysis.

(2) Study authors do not report mean (SD), only total doses per group. Study data not able to be extracted for meta-analysis.

(3) Medication use was measured but not reported by the study authors.

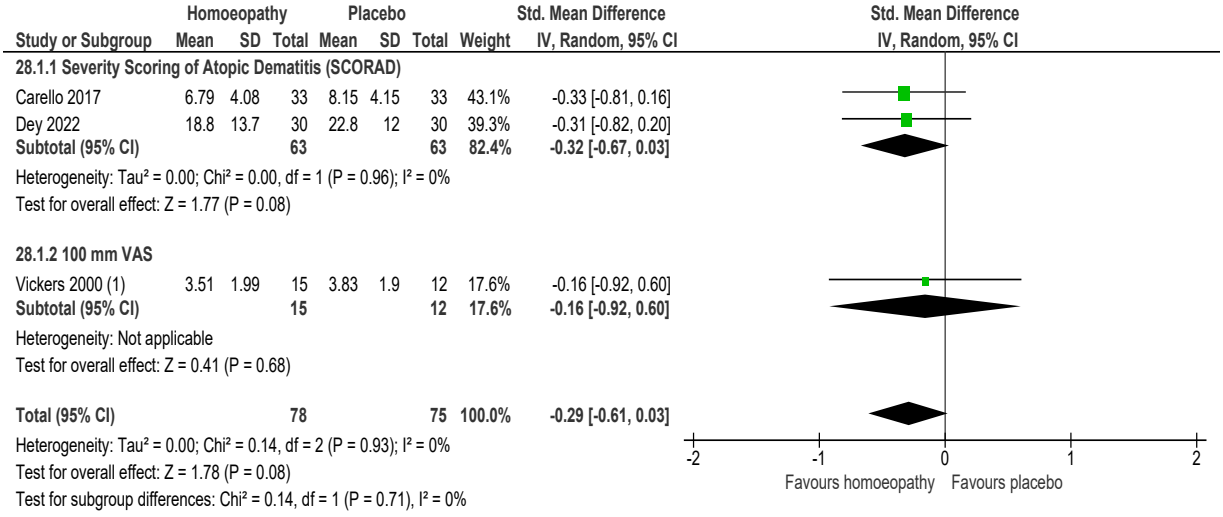
(4) Mean change from baseline to 5 weeks, end of treatment (3 weeks) scores not reported.

(5) Medication use was measured but not reported by the study authors.

4.2.5.2 Atopic dermatitis

Outcome results related to the primary comparison (homeopathy vs placebo) in people with atopic dermatitis are presented in Figure 7 (disease severity), Figure 8 (quality of life), Figure 9 (medication use).

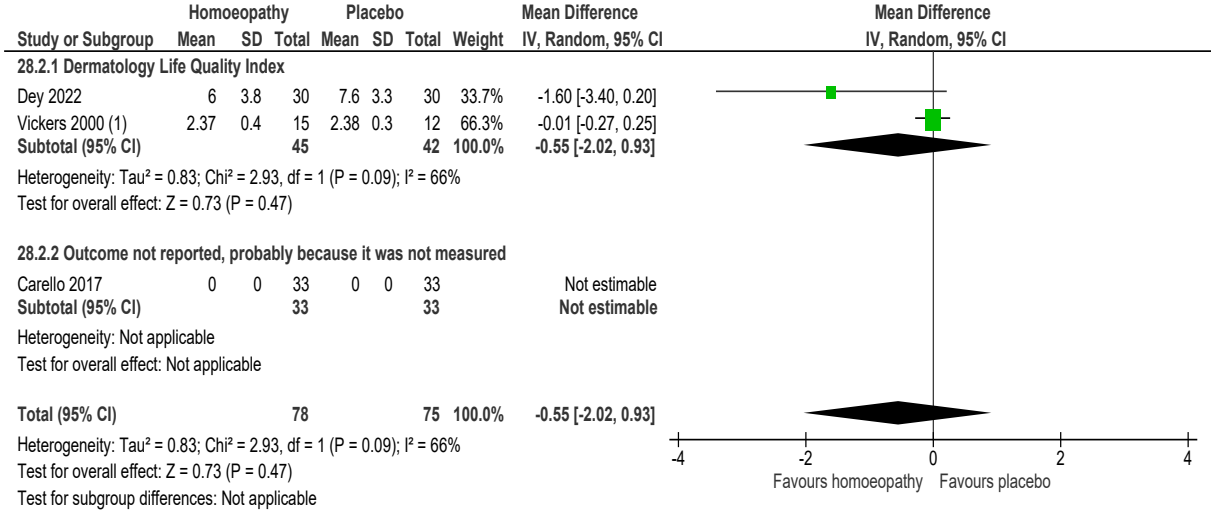
Figure 7 Forest plot of primary comparison: Homeopathy vs placebo: Atopic dermatitis – disease severity



Footnotes

(1) Study also includes an open label homeopathy arm to assess the effect of blinding. Only the blinded homeopathy arm is reported, to minimise risk of bias from this trial.

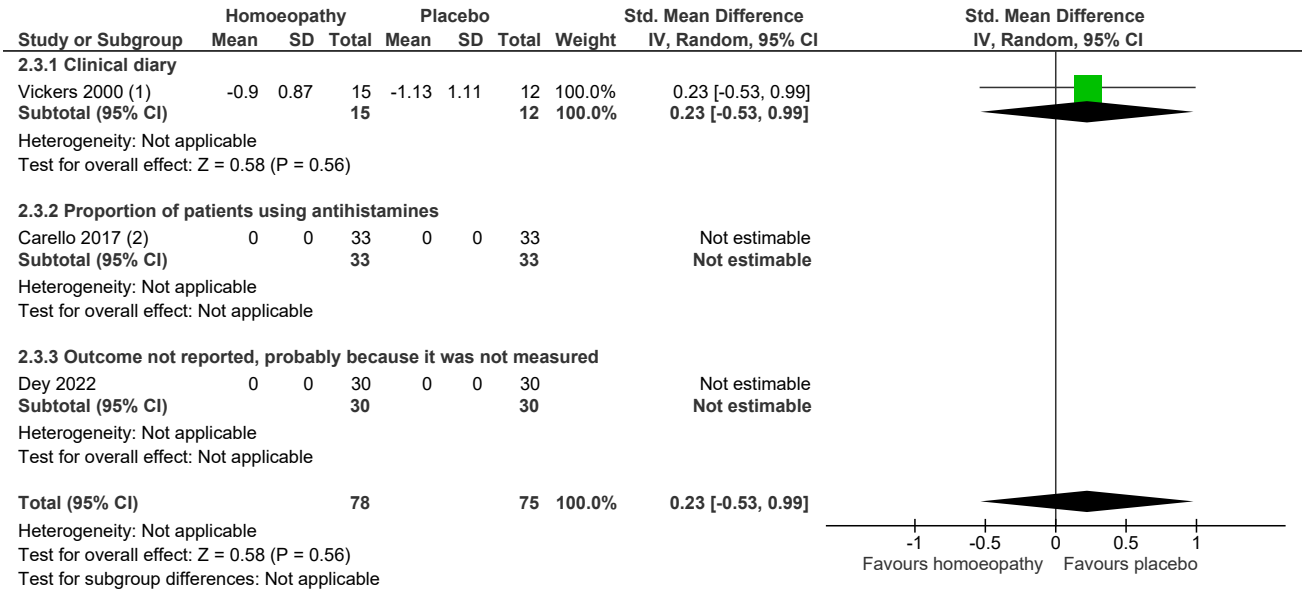
Figure 8 Forest plot of primary comparison: Homeopathy vs placebo: Atopic dermatitis – Health-related quality of life



Footnotes

(1) Study also includes an open label homeopathy arm to assess the effect of blinding. Only the blinded homeopathy arm is reported to minimise risk of bias from the trial.

Figure 9 Forest plot of primary comparison: Homoeopathy vs placebo: Atopic dermatitis – Medication use



Footnotes

(1) Study includes two homoeopathy arms (blinded, open-label). Results for blinded arm included here to minimise potential bias. Scores inverted for...

(2) Study reports the proporton of participants who are treated with antihistamines. Authors report no difference between groups.

4.3 Recurrent infections (childhood otitis media)

4.3.1 Description of the condition

Otitis media is a complex condition defined as inflammation and infection in the middle ear (85). The condition ranges in severity and encompasses a spectrum of diseases including acute otitis media, chronic suppurative otitis media and otitis media with effusion (86). It can affect any age group but is most commonly seen in children aged 6 to 24 months, with approximately 80% of children experiencing otitis media in their lifetime (86). Although most infections resolve spontaneously with no lasting effects, some children can experience recurrent infections and complications (87). Otitis media can cause temporary hearing loss, which can significantly impact a child's speech and language development, particularly if affected by recurrent episodes during school age (87).

Otitis media is often associated with acute ear pain and may be accompanied by a fever and cold and flu symptoms (88). It is diagnosed by physical examination, usually with an otoscope. Otitis media with effusion is the most common form of otitis media and is characterised by the presence of fluid in the middle ear that does not accompany an acute infection (89). The condition will generally resolve without treatment, however in serious chronic cases may require insertion of a tube to allow ventilation and prevention of fluid accumulation (89).

Acute otitis media can be caused by a viral or bacterial infection, or a combination of both. These infections usually resolve on their own and are recommended to be managed with analgesics unless the patient is at high risk, or a bacterial infection is strongly suspected (90). Chronic suppurative otitis media is a progression of an otitis media infection that is characterised by ongoing infection with a perforated tympanic membrane and persistent drainage (91).

Recurrent otitis media is defined as 3 or more episodes of acute otitis media in 6 months, or 4 or more episodes in one year (92). Children who have their first episode of otitis media prior to 12 months of age are at greater risk of developing recurrent otitis media (93). Treatment options for recurrent otitis media can be limited, as antibiotics are only effective for bacterial infections and are not always recommended. While most cases of otitis media will resolve spontaneously, the symptoms can be uncomfortable and unresolving with simple analgesics. Complementary and alternative therapies such as homeopathy are suggested to be able to relieve symptoms and prevent recurrence.

4.3.2 Description of studies

There were 8 citations (94-101) corresponding to 5 RCTs (Jacobs 2001, Pedrero-Escalas 2016, Sinha 2012, Taylor 2011 and Taylor 2014) and one quasi RCT (Harrison 1999) identified in the literature search. No studies were identified in the Department's public call for evidence. There were 2 ongoing studies, and one study awaiting classification. An overview of the PICO criteria of included studies is provided in Appendix D1.3.1.

Five studies (Jacobs 2001, Pedrero-Escalas 2016, Sinha 2012, Taylor 2011 and Taylor 2014) were set in outpatient clinics in various international locations including India (Sinha 2012) Spain (Pedrero-Escalas 2016) and the United States (Jacobs 2001, Taylor 2011, Taylor 2014). One study (Harrison 1999) was set in general practices in 2 locations in England.

Four studies (Jacobs 2001, Sinha 2012, Taylor 2011, Taylor 2014) enrolled children with acute otitis media, with sample sizes ranging from 75 to 210 (total 486 participants). The other 2 studies (Harrison 1999, Pedrero-Escalas 2016) enrolled children with otitis media with effusion, with sample sizes ranging from 33 to 96 (total 129 participants)

Two studies (Jacobs 2091, Pedrero-Escalas 2016) compared homeopathy with placebo. In Jacobs 2001, participants from both treatment groups met with a homeopath. Participants in the homeopathy group received individualised homeopathy, and those in the placebo group received an identical placebo. Treatments were administered orally 3 times daily for 5 days or until improvement occurred. In Perero-Escalas 2016, non-individualised homeopathy was used, consisting of Agraphis nutans 5CH and Thuya Occidentalis 5CH, taken orally once daily and Kalium muriaticum 9CH and Arsenicum iodatum 9CH taken twice daily. Participants in the placebo group received a placebo treatment under the same regimen, with both groups receiving a co-intervention consisting of corticosteroids and mucolytics.

There were 3 studies (Harrison 1999, Taylor 2011, Taylor 2014) that compared homeopathy with no intervention, delivered as an adjunct to standard care. Of these, 2 studies (Taylor 2011, Taylor 2014) administered homeopathic ear drops, consisting of 6 products at 30c potency, to relieve symptoms up to 3 times daily. Standard care consisted of analgesics and antibiotics. One study (Harrison 1999) used individualised homeopathy, where participants in the homeopathy group received consultations with a homeopath and were prescribed treatments based on the totality of symptoms. Participants in both groups received standard care, consisting of GP visits and antibiotics as required.

One study (Sinha 2012) compared individualised homeopathy with an active control. Participants in the homeopathy group received consultations with a homeopath and were prescribed an individualised treatment based on the totality of symptoms. Participants in the active control group received analgesic, anti-inflammatory and antipyretic medications. If less than a 50% improvement was observed in the first 3 days of treatment in both groups, antibiotics were prescribed.

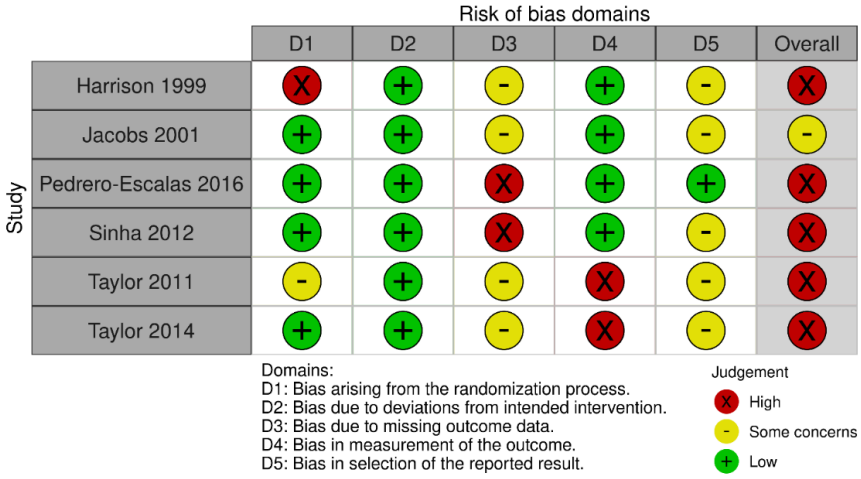
Results for the Primary Comparison: homeopathy versus placebo and the Secondary Comparison: homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings tables (see Section 4.3.4). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.3.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for recurrent infections (otitis media) is summarised in Figure 10. Details are provided in Appendix D1.3.2. No studies were judged to be at overall low risk of bias.

Figure 10 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Recurrent infections (otitis media)



4.3.4 Summary of findings and evidence statements

4.3.4.1 Primary Comparison (vs placebo)

Two RCTS (Jacobs 2001, Pedrero-Escalas 2016) comparing homeopathy with placebo in children with recurrent otitis media were eligible for this comparison.

Homeopathy compared to placebo for Recurrent infections (otitis media)

Patient or population: Recurrent infections (otitis media)
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with Placebo	Risk with Homeopathy				
Infection frequency assessed with: Number who experience at least one episode of AOM follow-up: 3 months	280 per 1,000	**218 per 1,000** (106 to 440)^	**RR 0.78** (0.38 to 1.57)	96 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in the number of episodes of acute otitis media in children with recurrent otitis media **
Infection frequency assessed with: Number who experience recurrent OME follow-up: 3 months	100 per 1,000	**43 per 1,000** (9 to 213)^^	**RR 0.43** (0.09 to 2.13)	96 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in the recurrence of otitis media with effusion in children with recurrent otitis media **

Homeopathy compared to placebo for Recurrent infections (otitis media)

Patient or population: Recurrent infections (otitis media)
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI) Risk with Placebo	Risk with Homeopathy	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
Symptom severity assessed with: Symptom diary Scale from: 0 to 9 (higher is worse) follow-up: 72 hours	The authors did not provide usable data^^^		-	75 (1 RCT)	⨁◯◯◯ VERY LOW a,b,e,f,g	The evidence is very uncertain about the effect of homeopathy on symptom severity in children with recurrent otitis media
Infection duration - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on infection duration in children with recurrent otitis media is unknown
Quality of life - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on quality of life in children with recurrent otitis media is unknown

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** A 25% relative reduction was considered important (i.e. RR < 0.75). Where absolute risk (ARD) was available this was also considered. Less than 10% ARD was considered small.

^ The ARD is 62 fewer per 1000 (from 174 fewer to 160 more) i.e. 6.2% reduction.
^^ The ARD is 57 fewer per 1000 (from 91 fewer to 113 more) i.e. 5.7% reduction.
^^^ Data were presented in a line graph, but the authors did not provide means, SD, or 95% confidence intervals.

AOM: acute otitis media; **ARD:** absolute risk difference; **CI:** confidence interval; **OME:** otitis media with effusion; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One RCT contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.
b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.
c. No serious indirectness. The evidence is directly generalisable to the Australian population with few caveats. The available evidence is in children with otitis media with effusion. Certainty of evidence not downgraded.
d. Serious imprecision. One study with wide confidence intervals (upper and lower bounds overlap with both an important and no important difference). Certainty of evidence downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.

f. No serious indirectness. The available evidence is in children with otitis media and is directly generalisable to the Australian population. Certainty of evidence not downgraded.

g. Very serious imprecision. One study suggested no importance difference between treatment groups but did not provide data. Certainty of evidence downgraded 2 levels.

4.3.4.2 Secondary Comparison (vs inactive control)

There were 3 studies (Taylor 2011, Taylor 2014, Harrison 1999) comparing homeopathy with an inactive control (no intervention) in children with recurrent otitis media that were eligible for this comparison. Two studies (Taylor 2011, Taylor 2014) contributed data to one outcome considered critical or important for this review. One study (Harrison 1999) did not report any outcomes that were considered critical or important for this review.

Homeopathy compared to inactive control (no intervention) for Recurrent infections (otitis media)

Patient or population: Recurrent infections (otitis media)
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI) Risk with Control	Risk with Homeopathy	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
Infection frequency assessed with: Number episodes of AOM follow-up: 3 months	-	-	-	(0 studies)	-	The effect of homeopathy on infection frequency in children with recurrent otitis media is unknown
Symptom severity assessed with: ETG-5 Scale from: 0 to 35 (higher is worse) follow-up: 5 to 7 days	The mean ETG-5 score was **3.3**	**MD 1.3** (0.11 lower to 2.71 higher)	-	210 (1 RCT) ^	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference on symptom severity in children with recurrent otitis media **
Infection duration - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on infection duration in children with recurrent otitis media is unknown
Quality of life - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on quality of life in children with recurrent otitis media is unknown

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

^ Missing data from 1 RCT (119 participants) that reported no difference between groups at the end of treatment.

AOM: acute otitis media; **CI:** confidence interval; **ETG-5:** ear treatment group symptom questionnaire; **RR:** risk ratio

Homeopathy compared to inactive control (no intervention) for Recurrent infections (otitis media)

Patient or population: Recurrent infections (otitis media)
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with Control	Risk with Homeopathy				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One RCT contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The evidence is directly generalisable to the Australian population with few caveats. The available evidence is in children with otitis media. Certainty of evidence not downgraded.

d. Serious imprecision. One study with wide confidence intervals (upper and lower bounds overlap with both an important and no important difference). Certainty of evidence downgraded.

e. Publication bias not suspected. Certainty of evidence downgraded not downgraded.

4.3.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in children with recurrent otitis media are presented in Figure 11 (infection frequency).

Outcome results related to the secondary comparison (homeopathy vs inactive control) are presented in Figure 12 (symptom severity).

Figure 11 Forest plot of primary comparison: Homeopathy vs placebo: Recurrent infections (childhood otitis media) – infection frequency

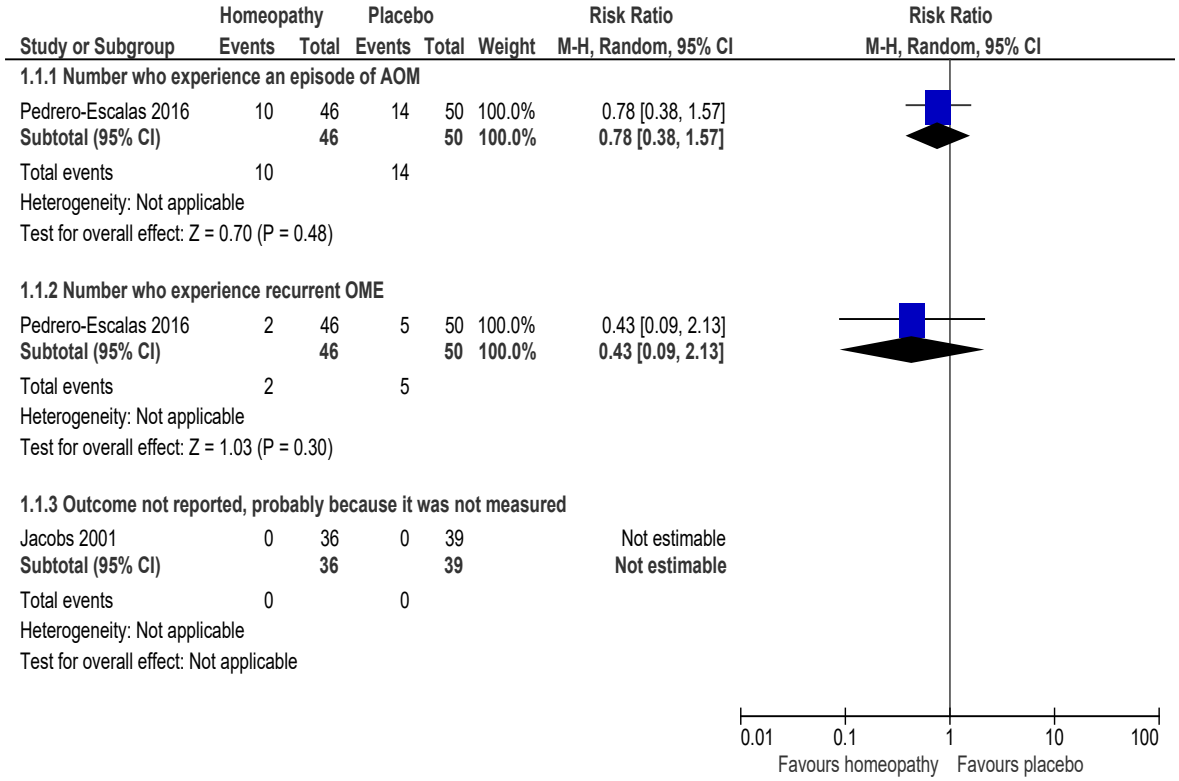
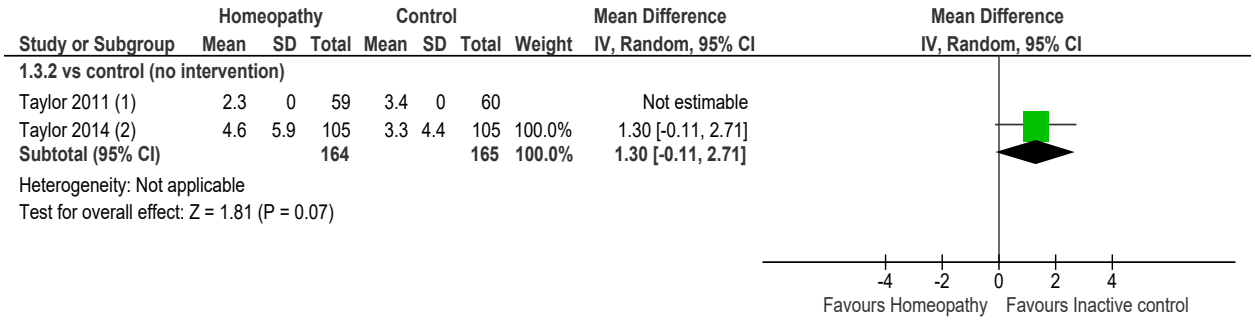


Figure 12 Forest plot of secondary comparison: Homeopathy vs inactive control: Recurrent infections (childhood otitis media) – symptom severity (ETG-5)



Footnotes

(1) No SD, SE, or 95% CI reported. No significant difference between groups 5 days after the initial visit.

(2) Data not adjusted for baseline differences.

4.4 Recurrent infections (upper respiratory tract infection)

4.4.1 Description of the condition

Upper respiratory tract infections (URTIs) are self-limiting infections of the nose, sinuses, pharynx, larynx and upper airways that can be caused by a virus or bacteria (102). One of the most common viral causes of URTIs is rhinovirus, often referred to as the common cold. Other viruses such as influenza, adenovirus, enterovirus, respiratory syncytial virus and coronaviruses are also frequently seen (102). Bacterial upper respiratory tract infections, although accounting for a relatively small proportion of infections, are often caused by *Streptococci* species (102).

URTIs are characterised by swelling or irritation of the upper airway mucosa and often present with symptoms such as cough, sore throat, running nose, headache, and fever (102). A diagnosis can be made by a medical professional based on symptom presentation, with laboratory confirmation often not performed (103). URTIs are amongst the most common conditions managed by general practitioners in Australia, representing a considerable burden on the health system (104). A significant proportion (31%) of these presentations are estimated to belong to children under 15 years of age (104).

Recurrent URTIs are common in children, with sources estimating an average frequency as high as 6 to 8 infections per year (105-107). Risk factors for recurrent episodes in children include close contact in settings such as daycares and schools, medical conditions such as asthma or those that make the individual immunocompromised (102). As most infections are mild and uncomplicated, they can be self-managed; which is typically centred on symptom relief (102). Pharmacological interventions may include analgesics, anti-inflammatory and decongestant medications. If the infection is caused by bacteria, antibiotics may be prescribed; noting that, in Australia, antibiotics are often prescribed to treat URTIs, despite the cause of most URTIs being viral pathogens (108).

Complementary or alternative medicines such as homeopathy have gained popularity due to the belief in their potential to treat symptoms as well as prevent the recurrence of infections (109).

4.4.2 Description of studies

There were 9 citations (110-118) corresponding to 3 RCTs (De Lange de Klerk 1993, Palm 2017, Steinsbekk 2004) and one quasi RCT (Furuta 2017) identified in the literature search. No additional studies were identified in the Department's public call for evidence. There were 6 ongoing studies, and 5 studies awaiting classification, 4 of which were published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D1.4.1.

Two studies were carried out in outpatient clinics in either Brazil (Furuta 2017) or the Netherlands (De Lange de Klerk 1993). One study was conducted in a community setting in Norway (Steinsbekk 2004), and one multi-centre trial was conducted in private practices or medical institutions in locations across Germany, Spain and the Ukraine (Palm 2017).

Two studies (De Lange de Klerk 1993, Steinsbekk 2004) enrolled children with URTIs, with sample sizes ranging from 170 to 420 participants. One study (Furuta 2017) enrolled children with recurrent tonsillitis who had been scheduled for tonsillectomy (40 participants) and one study (Palm 2017) enrolled children and adults with recurrent tonsillitis (256 participants).

Two studies (De Lange de Klerk 1993, Furuta 2017) compared individualised homeopathy with placebo. In both studies, all participants received consultations with a homeopath. Participants in the homeopathy treatment group were prescribed individualised treatments and those in the placebo group received identical placebo. Participants in one study (Futura 2017) also received non-individualised homeopathic products. Both studies had co-interventions consisting of conventional treatment (De Lange de Klerk 199) or treatment with antimicrobial agents (Furuta 2017).

One study (Palm 2017) compared non-individualised homeopathy with an inactive control (no intervention). Participants in the homeopathy treatment group received the oral treatment SilAtro 5-90, taken in 3 treatment periods of 8 weeks each, over the course of a year. Participants in the inactive control group received no intervention, and participants in both groups received standard care, which consisted of local antiseptics, local anaesthetics (throat lozenges) and antibiotics as needed.

One study (Steinsbekk 2004) had 4 treatment groups. Group one was assigned to a waitlist control (no intervention), group 2 received an individualised homeopathic treatment prescribed by a homeopath, group 3 received an individualised homeopathic treatment that was self-prescribed by participants (parent-selected), and group 4 received a placebo[10]. A co-intervention that allowed all participants access to medications other than homeopathic treatments was implemented.

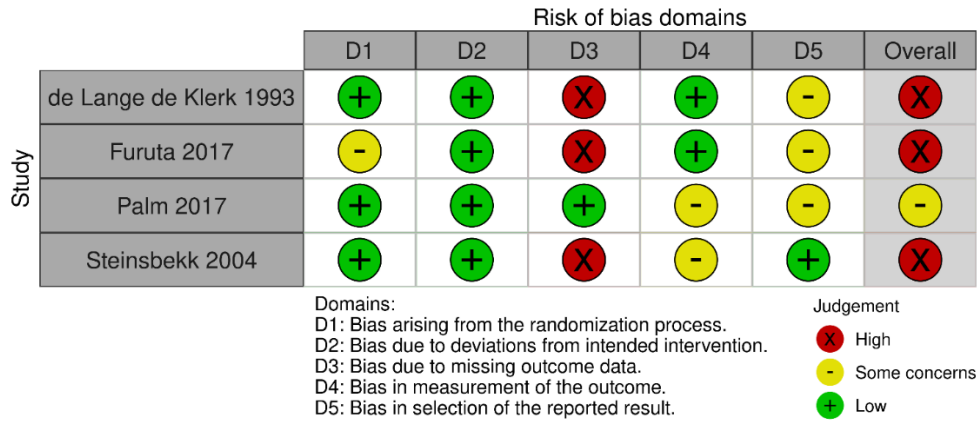
Results for the Primary Comparison: homeopathy versus placebo and the Secondary Comparison: homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings tables (see Section 4.4.4). There were no studies found for the Tertiary Comparison: homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.4.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for recurrent upper respiratory tract infections is summarised in Figure 13. Details are provided in Appendix D1.4.2. No studies were judged to be at overall low risk of bias.

Figure 13 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Recurrent upper respiratory tract infections



[10] For this review, Group 2 (homeopath-prescribed) was selected for inclusion in the analysis as it was judged to better align with the practise of homeopathy in the Australia (for health insurance rebates). The included comparisons were (i) Group 2 versus Group 4 (placebo) and (ii) Group 2 versus Group 1 (waitlist). Group 3 (parent-selected) results are presented but were not further considered.

4.4.4 Summary of findings and evidence statements

4.4.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Recurrent upper respiratory tract infections

Patient or population: Recurrent upper respiratory tract infections (URTI)
Setting: Community, outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with Placebo	Risk with Homeopathy				
Infection frequency assessed with: number participants having at least one episode of acute tonsillitis follow-up: 4 months	500 per 1,000	**200 per 1,000** (75 to 535)^	**RR 0.40** (0.15 to 1.07)	40 (1 RCT) †	⊕◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effect of homeopathy on infection frequency in people with recurrent URTIs **
Infection duration assessed with: symptom diary, median number of days with URTI symptoms follow-up: 12 weeks	The median duration of URTI symptoms was **8 days** (95% CI 6 to 9 days) in the placebo group	The median duration of URTI symptoms was **8 days** (95% CI 4 to 11.6 days) in the homeopathy group (homeopath-prescribed)	-	207 (1 RCT) ††	⊕◯◯◯ VERY LOW [a,b,e,f,g]	The evidence is very uncertain about the effect of homeopathy on infection duration in people with recurrent URTIs #
Symptom severity assessed with: symptom score (higher is worse) Scale from: 0 to 56 follow-up: range 12 weeks to 52 weeks	The mean daily score was **2.21**	MD **0.40 higher** (0.02 lower to 0.82 higher)	-	170 (1 RCT) †††	⊕◯◯◯ VERY LOW [a,b,f,j,k]	The evidence is very uncertain about the effect of homeopathy on symptom severity in people with recurrent URTIs. ***
Quality of life assessed with: general-wellbeing scale (higher is worse) Scale from: 0 to 20 follow-up: 52 weeks	The mean change in score was **4.17**	MD **0.64** (1.73 lower to 3.01 higher)	-	170 (1 RCT)	⊕⊕◯◯ LOW [a,b,e,f,j]	Homeopathy may result in little to no difference in quality of life in people with recurrent URTIs ***
Medication use assessed with: number of participants who used antibiotics follow-up: range 12 weeks to 52 weeks	287 per 1,000	**218 per 1,000** (161 to 296)^^	**RR 0.76** (0.56 to 1.03)	377 (2 RCTs) ††	⊕⊕◯◯ LOW [e,f,h,i,j]	Homeopathy may result in little to no difference in antibiotic use in people with recurrent URTIs **

Homeopathy compared to placebo for Recurrent upper respiratory tract infections

Patient or population: Recurrent upper respiratory tract infections (URTI)
Setting: Community, outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with Placebo	Risk with Homeopathy				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** A 25% relative risk reduction was considered important (i.e. RR < 0.75).
*** Effect estimate considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale), large (MD more than 20% of the scale)

^ The ARD is 300 fewer per 1000 (from 425 fewer to 35 more) i.e. 30% reduction.
^^ The ARD is 69 fewer per 1000 (from 126 fewer to 9 more) i.e. 6.9% reduction.

Results should be interpreted with caution. Data are skewed and contain outliers.

† Missing data from 1 RCT (170 participants) (data were not able to be included here). The mean number of episodes of respiratory tract infections was 7.9 in the homeopathy group, compared to 8.4 in the placebo group.
†† The study also assessed parent-selected homeopathy, with similar results observed (median duration of URTI symptoms was 9 days [95% CI 16 to 44]).
††† Missing data from 1 RCT (267 participants). Authors report median (95% CIs) and unable to be interpreted. The study suggests there is no important difference between groups.

ARD: absolute risk difference; **CI:** confidence interval; **RR:** risk ratio; **URTI:** upper respiratory tract infection.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One RCT contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.
b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.
c. No serious indirectness. The evidence is directly generalisable to the Australian population with few caveats. The available evidence is in children with recurrent tonsilitis scheduled for tonsillectomy. Certainty of evidence not downgraded.
d. Very serious imprecision. One small study with wide confidence intervals (upper and lower bounds overlap with both an important and no important difference). Certainty of evidence downgraded 2 levels.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. No serious indirectness. The evidence is directly generalisable to the Australian population with few caveats. The available evidence is in children with URTI and increased risk of recurrent infection. Certainty of evidence not downgraded.
g. Very serious imprecision. Median (95% CI) data reported by study authors and not able to be interpreted. Data were skewed and had outliers. Authors suggest a 20% reduction in symptom duration as being important. Certainty of evidence downgraded 2 levels.
h. Serious risk of bias. Two RCTs contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.
i. No serious inconsistency. Certainty of evidence not downgraded.

j. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both no important difference and important harms). Certainty of evidence downgraded.

k. Publication bias suspected. There is a strong suspicion of non-reporting of results likely to be related to p-value, direction, or magnitude of effect. Certainty of evidence downgraded.

4.4.4.2 Secondary Comparison (vs inactive control)

Homeopathy compared to inactive control (no intervention) for Recurrent infections (upper respiratory tract infections)

Patient or population: Recurrent infections (upper respiratory tract infections)
Setting: Community, outpatient clinics
Intervention: Homeopathy
Comparison: Inactive control (no intervention, usual care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with control (no intervention, usual care)	Risk with Homeopathy				
Infection frequency assessed with: Number with acute throat infections follow-up: 60 weeks	318 per 1,000	**169 per 1,000** (124 to 223)^	**RR 0.53** (0.39 to 0.70)	256 (1 RCT)	⊕⊕⊕◯ MODERATE a,b,c,d,e	Compared with no intervention homeopathy probably results in a reduction in infection frequency in people with recurrent URTIs **
Infection duration assessed with: symptom diary, median number of days with URTI symptoms follow-up: 12 weeks	The median duration of URTI symptom was **13 days** (95% CI 9.1 to 15 days) in the control group	The median duration of URTI symptom was **8 days** (95%CI 4 to 11.6 days) in the homeopathy group (homeopath-prescribed) ††	-	169 (1 RCT) †	⊕◯◯◯ VERY LOW b,e,f,g,h	The evidence is very uncertain about the effect of homeopathy on infection duration in people with recurrent URTIs #
Symptom severity assessed with: symptom score (higher is worse) follow-up: 12 weeks	The median symptom severity score was **44** points (95% CI 14 to 38) in the control group	The median symptom severity score was **24** points (95% CI 11.4 to 35.6) in the homeopathy group (homeopath-prescribed) ††	-	169 (1 RCT) †	⊕◯◯◯ VERY LOW b,e,f,g,h	The evidence is very uncertain about the effect of homeopathy on symptom severity in people with recurrent URTIs #
Quality of life - not reported	-	-	-	(0 studies) †	-	The effect of homeopathy on quality of life in people with recurrent URTIs is unknown

Homeopathy compared to inactive control (no intervention) for Recurrent infections (upper respiratory tract infections)

Patient or population: Recurrent infections (upper respiratory tract infections)
Setting: Community, outpatient clinics
Intervention: Homeopathy
Comparison: Inactive control (no intervention, usual care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with control (no intervention, usual care)	Risk with Homeopathy				
Medication use assessed with: number of participants who used antibiotics follow-up: range 12 weeks to 60 weeks	437 per 1,000	**319 per 1,000** (240 to 424)^^	**RR 0.74** (0.56 to 0.97)	306 (2 RCTs) ^	⨁⨁◯◯ LOW [c,e,i,j,k]	Compared with no intervention, homeopathy may result in a slight reduction in antibiotic use in people with recurrent URTIs **

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** A 25% relative risk reduction was considered important (i.e. RR < 0.75).
*** As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (83)

^ The ARD is 150 fewer per 1000 (from 194 fewer to 95 fewer) i.e. 15% reduction.
^^ The ARD is 118 fewer per 1000 (from 197 fewer to 13 fewer) i.e. 11.8% reduction.

† Missing data from one study (total 256 participants) that reported an effect favouring the homeopathy group ($p < 0.0001$).
†† The study included a second intervention group (parent-selected homeopathy) that is not included here.
# Results should be interpreted with caution. Data are skewed and contain outliers.

ARD: absolute risk difference; **ATI:** acute throat infection; **CI:** confidence interval; **RR:** risk ratio; **URTI:** upper respiratory tract infection.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.
b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.
c. No serious indirectness. The evidence is directly generalisable to the Australian population with few caveats. The available evidence is in adults and children (age 6 to 60 years) with recurrent tonsilitis. Certainty of evidence not downgraded.
d. Serious imprecision. Single study. Certainty of evidence downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. Serious risk of bias. One RCT contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.
g. No serious indirectness. The evidence is directly generalisable to the Australian population with few caveats. The available evidence is in children with URTI and increased risk of recurrent infection. Certainty of evidence not downgraded.

h. Very serious imprecision. Median (95% CI) data reported by study authors and not able to be interpreted. Data were skewed and had outliers. Authors suggest a 20% reduction in symptom duration as being important. Certainty of evidence downgraded 2 levels.

i. Serious risk of bias. One RCT contributing 14% of data at high risk of bias, that influences the results in favour of the intervention. Certainty of evidence downgraded.

j. No serious inconsistency. Certainty of evidence not downgraded.

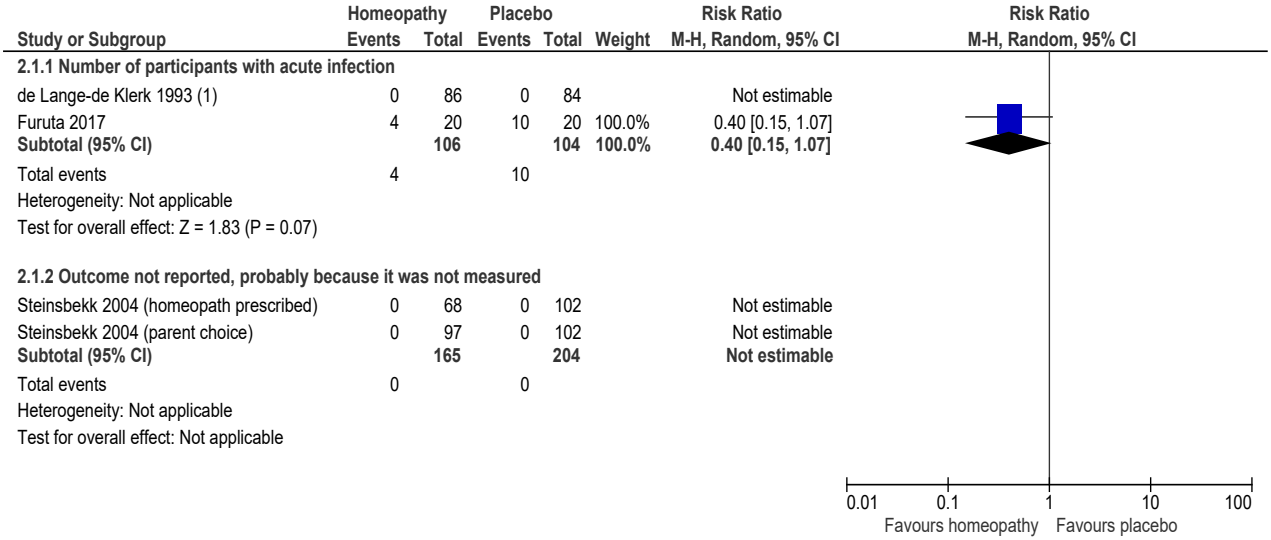
k. Serious imprecision. Wide confidence interval (upper and lower bounds overlap with both an important and no important effect). Certainty of evidence downgraded.

4.4.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with recurrent upper respiratory tract infections are presented in Figure 14 (infection frequency), Figure 15 (infection duration), Figure 16 (symptom severity), Figure 17 (quality of life) and Figure 18 (medication use).

Outcome results related to the secondary comparison (homeopathy vs inactive control) in people with recurrent upper respiratory tract infections are presented in Figure 19 (infection frequency) and Figure 20 (medication use).

Figure 14 Forest plot of primary comparison: Homeopathy vs placebo: Recurrent infections (upper respiratory tract infections) – infection frequency

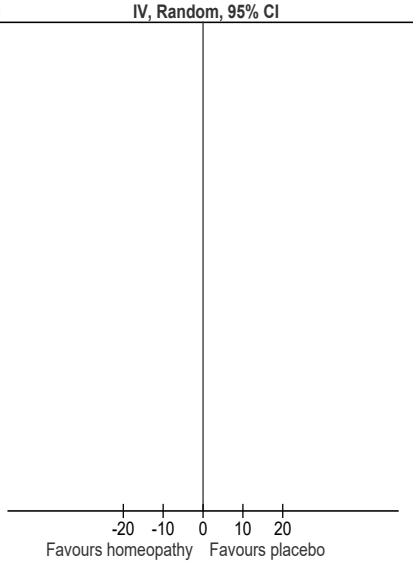


Footnotes

(1) Estimated mean number of episodes of URTIs = 7.9 in the homeopathy group versus 8.4 in the placebo group. No other data reported.

Figure 15 Forest plot of primary comparison: Homeopathy vs placebo: Recurrent infections (upper respiratory tract infections) – infection duration

Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Symptom diary, median number of days								
Steinsbekk 2004 (homeopath prescribed) (1)	0	0	68	0	0	102		Not estimable
Steinsbekk 2004 (parent choice) (2)	0	0	97	0	0	0		Not estimable
Subtotal (95% CI)			**165**			**102**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
2.2.2 total days spent with infection during the followup period								
de Lange-de Klerk 1993 (3)	0	0	86	0	0	84		Not estimable
Subtotal (95% CI)			**86**			**84**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
2.2.3 Outcome not reported, probably becuase it was not measured								
Furuta 2017	0	0	20	0	0	20		Not estimable
Subtotal (95% CI)			**20**			**20**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Footnotes

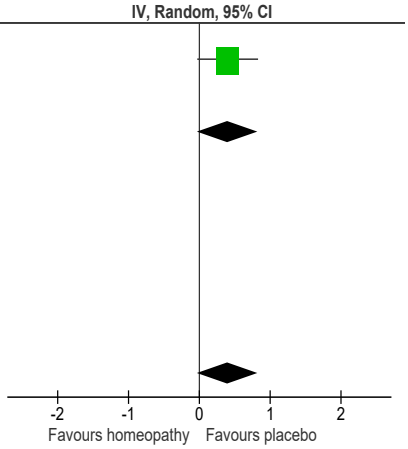
(1) Authors report median (95% CI) and not able to be included here.

(2) Authors report median (95% CI) and not able to be included here.

(3) Authors measured Frequency, duration and severity of URTI episodes during the year of participation but data not adequately reported.

Figure 16 Forest plot of primary comparison: Homeopathy vs placebo: Recurrent infections (upper respiratory tract infections) – symptom severity

Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 Symptom score								
de Lange-de Klerk 1993 (1)	2.61	1.3969	86	2.21	1.3969	84	100.0%	0.40 [-0.02, 0.82]
Steinsbekk 2004 (homeopath prescribed) (2)	0	0	68	0	0	102		Not estimable
Steinsbekk 2004 (parent choice) (3)	0	0	97	0	0	102		Not estimable
Subtotal (95% CI)			**154**			**186**	**100.0%**	**0.40 [-0.02, 0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.87 (P = 0.06)								
2.3.2 Outcome not reported, probably because it was not measured								
Furuta 2017	0	0	20	0	0	20		Not estimable
Subtotal (95% CI)			**20**			**20**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**174**			**206**	**100.0%**	**0.40 [-0.02, 0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.87 (P = 0.06)								
Test for subgroup differences: Not applicable								



Footnotes

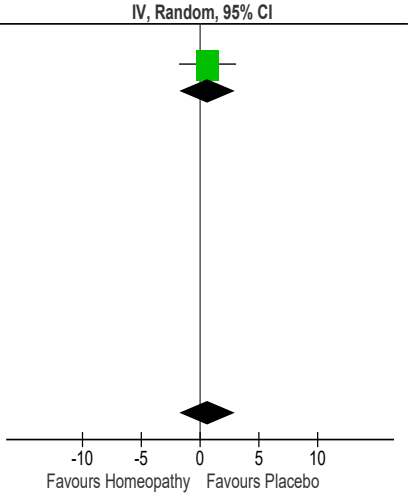
(1) mean daily score

(2) Authors report median (95% CI) and not able to be included here.

(3) Authors report median (95% CI) and not able to be included here.

Figure 17 Forest plot of primary comparison: Homeopathy vs placebo: Recurrent infections (upper respiratory tract infections) – quality of life

Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.5.1 General wellbeing score								
de Lange-de Klerk 1993 (1)	4.81	7.8825	86	4.17	7.8825	84	100.0%	0.64 [-1.73, 3.01]
Subtotal (95% CI)			**86**			**84**	**100.0%**	**0.64 [-1.73, 3.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.53 (P = 0.60)								
2.5.2 Outcome not reported, probably because it was not measured								
Furuta 2017	0	0	20	0	0	20		Not estimable
Steinsbekk 2004 (homeopath prescribed) (2)	0	0	82	0	0	125		Not estimable
Steinsbekk 2004 (parent choice) (3)	0	0	126	0	0	125		Not estimable
Subtotal (95% CI)			**228**			**270**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**314**			**354**	**100.0%**	**0.64 [-1.73, 3.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.53 (P = 0.60)								
Test for subgroup differences: Not applicable								



Footnotes

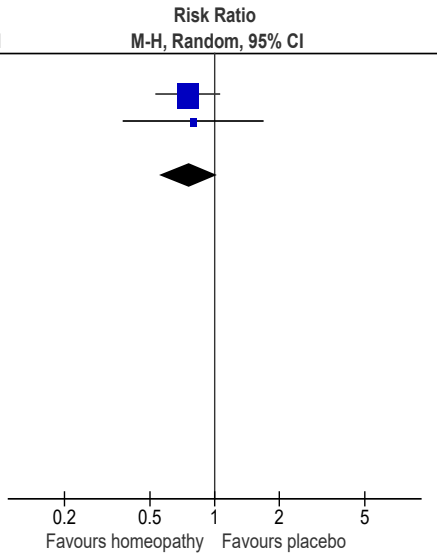
(1) mean change from baseline.

(2) Total score. Data calculated from mean (95%CI)

(3) Total score. Data calculated from mean (95%CI). Data not included in meta-analysis (to avoid double-counting of the control group).

Figure 18 Forest plot of primary comparison: Homeopathy vs placebo: Recurrent infections (upper respiratory tract infections) – medication use

Study or Subgroup	Homeopathy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Number of participants who used antibiotics						
de Lange-de Klerk 1993	33	86	43	84	82.9%	0.75 [0.53, 1.05]
Steinsbekk 2004 (homeopath prescribed)	9	68	17	102	17.1%	0.79 [0.38, 1.68]
Steinsbekk 2004 (parent choice) (1)	19	97	17	102	0.0%	1.18 [0.65, 2.13]
Subtotal (95% CI)		**154**		**186**	**100.0%**	**0.76 [0.56, 1.03]**
Total events	42		60			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
2.4.2 Outcome not reported, probably because it was not measured						
Furuta 2017	0	20	0	20		Not estimable
Subtotal (95% CI)		**20**		**20**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

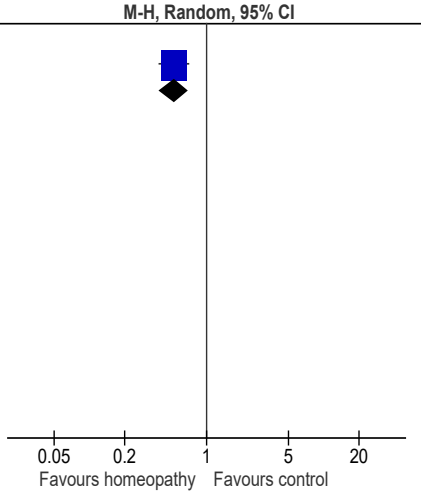


Footnotes

(1) Data not included in meta-analysis (to avoid double-counting of the control group).

Figure 19 Forest plot of secondary comparison: Homeopathy vs inactive control: Recurrent infections (upper respiratory tract infections) – infection frequency

Study or Subgroup	Homeopathy Events	Total	No intervention Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Number of participants with acute infection						
Palm 2017 (1)	42	132	75	124	100.0%	0.53 [0.39, 0.70]
Subtotal (95% CI)		**132**		**124**	**100.0%**	**0.53 [0.39, 0.70]**
Total events	42		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.38 (P < 0.0001)						
3.1.2 Outcome not reported, probably because it was not measured						
Steinsbekk 2004 (homeopath prescribed)	0	68	0	74		Not estimable
Steinsbekk 2004 (parent choice)	0	97	0	74		Not estimable
Subtotal (95% CI)		**68**		**74**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

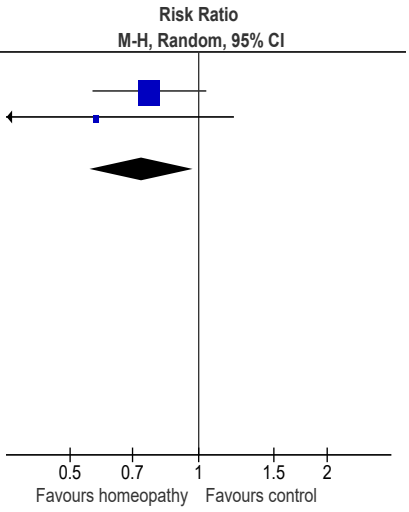


Footnotes

(1) Estimated episodes per year = 0.59 (95% CI 0.41, 0.86) in the homeopathy group versus 1.34 (95% CI 1.08, 1.66) in the control group.

Figure 20 Forest plot of secondary comparison: Homeopathy vs inactive control: Recurrent infections (upper respiratory tract infections) – medication use

Study or Subgroup	Homeopathy Events	Total	No intervention Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Number of participants who used antibiotics						
Palm 2017	26	50	59	87	85.6%	0.77 [0.57, 1.04]
Steinsbekk 2004 (homeopath prescribed)	9	68	17	74	14.4%	0.58 [0.28, 1.20]
Steinsbekk 2004 (parent choice) (1)	19	97	17	74	0.0%	0.77 [0.43, 1.40]
Subtotal (95% CI)		**118**		**161**	**100.0%**	**0.74 [0.56, 0.97]**
Total events	35		76			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.14 (P = 0.03)						
3.4.2 Outcome not reported, probably because it was not measured						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Footnotes

(1) Data not included in meta-analysis (to avoid double-counting of the control group).

4.5 Recurrent infections (genitourinary)

4.5.1 Description of the condition

Recurrent genitourinary infections is an umbrella term used in this review to describe bacterial urinary tract infections (UTIs) and vaginal candidiasis (thrush). UTIs are common infections, experienced more frequently in females than males (119). They are most often caused by bacteria (usually *Escherichia coli*) entering the urinary tract and multiplying, causing uncomfortable symptoms such as the frequent urge to urinate, feelings of bladder fullness even after urinating and burning pain (45).

Approximately 50-60% of females will experience a UTI in their lifetime, and over a quarter of these will experience a repeat infection within 6-months (119). Recurrent UTIs are often caused by infection by the same pathogen, and require antibiotics to treat (119). Recurrent UTIs can significantly impact quality of life and lead to frequent exposure to antibiotics. As a result, prophylactic measures and alternative therapies such as homeopathy are sometimes explored.

Vaginal candidiasis (thrush) is also a common condition in females, with 70% experiencing an incidence of thrush in their lifetime (120). Vaginal candidiasis is caused by an infection of Candida species (usually *Candida albicans*) in the vagina and/or vulva, causing symptoms such as inflammation, itching and discomfort when urinating (120).

Approximately 8% of females will experience recurrent episodes of vaginal thrush, however it is noted that most cases of vaginal thrush may go unreported as females will often not seek clinical care to treat the condition (120). Uncomplicated vaginal thrush can be treated by over-the-counter oral or intravaginal anti-fungal treatments. Females who suffer from recurrent infections may benefit from extended antifungal treatment (at least 6 months) (120). Alternative therapies such as homeopathy are commonly sought for this condition.

4.5.2 Description of studies

Two citations (121, 122) corresponding to one RCT (Witt 2009) and one quasi RCT (Pannek 2019) were identified in the literature search. No additional studies were identified in the Department's public call for evidence. There were no ongoing studies, and no studies awaiting classification identified. An overview of the PICO criteria of included studies is provided in Appendix D1.5.1.

Two studies were conducted at outpatient clinics in Switzerland (Pannek 2019) or Vienna (Witt 2009). Participants in Pannek 2019 (total 46 participants) had spinal cord injuries and experienced recurrent UTIs. The majority of participants were male (66%). Participants in Witt 2009 were female (total 150 participants) with recurrent vulvovaginal candidiasis.

One study (Pannek 2019) compared individualised homeopathy with inactive control (no intervention) over a treatment period of 12 months. The intervention was prescribed by a homeopath on the basis of the participants' medical history, in the form of a high potency liquid, taken orally. Standard prophylaxis was provided to both treatment groups as a co-intervention.

One study (Witt 2009) comprised 3 treatment groups, comparing individualised homeopathy with 2 different active control groups. The homeopathic treatment group was a 12-month intervention consisting of an individually prescribed, single homeopathic remedy. The active control groups were prescribed an oral antifungal treatment (itraconazole) or itraconazole plus a vaginal probiotic tablet (lactobacilli) for a period of 6-months, followed by 6 months of no treatment.

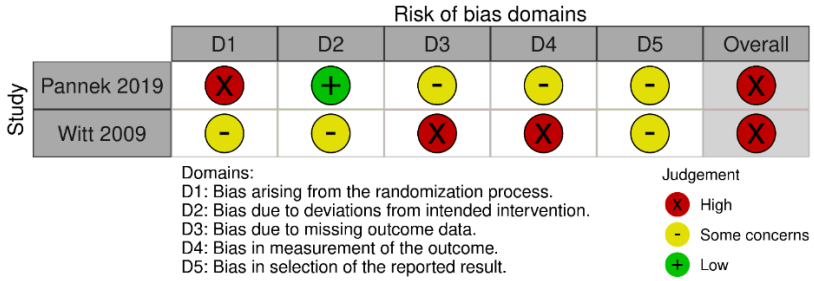
There were no studies found for the Primary Comparison: homeopathy versus placebo. Results for the Secondary Comparison: homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings table (see Section 4.5.4). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.5.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for recurrent genitourinary infections is summarised in Figure 21. Details are provided in Appendix D1.5.2. No studies were judged to be at overall low risk of bias.

Figure 21 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Recurrent genitourinary infections



4.5.4 Summary of findings and evidence statements

4.5.4.1 Primary Comparison (vs placebo)

There were no studies found comparing homeopathy with placebo in people with recurrent genitourinary infections, therefore the effect of homeopathy compared to placebo on the following outcomes is unknown:

- Number of urinary tract infections (symptomatic and/or combined with asymptomatic)
- Health-related quality of life

4.5.4.2 Secondary Comparison (vs inactive control)

Homeopathy compared to inactive control for Recurrent genitourinary infections

Patient or population: Recurrent genitourinary infections
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with Control	Risk with Homeopathy				
Infection frequency assessed with: Number of confirmed UTIs per year follow-up: 12 months	300 per 1,000	**81 per 1,000** (15 to 408) ^	**RR 0.27** (0.05, 1.36)	35 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on recurrent genitourinary infections**
Health-related quality of life assessed with EQ-5D Follow up: 12 months	The authors reported homeopathy did not have an effect on health-related quality of life ($p > 0.9$) but did not provide any data.		-	35 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on health-related quality of life in people with recurrent genitourinary infections

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** A 25% relative risk reduction was considered important (i.e. RR < 0.75).

^ The ARD is 219 fewer per 1000 (from 285 fewer to 108 more) i.e. 21.9% reduction.

ARD: absolute risk difference; **CI:** confidence interval; **EQ-5D:** EuroQol five dimensions questionnaire; **RR:** risk ratio **UTI:** urinary tract infection

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One RCT contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The evidence is directly generalisable to the Australian population with some caveats. The available evidence is in people (predominantly males) with spinal cord injury who have neurogenic lower urinary tract dysfunction and may not be applicable to the wider population. Certainty of evidence not downgraded.

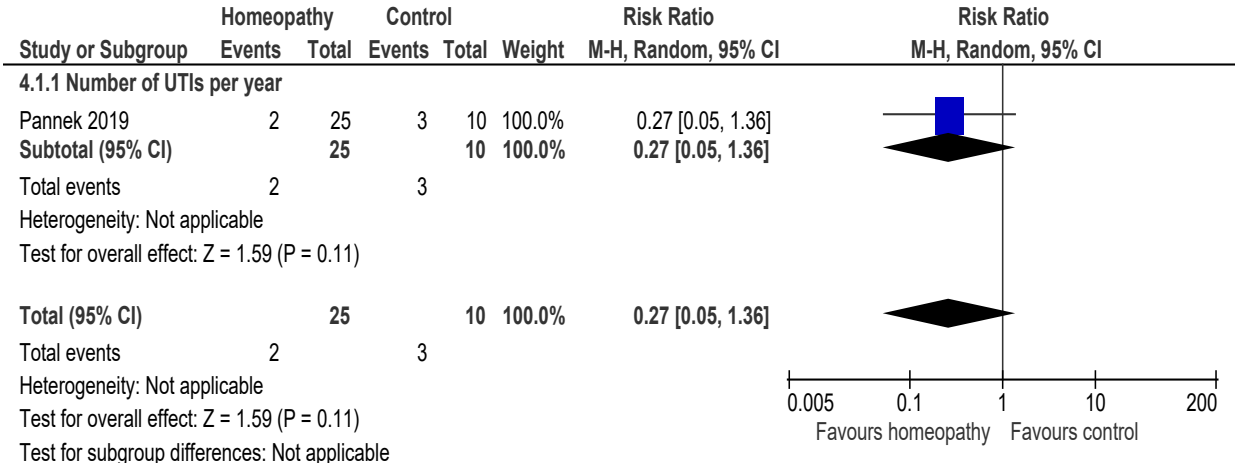
d. Very serious imprecision. One small study with wide confidence intervals (upper and lower bounds overlap with both an important and no important difference). Certainty of evidence downgraded 2 levels.

e. Publication bias not suspected. Certainty of evidence not downgraded.

4.5.5 Forest plots

Outcome results related to Secondary Comparison (homeopathy vs inactive control) in people with recurrent urinary tract infections are presented in Figure 22 (infection frequency).

Figure 22 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Recurrent infections (genitourinary) – infection frequency



4.6 Anxiety

4.6.1 Description of the condition

Anxiety is the most common mental health condition in Australia and the sixth largest contributor to burden of disease, with one in 4 people experiencing anxiety at some stage in their life (123, 124). While it is normal to feel anxious or stressed in certain situations, those with an anxiety disorder experience these symptoms more frequently and persistently without an obvious cause. Feelings of anxiety can impact quality of life and day-to-day functioning (123) and can also have significant direct and indirect economic consequences (125). It is not uncommon for anxiety disorders to become chronic, with the 12-month prevalence rate estimated at 17% and a lifetime prevalence rate of close to 25% (126).

There are different types of anxiety presenting with different symptoms, including acute performance anxiety, generalised anxiety disorder, social anxiety, specific phobias, and panic disorders. Each type of anxiety disorder has its own features, however there are some common symptoms including excessive fear or worrying, panic attacks, racing heart, tightening of the chest, shortness of breath, and avoidance of situations that cause anxiety.

Treatments for anxiety focus on controlling symptoms to minimise their impact on daily life. This can include a range of psychological treatments such as Cognitive Behavioural Therapy, medical interventions such as antidepressants, or an anxiety management strategy (123). Natural and holistic forms of therapy to assist pharmacological approaches or to act as an alternative in a variety of anxiety-related conditions are also used. This includes a variety of complementary and lifestyle interventions such as acupuncture, aromatherapy, Western herbal medicines, homeopathy, and meditative forms of exercise such as yoga and Tai Chi (127).

4.6.2 Description of studies

Four citations (128-131) corresponding to 3 RCTs (Baker 2003, Bonne 2003, Parewa 2021) and one quasi RCT (Nux-Foy 2018) were identified in the literature search. One additional quasi RCT (Dimpfel 2016) (132) was identified in the Department's public call for evidence. There were 3 ongoing studies, and 2 studies awaiting classification, one of which was published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D2.1.1.

Two studies were carried out in community settings in either Israel (Bonne 2003) or Germany (Dimpfel 2016). One study was carried out at an outpatient setting in India (Parewa 2021). The remaining 2 studies were carried out at university centres in either Australia (Baker 2003) or Israel (Fux-Noy 2018). Sample sizes ranged from 22 to 70 (total 222 participants), with studies enrolling students with examination or test anxiety (Baker 2003, Dimpfel 2016), generalised anxiety disorder (Parewa 2021, Bonne 2003) or children aged 5 to 9 years old exhibiting anxiety on their initial dental diagnostic appointment (Fux-Noy 2018).

All 5 studies compared homeopathy to placebo, with one study also using a second homeopathic intervention prepared in a different way (Baker 2003). In 2 studies (Bonne 2003, Parewa 2021) participants received individualised, oral homeopathy based on the totality of symptoms. In one study (Bonne 2003), participants received a single dose as per the assessment of the homeopath with the potential for a second alternative dose or increased dose 5 weeks later. The other 3 studies provided non-individualised homeopathy (Baker 2003, Nux-Foy 2018, Dimpfel 2016), with one study (Fux-Noy 2018) providing a combination preparation. Treatments were to be taken twice a day for 4 consecutive days (Baker 2003), twice a day the day before and on the morning of the dental treatment (Nux-Foy 2018) and as a single dose on the experimental day (Dimpfel 2016).

Length of follow-up ranged from one week (Baker 2003), ten weeks (Bonne 2003), three months (Parewa 2021) to none (follow-up completed the day of outcome collection) (Fux-Noy 2018 and Dimpfel 2016).

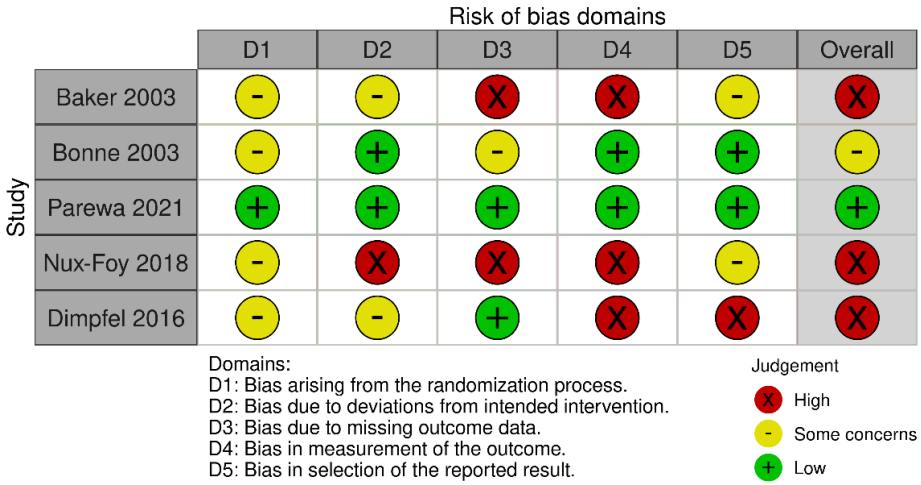
Results for the primary comparison: homeopathy versus placebo are provided in the Summary of Findings table (see Section 4.6.4). There were no studies found for the secondary comparison: homeopathy versus inactive control (no intervention, waitlist or usual care) or tertiary comparison: homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.6.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for anxiety is summarised in Figure 23. Details are provided in Appendix D2.1.2. One study was judged to be at overall low risk of bias.

Figure 23 Risk of bias summary: review author's judgements about each risk of bias item for each included study – Anxiety (or symptoms of anxiety)



4.6.4 Summary of findings and evidence statements

4.6.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Anxiety (or symptoms of anxiety)

Patient or population: Anxiety (or symptoms of anxiety)
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with Placebo	Risk with Homeopathy				
Anxiety severity assessed with: HAM-A, RTA (higher is worse) follow-up: range 4 days to 3 months	-	SMD **0.05 SD lower** (0.66 lower to 0.56 higher)	-	150 (3 RCTs) ^	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in anxiety severity in people with anxiety **
Depression severity assessed with: HAM-D (higher is worse) Scale from: 0 to 52 follow-up: 10 weeks	The mean HAM-D score was **12.0**	MD **1.5 higher** (2.16 lower to 5.16 higher)	-	44 (1 RCT)	⊕⊕◯◯ LOW [c,e,f,g,h]	Homeopathy may result in little to no difference in symptoms of depression in people with anxiety ***
Emotional function assessed with: BSI (higher is worse) follow-up: range 10 weeks to 10 weeks	The mean BSI score was **0.25**	MD **0.00** (0.08 lower to 0.08 higher)	-	44 (1 RCT)	⊕⊕◯◯ LOW [c,e,f,g,h]	Homeopathy may result in little to no difference in emotional function in people with anxiety ***
Physical functioning - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on physical functioning in people with anxiety is unknown
Health-related quality of life - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on quality of life in people with anxiety is unknown

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (83)
*** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

^ One study (41 participants) also compared radionically prepared homeopathy to placebo, with similar results observed.

BSI: brief symptom inventory; **CI**: confidence interval; **HAM-A:** Hamilton anxiety rating scale; **HAM-D:** Hamilton depression rating scale; **MD**: mean difference; **RCT**: randomised controlled trial; **SMD**: standardised mean difference;

Homeopathy compared to placebo for Anxiety (or symptoms of anxiety)

Patient or population: Anxiety (or symptoms of anxiety)
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with Placebo	Risk with Homeopathy				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. One study contributing 32% data was at high risk of bias. In a sensitivity analysis considering the impact of this study, the effect size did not meaningfully change. Certainty of evidence not downgraded.

b. Serious inconsistency. Point estimates vary, with one study suggesting an effect favouring homeopathy and 2 studies favouring placebo. Statistical heterogeneity was high (I^2 = 71%). Certainty of evidence downgraded.

c. No serious indirectness. The available evidence is in people with generalised anxiety disorder or test anxiety and is directly generalisable to the Australian population with few caveats. Certainty of evidence not downgraded.

d. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both a meaningful benefit and meaningful harm). Certainty of evidence downgraded.

e. Publication bias not suspected. Certainty of evidence not downgraded.

f. No serious risk of bias. Certainty of evidence not downgraded.

g. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

h. Very serious imprecision. Single small study. Wide confidence intervals (upper and lower bounds overlap with both a meaningful benefit and meaningful harm). Certainty of evidence downgraded 2 levels.

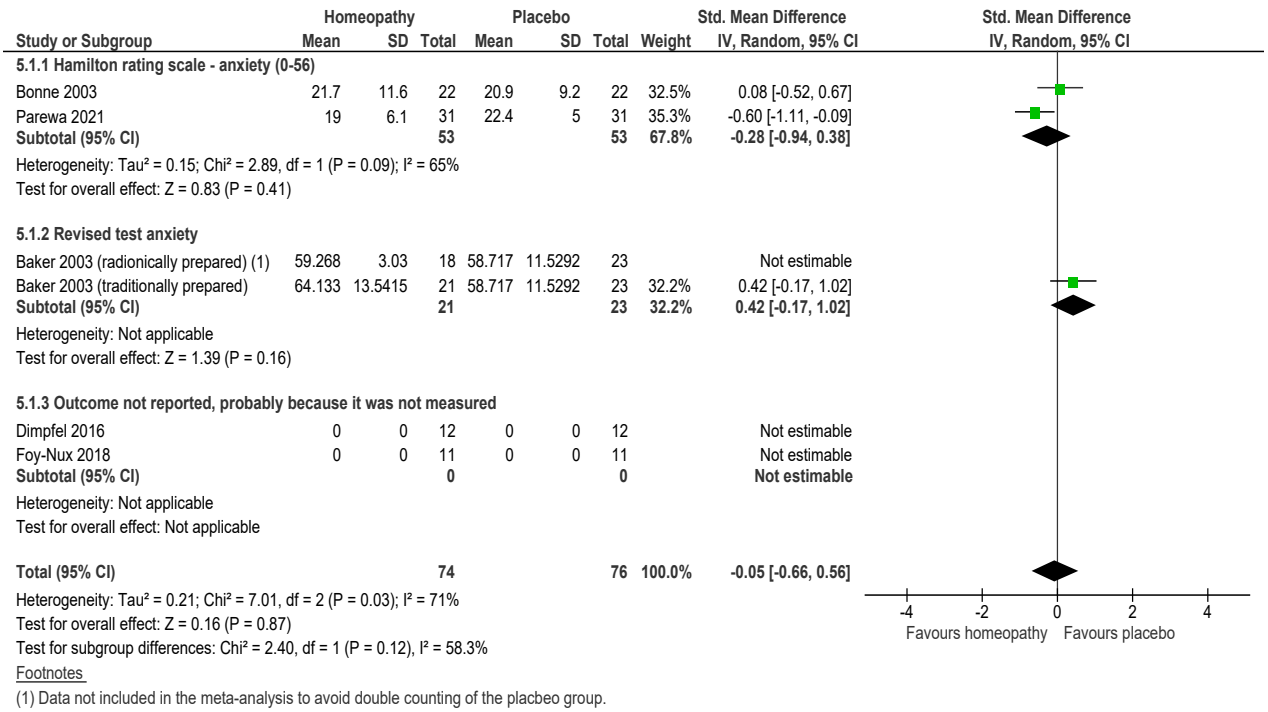
4.6.4.2 Secondary Comparison (vs inactive control)

There were no studies found that compared homeopathy to inactive control (no intervention, usual care or waitlist) in people with anxiety. Therefore, the effect of homeopathy compared to inactive control is unknown.

4.6.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with anxiety are presented in Figure 24 (anxiety severity), Figure 25 (depression severity), and Figure 26 (emotional functioning).

Figure 24 Forest plot of primary comparison: Homeopathy vs placebo: Anxiety – anxiety severity



Footnotes

(1) Data not included in the meta-analysis to avoid double counting of the placbeo group.

Figure 25 Forest plot of primary comparison: Homeopathy vs placebo: Anxiety – depression severity

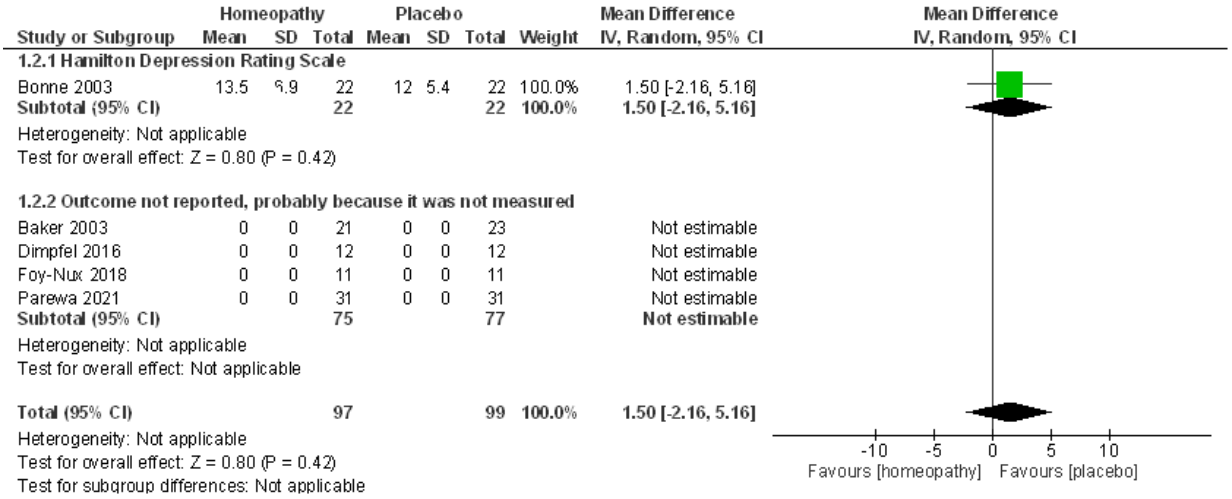
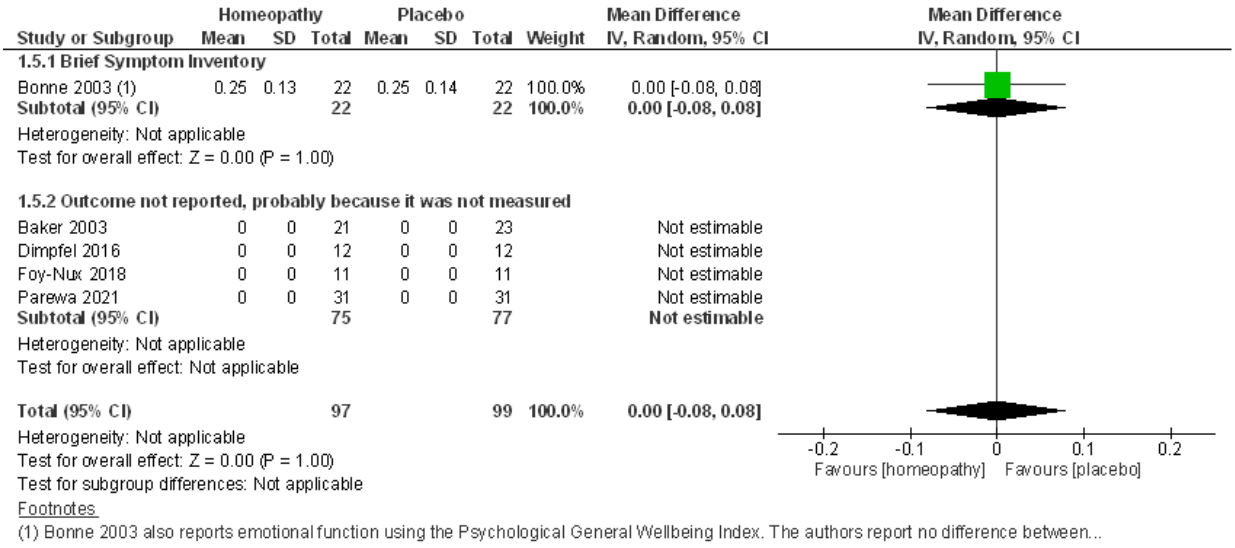


Figure 26 Forest plot of primary comparison: Homeopathy vs placebo: Anxiety – emotional functioning



Footnotes

(1) Bonne 2003 also reports emotional function using the Psychological General Wellbeing Index. The authors report no difference between...

4.7 Depression

4.7.1 Description of the condition

Depression is a highly prevalent mood disorder, and the third largest contributor to burden of disease in Australia (133), affecting one in every 16 Australians (134) and more than 300 million people worldwide (135). Depression is characterised by intense feelings of sadness that impact one's physical and mental health for extended periods of time. Those experiencing depression will often report symptoms of low mood, loss of interest or pleasure in most activities, sleep disturbances, changes in appetite or unintentional changes of weight, decreased energy, either slowed or agitated movement, decreased concentration and, in some cases, feelings of guilt, worthlessness and thoughts of suicide (136). Depressive symptoms can become chronic, leading to substantial impairment in an individual's ability to function in everyday life (137).

There are several different types of depressive disorders that are characterised by the specific symptoms experienced by the person, as well as the severity of the symptoms - either mild, moderate, or severe. Major depressive disorder is the most commonly diagnosed depressive disorder in Australia, however, several other types including bipolar disorder, cyclothymic disorder, dysthymic disorder and seasonal affective disorder are also recognised with the Australian healthcare context (138). A variety of social, psychological, and biological factors contribute to depression. In particular, people who have experienced adverse life events are at higher risk of developing depression and females are more likely to be diagnosed (134).

There are many known and effective treatments for depression that are highly dependent on the severity and pattern of depressive episodes. Traditional treatments offered by health-care providers include psychological treatments such as behavioural activation, Cognitive Behavioural Therapy, interpersonal psychotherapy, and/or antidepressant medication (135). In addition to traditional therapy, prevention programmes and alternative treatments have been shown to reduce depression. Still, these interventions may not help all patients, leaving patients to seek alternative treatment options such as homeopathy, yoga, meditation and breathing exercises (139).

4.7.2 Description of studies

Nine citations (140-148) corresponding to 4 RCTs (Adler 2009, Adler 2011, Katz 2005, Viksveen 2014) were identified in the literature. No additional studies were identified in the Department's public call for evidence. There were 6 ongoing studies, and one study awaiting classification. An overview of the PICO criteria of included studies is provided in Appendix D2.2.1.

Two studies were carried out in outpatient clinics in either Brazil (Adler 2009) or Germany (Adler 2011), one study was conducted at a group practice in England (Katz 2005) and one multicentre study took place across 3 health clinics and one medical centre in England with patients recruited from 43 GPs for a longitudinal health study (Viksveen 2014).

One RCT (Adler 2009) included referred patients who met DSM-IV criteria for single or recurrent depression. Two RCTs included patients diagnosed by a psychiatrist with major depression, which was rated as moderately severe by a psychologist (Adler 2011), or enrolled patients suffering from a major depressive episode of moderate severity (Katz 2005). The fourth study included patients with self-reported major depressive disorder (Viksveen 2014). Sample sizes ranged from 11 to 566 (total 712 participants).

Two studies examined the effectiveness of homeopathy compared to placebo (Adler 2011, Katz 2005). In Adler 2011, participants received individualised homeopathy after a comprehensive case history was taken by a homeopath, with the case history and consultation received by the placebo group being shorter in duration. The study excluded anyone who had taken antidepressant or anxiolytic drugs at the time of inclusion (with the exception of Lorazepam as rescue medication). The study reported by Katz 2005 also excluded patients who had used tricyclics or antidepressants in the preceding 2 weeks, as well as those who had depot neuroleptics in the preceding 6 months or electroconvulsive therapy in the preceding 3 months. In this study, the homeopathy treatment was individualised and involved a GP qualified in homeopathy selecting a treatment from a list of approximately 30 homeopathic medicines. Katz 2005 also included a third active treatment group (fluoxetine).

One study (Viksveen 2014) compared individualised homeopathy to no intervention, with participants in the homeopathy group offered treatment by a homeopath[11]. Participants in both groups continued treatment as usual. One study (Adler 2009) compared individualised homeopathy to an active comparator (fluoxetine). Participants in Adler 2009 were excluded if they had taken antidepressants in the 30 days prior to screening.

Frequency of homeopathic therapy ranged from one drop three times a week (Adler 2009, Adler 2011) to different frequencies depending on the homeopathic treatment chosen (Katz 2005, Viksveen 2014). Length of follow-up ranged between 6, 8 or 12 weeks (Adler 2011, Adler 2009, Katz 2005) up to 12 months (Viksveen 2014).

Results for the Primary Comparison: Homeopathy versus placebo and Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings table (see Section 4.7.4). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

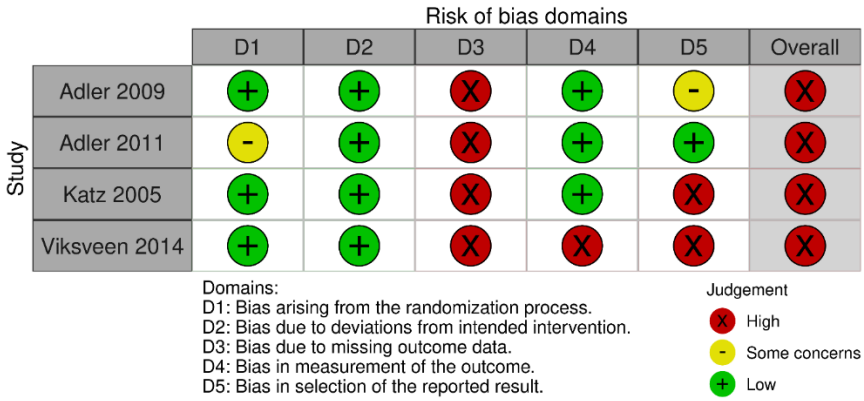
We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.7.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for depression (or symptoms of depression) is presented in Figure 27. Details are provided in Appendix D2.2.2. No studies were judged to be at overall low risk of bias.

[11] 60% of participants (111/185) did not take up the offer.

Figure 27 Risk of bias summary: review author's judgements about each risk of bias item for each included study – Depression



4.7.4 Summary of findings and evidence statements

4.7.4.1 Primary Comparison (vs placebo)

Homeopathy compared to Placebo for Depression (or symptoms of depression)

Patient or population: Depression
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Depression severity assessed with: HAM-D (higher is worse) Scale from: 0 to 52 follow-up: 6 weeks	The mean HAM-D score was **11.1 points**	MD **2.33 points higher** (0.51 lower to 5.17 higher)	-	44 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on depression severity in people with depression #
Psychological distress - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on psychological distress in people with depression is unknown
Emotional functioning assessed with: SF-12 MCS (higher is worse) Scale from: 0 to 100 follow-up: 6 weeks	The mean MCS score was **42.85 points**	MD **1.9 points lower** (9.14 lower to 5.35 higher)	-	44 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on emotional functioning in people with depression ##

Homeopathy compared to Placebo for Depression (or symptoms of depression)

Patient or population: Depression
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Physical functioning assessed with: SF-12 PCS (higher is worse) Scale from: 0 to 100 follow-up: 6 weeks	The mean PCS score was **48.2 points**	MD **4.77 points lower** (11.29 lower to 1.75 higher)	-	44 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effect of homeopathy on physical functioning in people with depression ##
Health-related quality of life - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on health-related quality of life in people with depression is unknown.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

The MCID for the HAM-D ranges between 3 and 8 points (149, 150).
The MCID for the SF-12 is estimated to be around 2 to 4 points for the general population (i.e. ~0.5 of the SD) (151).

CI: confidence interval; **HAM-D:** Hamilton depression rating scale; **MD**: mean difference; **RCT**: randomised controlled trial; **SF-12:** 12-item short form

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One study contributing 100% of the data was at high risk of bias. Certainty of evidence downgraded.
b. Single study, inconsistency not assessed. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in people diagnosed with major depression and generalisable to the Australian population with few caveats. Certainty of evidence not downgraded.
d. Very serious imprecision. Single small study with wide confidence intervals (upper and lower bounds overlap with both important benefits and harms). Certainty of evidence downgraded 2 levels.
e. Publication bias not suspected. Certainty of evidence not downgraded.

4.7.4.2 Secondary Comparison (vs inactive control)

Homeopathy compared to inactive control for Depression (or symptoms of depression)

Patient or population: Depression
Setting: Community
Intervention: Homeopathy
Comparison: Inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control	Risk with Homeopathy				
Depression severity assessed with: PHQ-9 (higher is worse) Scale from: 0 to 27 follow-up: 6 months	The mean (SD) score in the homeopathy and control groups not reported.	Study authors report a between group **MD of 1.4 points ^** (0.2 lower to 2.5 lower)	-	566 (1 RCT)	⊕⊕⊕◯ MODERATE a,b,c,d,e	Homeopathy probably results in little to no reduction in depression severity in people with depression #
Psychological distress - not reported	-	-	-	(0 RCTs)	-	The effect of homeopathy on psychological distress in people with depression is unknown
Emotional functioning - not reported	-	-	-	(0 RCTs)	-	The effect of homeopathy on emotional functioning in people with depression is unknown
Physical functioning - not reported	-	-	-	(0 RCTs)	-	The effect of homeopathy on physical functioning in people with depression is unknown
Health-related quality of life - not reported	-	-	-	(0 RCTs)	-	The effect of homeopathy on health-related quality of life in people with depression is unknown.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

^ The results reflect the primary analysis of the trial (ITT analysis using a general linear model).
# A reduction of 5-points is considered clinically important (152).

CI: confidence interval; **HAM-D:** Hamilton depression rating scale; **MD**: mean difference; **RCT**: randomised controlled trial; **SF-12:** 12-item short form

Homeopathy compared to inactive control for Depression (or symptoms of depression)

Patient or population: Depression
Setting: Community
Intervention: Homeopathy
Comparison: Inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control	Risk with Homeopathy				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One study contributing 100% of the data was at high risk of bias. Risk of bias is likely to influence the reported result but is not expected to substantially change the interpretation of effect vs control. Certainty of evidence downgraded.

b. Single study, inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people diagnosed with major depression and generalisable to the Australian population with few caveats. Certainty of evidence not downgraded.

d. No serious imprecision. Single study. Confidence interval for the reported result does not include either benefit or harm (i.e. trivial effect). Certainty of evidence not downgraded.

e. Publication bias not suspected. Certainty of evidence not downgraded.

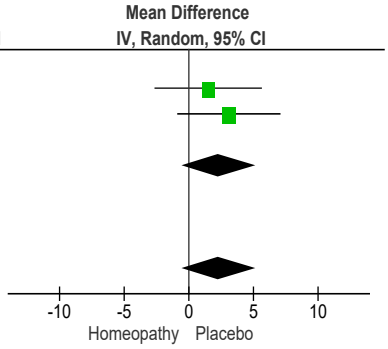
4.7.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with depression are presented in Figure 28 (depression severity) and Figure 29 (mental and physical functioning).

Outcome results related to the secondary comparison (homeopathy vs inactive control) in people with depression are presented in Figure 30 (depression severity).

Figure 28 Forest plot of primary comparison: Homeopathy vs placebo: Depression – symptoms of depression

Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
6.1.1 HAM-D								
Adler 2011 (+ conventional case history taking)	14.3	5.7	14	12.8	3.8	7	48.0%	1.50 [-2.60, 5.60]
Adler 2011 (+ homeopathic case history taking)	12.5	7.1	16	9.4	2.5	7	52.0%	3.10 [-0.84, 7.04]
Katz 2005 (1)	25.5	0	2	26	0	2		Not estimable
Subtotal (95% CI)			**30**			**14**	**100.0%**	**2.33 [-0.51, 5.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%								
Test for overall effect: Z = 1.61 (P = 0.11)								
Total (95% CI)			**30**			**14**	**100.0%**	**2.33 [-0.51, 5.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.30, df = 1 (P = 0.58); I² = 0%								
Test for overall effect: Z = 1.61 (P = 0.11)								
Test for subgroup differences: Not applicable								

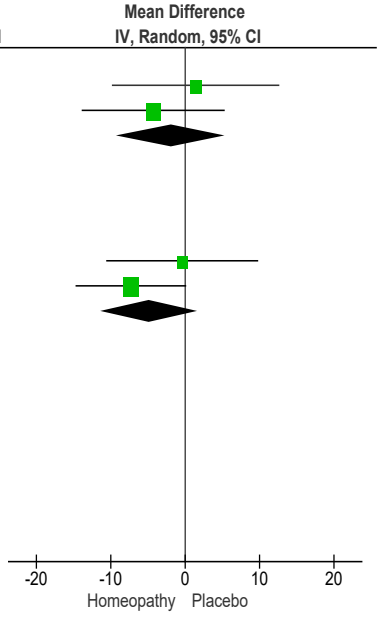


Footnotes

(1) Study does not report SD.

Figure 29 Forest plot of primary comparison: Homeopathy vs placebo: Depression – mental and physical functioning

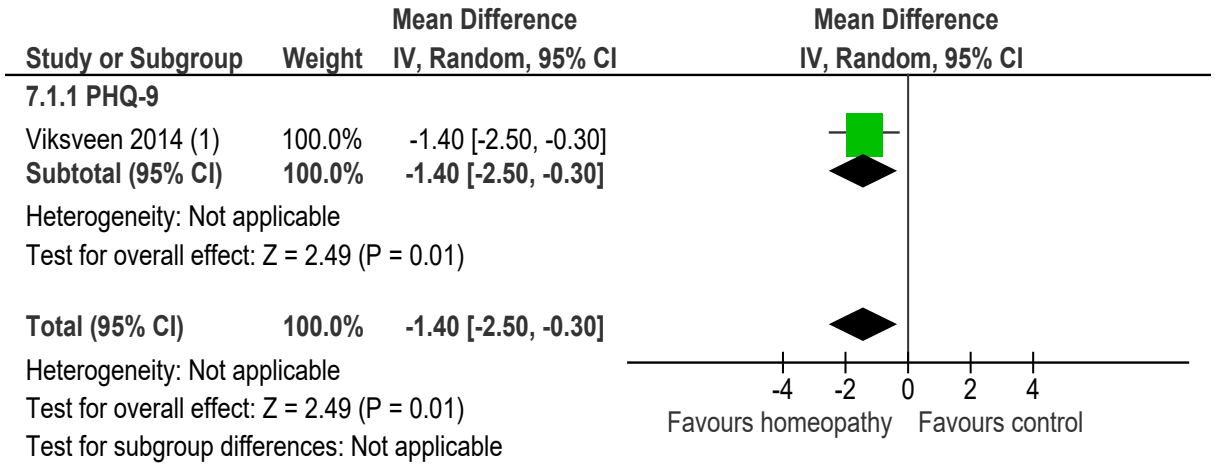
Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
6.2.1 SF-12 mental summary score								
Adler 2011 (+ conventional case history taking)	41	13.6	14	39.6	11.6	7	42.1%	1.40 [-9.76, 12.56]
Adler 2011 (+ homeopathic case history taking)	41.8	11	16	46.1	10.6	7	57.9%	-4.30 [-13.82, 5.22]
Subtotal (95% CI)			**30**			**14**	**100.0%**	**-1.90 [-9.14, 5.35]**
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.51 (P = 0.61)								
6.2.2 SF-12 physical summary score								
Adler 2011 (+ conventional case history taking)	45.9	9	14	46.3	12.1	7	36.7%	-0.40 [-10.53, 9.73]
Adler 2011 (+ homeopathic case history taking)	42.8	11.2	16	50.1	6.6	7	63.3%	-7.30 [-14.65, 0.05]
Subtotal (95% CI)			**30**			**14**	**100.0%**	**-4.77 [-11.29, 1.75]**
Heterogeneity: Tau² = 3.42; Chi² = 1.17, df = 1 (P = 0.28); I² = 14%								
Test for overall effect: Z = 1.43 (P = 0.15)								
6.2.3 SF-12 total score								
Katz 2005 (1)	0	0	2	0	0	2		Not estimable
Subtotal (95% CI)			**2**			**2**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Footnotes

(1) Study does not report results for this outcome.

Figure 30 Forest plot of secondary comparison: Homeopathy vs inactive control: Depression – symptoms of depression



Footnotes

(1) MD (95% CI) from the primary analysis of the trial (ITT analysis using general linear model).

4.8 Neurodevelopmental disorders

4.8.1 Description of the condition

Neurodevelopmental disorders is an umbrella term used in this review to encompass a range of cognitive and behavioural disorders that appear in infancy (or prior to the age of 18 years). As per the ICD-11 category, this includes conditions that involve difficulties in specific intellectual, motor, language, or social functions. Key among these is attention deficit disorder (ADHD), a neurodevelopmental disorder common in childhood that is characterised by symptoms of inattention and/or hyperactivity-impulsivity. According to the 2013-14 Australian Child and Adolescent Survey of Mental Health and Wellbeing, an estimated 8.2% of children aged 4 to 11 years old experience ADHD (153). ADHD tends to be underdiagnosed in adults, with an international prevalence somewhere between 2% to 6%. ADHD is more commonly diagnosed in boys than girls, with this disparity reducing somewhat in adulthood (154). This is likely due to girls with ADHD being be more easily missed in the diagnostic process (155).

ADHD is diagnosed by clinical assessment, most commonly using DSM-5 diagnostic criteria, which includes a list of 9 inattentive and 9 hyperactive-impulsive symptoms. For children, 6 of the 9 symptoms need to be present to reach a diagnosis for ADHD (154). Symptoms must have been present for at least 6-months and occur in more than one setting (154). Onset should occur before 12 years of age; however, it is common to not receive a diagnosis until after this age or later in adulthood (156).

The exact cause of ADHD is unknown, although a combination of genetic and environmental factors are likely to contribute (156). Studies have shown ADHD to have high heritability, although the genetic basis for ADHD is not completely understood and is likely to involve a number of genes and DNA variants (157). Environmental factors may include maternal smoking or drinking during pregnancy, premature birth or low birth weight and exposure to environmental toxins (158).

As there is no cure for ADHD, treatment involves the management of symptoms. Multimodal treatment is often the best approach, and includes a combination of pharmacological medication, behavioural or psychotherapy, training and support, and educational strategies (159). Psychostimulants are the most common medications used to treat ADHD, although non-stimulant medications can be used where stimulants may not be appropriate for the patient (159). As pharmacological interventions may not be appropriate for all patients, homeopathy has been viewed by some as a safe alternative.

4.8.2 Description of studies

There were 15 citations (160-174) corresponding to 4 RCTs (Fibert 2015, Frei 2005, Jacobs 2005, Oberai 2013) and 2 quasi RCTs (Lamont 1997, Strauss 2000) identified in the literature search. One additional quasi RCT (Dhawale 2014) (175) was identified in the Department's public call for evidence. There were 3 ongoing studies, and one study awaiting classification. An overview of the PICO criteria of included studies is provided in Appendix D2.3.1.

Two studies were conducted in outpatient clinics in either Switzerland (Frei 2005) or the United Kingdom (Fibert 2015). Three studies were conducted in community settings in the United States (Jacobs 2005, Lamont 1997) or South Africa (Strauss 2000). Two studies were conducted in India, with one study (Oberai 2013) conducted in a homeopathic research institute and one study (Dhawale 2014) enrolling participants across multiple schools in Mumbai.

Six studies (Fibert 2015, Frei 2005, Jacobs 2005, Lamont 1997, Oberai 2013, Strauss 2000) enrolled children with ADHD, with sample sizes ranging from 20 to 125 (total 354 participants). Participants in these studies were predominantly male (>70%). One study (Dhawale 2014) enrolled children with dyslexia and dysgraphia (total 67 participants).

Five studies (Dhawale 2014, Frei 2005, Jacobs 2005, Lamont 1997, Oberai 2013) compared individualised homeopathy with a placebo. The participants in these studies received consultations with a homeopath and were prescribed individualised homeopathic treatments based on presenting symptoms. One study (Fibert 2015) compared individualised homeopathy with both an inactive control (no intervention) and an active control group consisting of consultations with a nutritional therapist. The participants in the homeopathy and the nutritional therapy groups received up to 8 consultations with their respective clinicians.

One study (Strauss 2000) compared non-individualised homeopathy with an unspecified control (not clear if placebo or no intervention). The study had 4 treatment groups, with the homeopathy and control groups being stratified into participants taking pharmacotherapy (methylphenidate) and those who were not. The homeopathic treatment consisted of Selenium-Homaccord (selenium and potassium phosphate), which was administered orally over 60 days.

Results for the Primary Comparison: Homeopathy versus placebo and Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings table (see Section 4.8.4). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

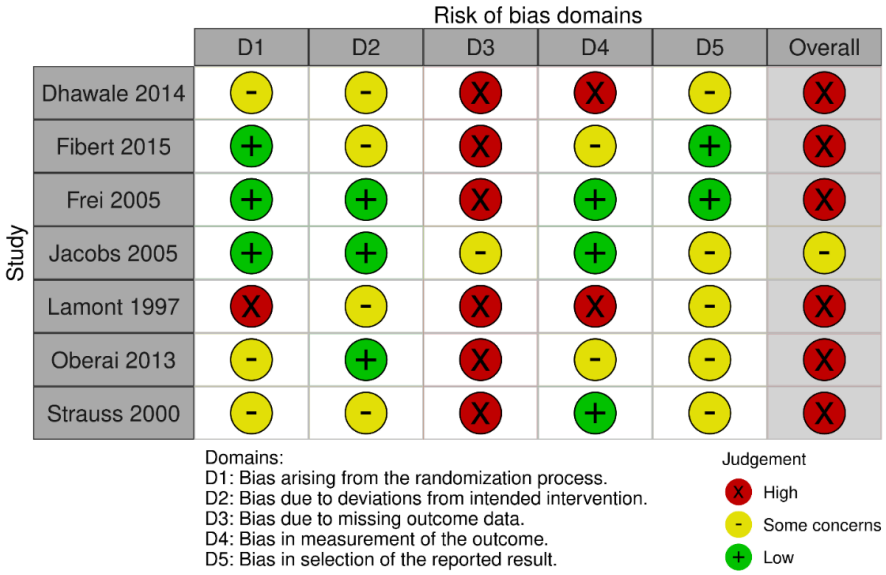
We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.8.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for neurodevelopmental disorders is presented in Figure 31. Details are provided in Appendix D2.3.2.

No studies were judged to be at overall low risk of bias.

Figure 31 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Neurodevelopmental disorders



4.8.4 Summary of findings and evidence statements

4.8.4.1 Primary Comparison (vs placebo)

Homeopathy compared to Placebo for Neurodevelopmental disorders

Patient or population: Attention deficit hyperactivity disorder (ADHD)
Setting: Community and outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
ADHD symptoms assessed with: Conner's Global Index - parent Scale from: 0 to 100 (higher is worse) follow-up: 18 weeks	The mean CGI score was **60.88**	MD **1.77 higher** (6.34 lower to 9.88 higher)	-	43 (1 RCT) †	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on ADHD symptoms for people with ADHD **
ADHD symptoms: oppositional assessed with: CPRS-R:S Scale from: 0 to 100 (higher is worse) follow-up: range 18 weeks to 12 months	The mean CPRS-R score was **64.43**	MD **8.01 lower** (25.73 lower to 9.72 higher)	-	104 (2 RCT) ††	⊕◯◯◯ VERY LOW c,e,f,g,h	The evidence is very uncertain about the effect of homeopathy on ADHD symptoms for people with ADHD **

Homeopathy compared to Placebo for Neurodevelopmental disorders

Patient or population: Attention deficit hyperactivity disorder (ADHD)
Setting: Community and outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
ADHD symptoms: cognition assessed with: CPRS-R:S Scale from: 0 to 100 (higher is worse) follow-up: range 18 weeks to 12 months	The mean CPRS-R score was **63.04**	MD **5.69 lower** (26.24 lower to 14.87 higher)	-	104 (2 RCT) ††	⨁◯◯◯ VERY LOW c,e,f,g,h	The evidence is very uncertain about the effect of homeopathy on ADHD symptoms for people with ADHD **
ADHD symptoms: hyperactivity assessed with: CPRS-R:S Scale from: 0 to 100 (higher is worse) follow-up: range 18 weeks to 12 months	The mean CPRS-R score was **71.28**	MD **10.02 lower** (35.15 lower to 15.11 higher)	-	104 (2 RCT) ††	⨁◯◯◯ VERY LOW c,e,f,g,h	The evidence is very uncertain about the effect of homeopathy on ADHD symptoms for people with ADHD **
ADHD symptoms: ADHD index assessed with: CPRS-R:S Scale from: 0 to 100 (higher is worse) follow-up: range 18 weeks to 12 months	The mean CPRS-R score was **65.03**	MD **7.54 lower** (25.76 lower to 10.68 higher)	-	104 (2 RCT) ††	⨁◯◯◯ VERY LOW c,e,f,g,h	The evidence is very uncertain about the effect of homeopathy on ADHD symptoms for people with ADHD **
Behaviour - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on behaviour in people with ADHD is unknown
Emotional function - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on symptom severity in people with ADHD is unknown.
Health-related quality of life - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on quality of life in people with ADHD is unknown

Homeopathy compared to Placebo for Neurodevelopmental disorders

Patient or population: Attention deficit hyperactivity disorder (ADHD)
Setting: Community and outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Data from one study (62 participants) not included in the meta-analysis as the study did not report means, SD or 95% CI. Study authors reported a mean difference of 1.67 points in favour of the homeopathy group.
†† Data from one study (20 participants) not included in the meta-analysis as the study did not report means, SD or 95% CI.

ADHD: attention deficit hyperactivity disorder; **CI:** confidence interval; **CPRS-R:S:** Connor's Parent Rating Scale – Revised: Short; **MD:** mean difference; **SMD:** standardised mean difference; **RCT**: Randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.
b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.
c. No serious indirectness. The evidence is generalisable to the Australian population with some caveats. The available evidence in is children aged 6 to 15 years (>75% male) with ADHD. It may not be applicable to adults with ADHD. Certainty of evidence not downgraded.
d. Very serious imprecision. Single small study with wide confidence intervals (upper and lower bound overlap with both and important benefit and harms). Certainty of evidence downgraded 2 levels.
e. Publication bias suspected. There is a strong suspicion of non-reporting of results likely to be related to p-value, direction, or magnitude of effect. At least one study listed as ongoing likely to be complete, but results were not available. Certainty of evidence downgraded.
f. Serious risk of bias. One study contributing ~50% of data was at high risk of bias. Certainty of evidence downgraded.
g. Serious inconsistency. Point estimates vary, with one study suggesting an effect favouring homeopathy and the other favouring placebo. Statistical heterogeneity was high (I^2 > 90%). Certainty of evidence downgraded.
h. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both and important benefit and harms). Certainty of evidence downgraded.

4.8.4.2 Secondary Comparison (vs inactive control)

Homeopathy compared to Inactive control for Neurodevelopmental disorders

Patient or population: Attention deficit hyperactivity disorder (ADHD)
Setting: Community and outpatient clinics
Intervention: Homeopathy
Comparison: inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control	Risk with Homeopathy				
ADHD symptoms assessed with: Conner's Global Index - parent Scale from: 0 to 100 (higher is worse) follow-up: 12 months	The mean CGI - total score was **17.88**	MD **2.03 higher** (0.72 lower to 4.78 higher)	-	83 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on ADHD symptoms for people with ADHD **
ADHD symptoms Behaviour: restless-impulsive assessed with: CGI – parent Scale from: 0 to 100 (higher is worse) follow-up: 12 months	The mean CGI – restless-impulsive score was **13.71**	MD **1.47 higher** (0.56 lower to 3.50 higher)	-	83 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on ADHD behavioural symptoms for people with ADHD **
ADHD symptoms Emotional function: emotional lability assessed with: CGI - parent Scale from: 0 to 100 (higher is worse) follow-up: 12 months	The mean CGI – emotional lability score was **4.18**	MD **0.55 higher** (0.55 lower to 1.65 higher)	-	83 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on emotional lability for people with ADHD **
Health-related quality of life: assessed with: Child Health Utility 9D Scale from: 0 to 1 (higher is better) follow-up: 12 months	The mean CHU-9 score was **0.885**	MD **0.01 lower** (0.07 lower to 0.05 higher)	-	83 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on quality of life for people with ADHD **

Homeopathy compared to Inactive control for Neurodevelopmental disorders

Patient or population: Attention deficit hyperactivity disorder (ADHD)
Setting: Community and outpatient clinics
Intervention: Homeopathy
Comparison: inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control	Risk with Homeopathy				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Data from one study (62 participants) not included in the meta-analysis as the study did not report means, SD or 95% CI. Study authors reported a mean difference of 1.67 points in favour of the homeopathy group.
†† Data from one study (20 participants) not included in the meta-analysis as the study did not report means, SD or 95% CI.

ADHD: attention deficit hyperactivity disorder; **CI:** confidence interval; **CGI:** Conner's Global Index; **MD:** mean difference; **SMD:** standardised mean difference; **RCT**: Randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

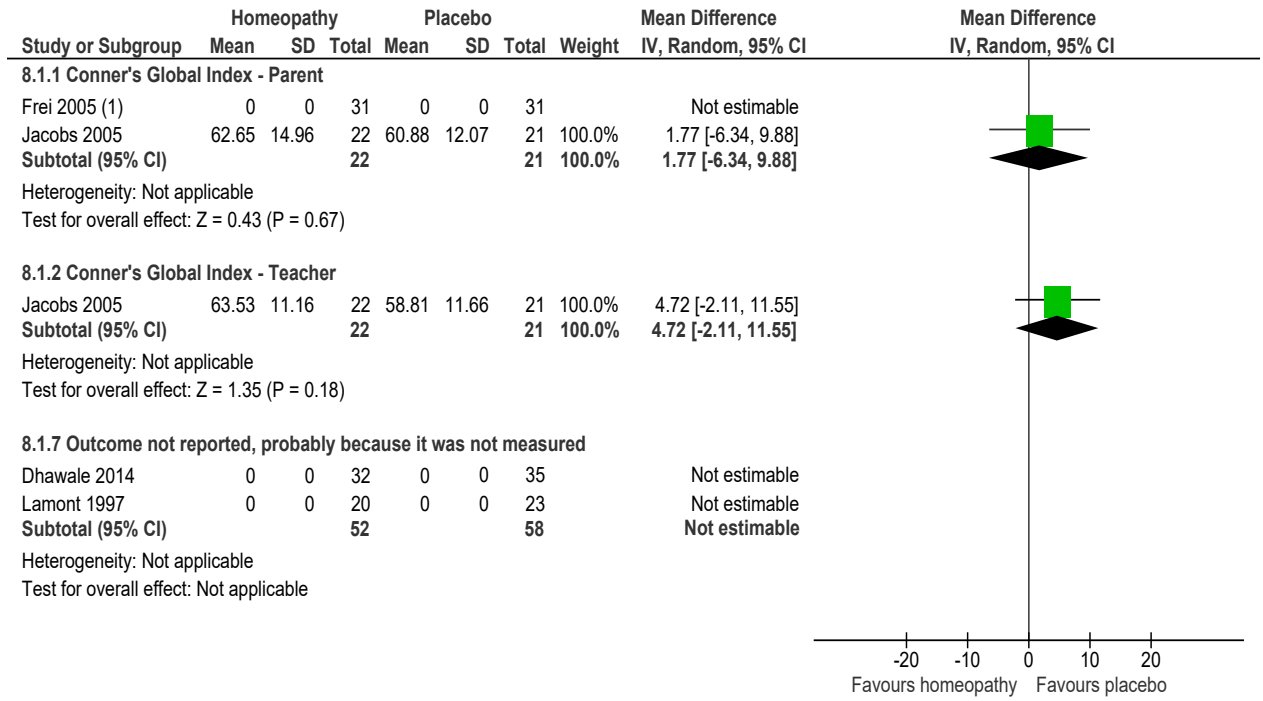
a. Serious risk of bias. One study contributing ~100% of data was at high risk of bias. Certainty of evidence downgraded.
b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.
c. No serious indirectness. The evidence is generalisable to the Australian population with some caveats. The available evidence in is children aged 5 to 18 years with ADHD. It may not be applicable to adults with ADHD. Certainty of evidence not downgraded.
d. Very serious imprecision. Single small study with wide confidence intervals (upper and lower bound overlap with both and important benefit and harms). Certainty of evidence downgraded 2 levels.
e. Publication bias not suspected. Certainty of evidence not downgraded.

4.8.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with ADHD are presented in Figure 32 (ADHD symptoms - global) and Figure 33 (ADHD symptoms - subscales).

Outcome results related to the secondary comparison (homeopathy vs inactive control) in people with ADHD are presented in Figure 34 (ADHD symptoms and Figure 35 (health-related quality of life).

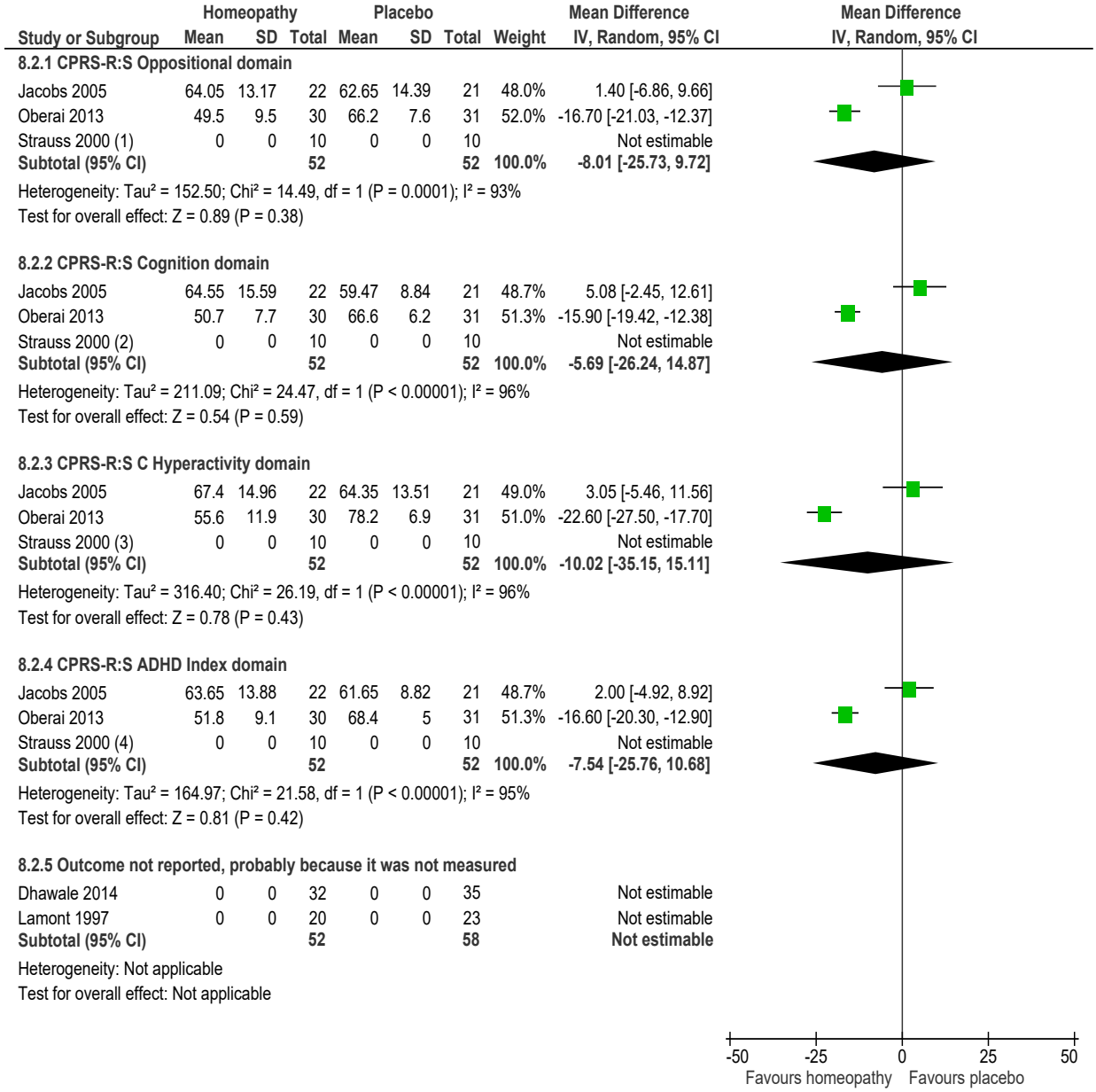
Figure 32 Forest plot of primary comparison: Homeopathy vs placebo: ADHD – ADHD symptoms (Global)



Footnotes

(1) Study reports an effect favouring homeopathy compared with placebo (MD -1.67, p = 0.0479) but no means, SD, 95% CIs reported.

Figure 33 Forest plot of primary comparison: Homeopathy vs placebo: ADHD – ADHD symptoms (subscales)



Footnotes

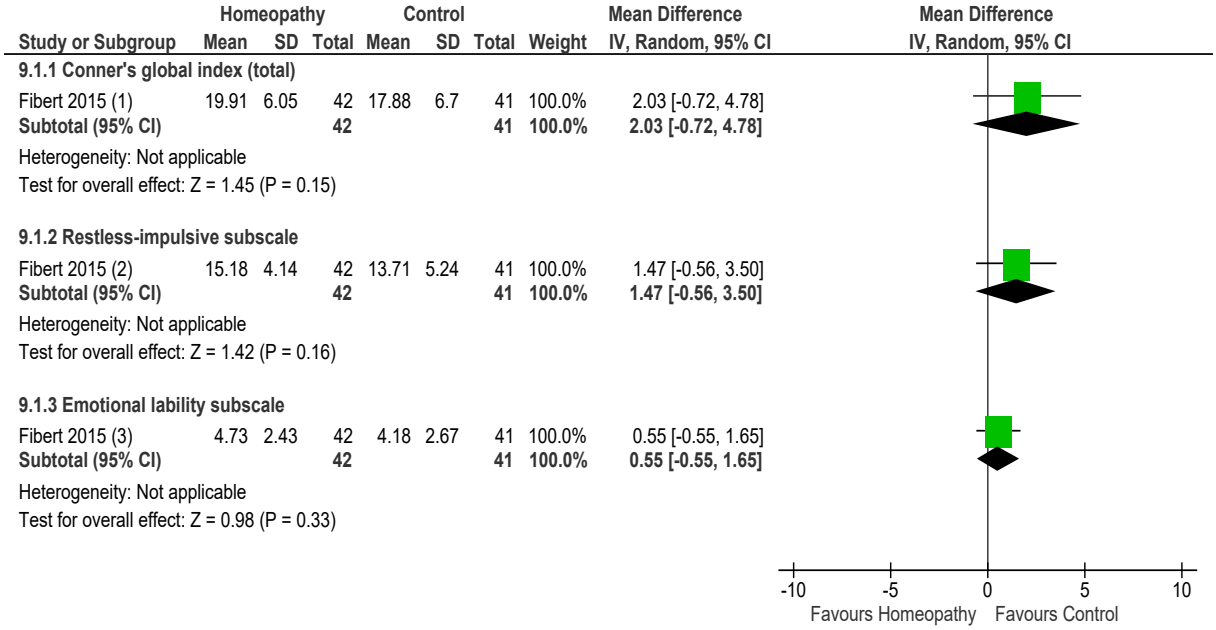
(1) Authors do not report usable data but report an effect favouring homeopathy (41.3% improvement vs 1.3% improvement).

(2) Authors do not report usable data but report an effect favouring homeopathy (33% improvement vs 23% worsening).

(3) Authors do not report usable data but report an effect favouring homeopathy (35.8% improvement vs 21.2% improvement).

(4) Authors do not report usable data but report an effect favouring homeopathy (45.5% improvement vs 22.1% improvement).

Figure 34 Forest plot of secondary comparison: Homeopathy vs inactive control: ADHD – ADHD symptoms at 12 months



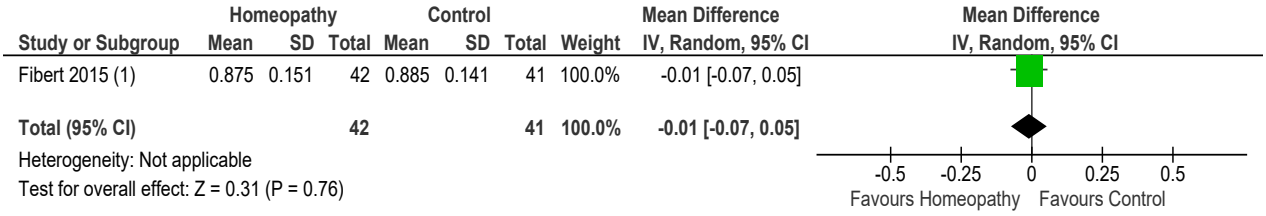
Footnotes

(1) Study reported no difference at 6-months in a regression analysis controlling for age, gender, ADHD severity at baseline (SMD 0.425; 95% -1.48,...

(2) Study reported no difference at 6-months in a regression analysis controlling for age, gender, ADHD severity at baseline (SMD 0.198; 95% -1.9, 2.8).

(3) Study reported effect favouring homeopathy at 6-months in a regression analysis controlling for age, gender, ADHD severity at baseline (SMD...

Figure 35 Forest plot of secondary comparison: Homeopathy vs inactive control: ADHD – health-related quality of life



Footnotes

(1) Study reported no difference at 6-months in a regression analysis controlling for age, gender, ADHD severity at baseline (SMD 0.44; 95% -0.12, 0.01).

4.9 Insomnia and sleep problems

4.9.1 Description of the condition

Sleep problems are characterised by an inability to fall asleep or a lack of sleep which can cause daytime impairment. Common across the adult population, sleep problems can range in severity from experiencing some sleep disturbances each week to a diagnosis of clinical insomnia (176). Insomnia is broadly defined as difficulty initiating and/or maintaining sleep, associated with significant daytime consequences that are present despite adequate opportunity for sleep (177-179). The assessment and diagnosis of insomnia is formulated mainly from a systematic sleep history and is considered chronic if symptoms persist for 3 or more days per week for at least 3 months. Insomnia can occur as a primary disorder or, more commonly, it can be comorbid with other physical or mental disorders (177).

Inadequate sleep and chronic insomnia are associated with a high burden of disease with an increased risk of depression, cardiovascular disease, and death. People with insomnia have greater work absenteeism, reduced productivity and are more likely to access healthcare with increased presentations to general practice and hospital (178). Australian population surveys have shown that 13%–33% of the adult population have regular difficulty either getting to sleep or staying asleep (177). In both males and females, the prevalence of chronic insomnia increases with age, with adults aged over 75 years reporting the highest rates of chronic insomnia (23.1%). Older people are also significantly more likely to report maintenance insomnia.

Acute insomnia can often be appropriately managed with short term approaches, including dealing with precipitating factors such as stress. Chronic insomnia has a high relapse and recurrence rate and is best managed with cognitive behavioural therapy, which includes sleep hygiene, stimulus control and sleep restriction. Herbal supplements (such as melatonin or valerian) or pharmacological treatment, including benzodiazepine-receptor agonists, antidepressants, antipsychotics and antihistamines, may also be used (177).

Although cognitive behavioural therapy remains the first line of therapy for insomnia, it is often underutilised due to time, cost involvement and the limited availability of trained specialists. Complementary and alternative medicine in the form of homeopathy, yoga, Tai Chi, mindfulness meditation, acupuncture and Chinese herbal medicines have been tried in people with insomnia to complement the existing treatment options (180).

4.9.2 Description of studies

Six citations (181-186) corresponding to 2 RCTs (James 2019, Jong 2016) and 2 quasi RCTs (Harrison 2013, Naude 2010) were identified in the literature search. No additional studies were identified in the Department's public call for evidence. There was one ongoing study, and 2 studies awaiting classification including one study published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D3.1.1.

Three studies were carried out in single centre settings in either South Africa (Harrison 2013, Naude 2010) or India (James 2019), one study was carried out in a multicentre setting in Russia (Jong 2016). Sample sizes ranged from 33 to 180 participants (total 307 participants), with studies enrolling participants with insomnia (Harrison 2013, James 2019, Naude 2010) or children younger than 6 years old with sleep disorders (Jong 2016).

Three studies compared homeopathy to placebo, of which one study (Harrison 2013) provided a non-individualised, homeopathic combination treatment, and 2 studies (James 2019, Naude 2010) used individualised homeopathy. One study (Jong 2016) compared a non-individualised homeopathic treatment to a nutritional supplement (glycine tablets). Treatments were to be taken before bed (Harrison 2013, Naude 2010) throughout the day (Jong 2016) or not specified (James 2019). Length of follow up ranged from 4 weeks (Harrison 2013, Jong 2016, Naude 2010) to 3 months (James 2019).

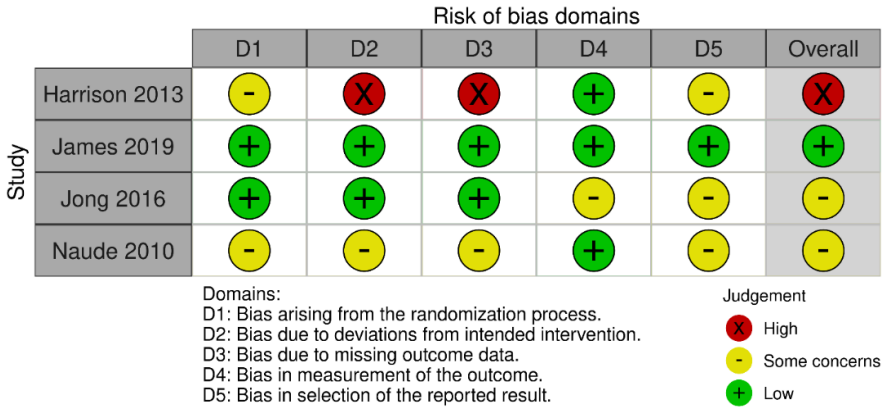
Results for the Primary Comparison: Homeopathy versus placebo are provided in the Summary of Findings table (see Section 4.9.4). There were no studies found for the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.9.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for insomnia and sleep disorders is summarised in Figure 36. Details are provided in Appendix D3.1.2. One study was judged to be at overall low risk of bias.

Figure 36 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Insomnia and sleep problems



4.9.4 Summary of findings and evidence statements

4.9.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Insomnia and sleep problems

Patient or population: Insomnia and sleep problems
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with Homeopathy				
Insomnia severity assessed with: ISI Scale from: 0 to 28 (higher is worse) follow-up: 3 months	The mean ISI score was **16.6 points**	MD **2.7 points lower** (4.73 lower to 0.67 lower)	-	60 (1 RCT) †	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in insomnia severity in people with insomnia #
Sleep duration assessed with: Sleep diary (hours of sleep per night) (higher is better) follow-up: 3 months	The mean duration of sleep per night was **3.3 hours**	MD **0.1 hours more** (0.56 fewer to 0.76 more)	-	60 (1 RCT) †	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in sleep quality in people with insomnia ##
Sleep onset latency assessed with: Sleep diary (minutes to fall asleep) (higher is worse) follow-up: 3 months	The mean time to fall asleep was **77.4 mins**	MD **22.2 mins fewer** (45.18 fewer to 0.78 more)	-	60 (1 RCT) ††	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in sleep latency in people with insomnia ###
Quality of life - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on quality of life in people with insomnia is unknown

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

† Results from one RCT (30 participants) not included in the meta-analysis as data were incomplete.
†† Results from one RCT (28 participants) not included in the meta-analysis as the data were incomplete.

An improvement of 8.4 points corresponds to a moderate improvement in insomnia (187).
A difference of less than one hour per night not clinically relevant (188).
A difference of less than 30 minutes in sleep onset latency not clinically relevant (188).

CI: confidence interval; **ISI;** Insomnia Severity Index; **MD:** mean difference

Homeopathy compared to placebo for Insomnia and sleep problems

Patient or population: Insomnia and sleep problems
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with Homeopathy				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence in people with insomnia and is directly applicable to the Australian population. Certainty of evidence not downgraded.

d. Serious imprecision. One study with wide confidence intervals (upper and lower bounds overlap with both an important and no important difference). Certainty of evidence downgraded.

e. Publication bias suspected. Evidence is limited to one study. There is a strong suspicion of non-reporting of results likely related to the *p* value, direction or magnitude of effect. Certainty of evidence downgraded.

4.9.4.2 Secondary Comparison (vs inactive control)

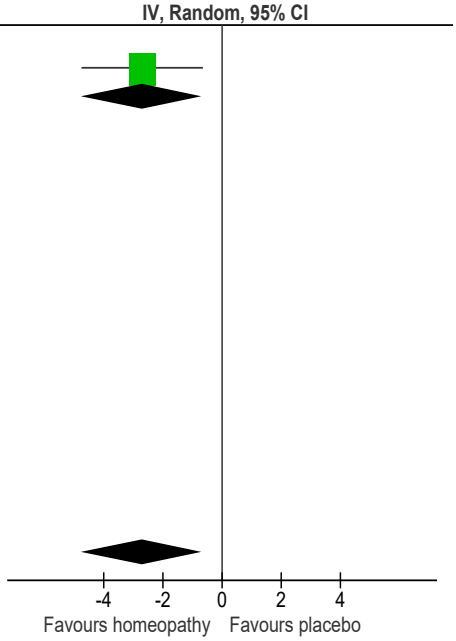
There were no studies found that compared homeopathy to inactive control (no intervention, usual care or waitlist) in people with insomnia. The effect of homeopathy compared to inactive control is unknown.

4.9.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with insomnia are presented in Figure 37 (insomnia severity), Figure 38 (sleep quality) and Figure 39 (sleep latency).

Figure 37 Forest plot of primary comparison: Homeopathy vs placebo: Insomnia – Insomnia severity

Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
10.1.1 Insomnia Severity Index								
James 2019	13.9	4.6	30	16.6	3.3	30	100.0%	-2.70 [-4.73, -0.67]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-2.70 [-4.73, -0.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.61 (P = 0.009)								
10.1.2 Sleep Impairment Index								
Naude 2010 (1)	1.47	0	14	3.35	0	16		Not estimable
Subtotal (95% CI)			**14**			**16**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
10.1.3 Outcome not reported, probably because it was not measured								
Harrison 2013	0	0	14	0	0	14		Not estimable
Subtotal (95% CI)			**14**			**14**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**58**			**60**	**100.0%**	**-2.70 [-4.73, -0.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.61 (P = 0.009)								
Test for subgroup differences: Not applicable								

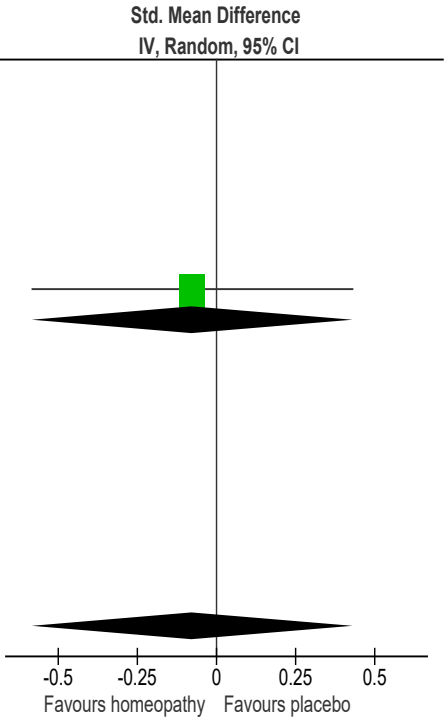


Footnotes

(1) Study does not report SD, SE or 95% CI and data do not correlate with expected values. A difference in favour of homeopathy reported (p = 0.000)

Figure 38 Forest plot of primary comparison: Homeopathy vs placebo: Insomnia – Sleep duration

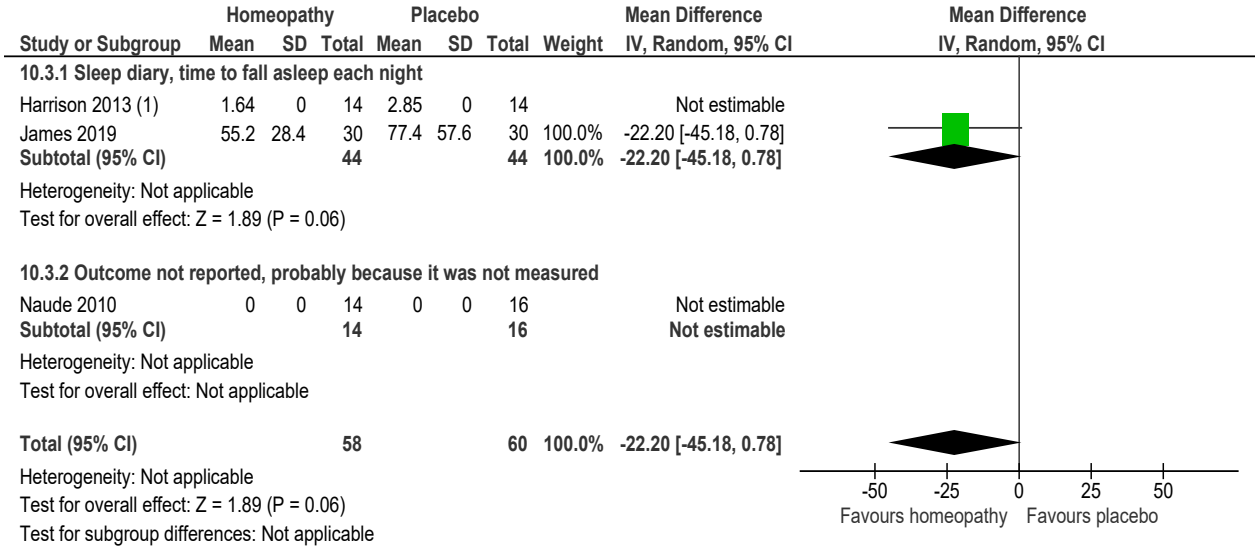
Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.2.1 Sleep diary, total hours per week								
Naude 2010 (1)	-41	0	14	-35	0	16		Not estimable
Subtotal (95% CI)			**14**			**16**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
3.2.2 Sleep diary, total hours per night								
James 2019	-3.4	1.3	30	-3.3	1.3	30	100.0%	-0.08 [-0.58, 0.43]
Subtotal (95% CI)			**30**			**30**	**100.0%**	**-0.08 [-0.58, 0.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.29 (P = 0.77)								
3.2.3 Outcome not reported, probably because it was not measured								
Harrison 2013	0	0	14	0	0	14		Not estimable
Subtotal (95% CI)			**14**			**14**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**58**			**60**	**100.0%**	**-0.08 [-0.58, 0.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.29 (P = 0.77)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Study does not report SD. Study authors report significant difference in favour of homeopathy (p = 0.036).

Figure 39 Forest plot of primary comparison: Homeopathy vs placebo: Insomnia – Sleep latency



Footnotes

(1) Data based on categorical outcome: 0=0-15 mins; 1=15-30 mins; 2=30-45 mins; 3=45-60 mins; 4=60+ mins

4.10 Headache disorders

4.10.1 Description of the condition

Headache disorders include tension headaches – a dull aching pain throughout the whole head; cluster headaches – piercing pain affecting one side of the head at a time which occur in a series that can last days or weeks at a time; and migraines – a pulsing or throbbing pain from deep within the head that can last up to days at a time and includes other symptoms such as nausea, vomiting, sensitivity to light and sound, and affected vision (189-191). Tension-type headaches can also be accompanied by tightness or tenderness of scalp, neck and shoulder muscles, along with trouble concentrating, depression and anxiety (189). While it is unknown what exactly causes headaches and migraines, episodes are thought to be triggered by diet, stress, sleep and hormonal influences among others (190, 191).

Headache disorders are one of the most common health-related conditions in Australia, imposing a significant burden to individuals, society and the economy (190, 192). International studies show that 36% of males and 42% of females suffer tension-type headaches, which translates to around 7 million Australians (189). For migraines, an estimated 1.4 to 4.9 million people in Australia are affected (193, 194). Onset usually begins in teenage years, with prevalence declining after one's 40s. Females are approximately 3 times more likely than men to be affected by migraines, being the 14th largest contributor to non-fatal disease burden for females in Australia (124). Migraines impair individuals' capacity to function in work and school environments, with the health and productivity burden of migraine in Australia estimated to lead to a loss of 2,577,783 quality adjusted life years between 2020 and 2030 (192).

Effective management of headaches and migraines includes both acute and preventative treatments to reduce the frequency of attacks. Treatments include pain relief medication, avoiding trigger factors, exercise, and relaxation techniques (191, 193). Complementary treatments thought to assist with headaches and migraines include homeopathy, aromatherapy, deep breathing, hypnotherapy, biofeedback, yoga, Tai Chi and neck and shoulder massage (191, 193).

4.10.2 Description of studies

There were 7 citations (195-201) corresponding to 2 RCTs (Gaus 1992, Straumsheim 1997), and one quasi RCT (Whitmarsh 1997) identified in the literature search. No additional studies were identified in the Department's public call for evidence. There were 3 ongoing studies and 6 studies awaiting classification including 2 studies published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D4.1.1

Two studies were carried out at single centres in either Norway (Straumsheim 1997) or England (Whitmarsh 1997), and one study was carried out in a multicentre setting in Germany (Gaus 1992). Sample size ranged from 63 to 98 participants (total 229 participants), with 2 studies enrolling participants with migraines (Straumsheim 1997, Whitmarsh 1997) and one study enrolling people with headache (Gaus 1992).

All three studies used individualised homeopathy which was compared to placebo. Treatments were twice weekly or individually prescribed. Length of treatment ranged from 3 (Whitmarsh 1997) or 4 months (Straumsheim 1997) to one year (Gaus 1992).

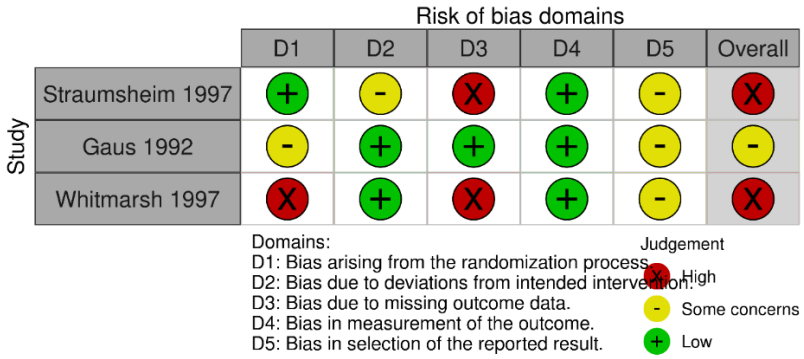
Results for the Primary Comparison: Homeopathy versus placebo are provided in the Summary of Findings table (see Section 4.10.4). There were no studies found for the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) or the Tertiary Comparison: Homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.10.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for insomnia and sleep disorders is summarised in Figure 40. Details are provided in Appendix D4.1.2. No studies were judged to be at overall low risk of bias.

Figure 40 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Headache disorders



4.10.4 Summary of findings and evidence statements

4.10.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Headache disorders

Patient or population: Headache disorders
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Headache/migraine frequency assessed with: self-reported diary, change in number of attacks per month (higher is worse) follow-up: 3 months	Two studies report no important difference between groups. One study suggested an estimate of effect favouring placebo but did not conduct statistical analysis.		-	226 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effects of homeopathy on headache or migraine frequency in people with headache disorders

Homeopathy compared to placebo for Headache disorders

Patient or population: Headache disorders
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Migraine severity assessed with: Patient rated mild-moderate-severe follow-up: 4 months	One study suggests both homeopathy and placebo groups had a reduction in the rate of mild, moderate and severe headaches. Reported data are incomplete and not able to be included in the quantitative analysis.		-	63 (1 RCT)	⊕◯◯◯ VERY LOW c,d,e,f,g	The evidence is very uncertain about the effects of homeopathy on headache severity in people with headache disorders
Pain intensity assessed with: VAS (higher is worse) Scale from: 0 to 100 follow-up: 3 months	Data from two studies not able to be included in the meta-analysis suggests no difference between homeopathy and placebo.		-	163 (2 RCTs)	⊕◯◯◯ VERY LOW b,c,d,e,h	The evidence is very uncertain about the effects of homeopathy on pain in people with headache disorders
Headache/migraine duration assessed with: self-reported diary, hours (higher is worse) follow-up: 3 months	Results from one study not able to be included in the quantitative analysis. Study authors report no difference between groups.		-	98 (1 RCT)	⊕◯◯◯ VERY LOW c,d,e,g,h	The evidence is very uncertain about the effects of homeopathy on headache duration in people with headache disorders
Headache impact – not reported	-	-	-	(0 studies)	-	The effect of homeopathy on headache impact in people with headache disorders is unknown
Quality of life – not reported	-	-	-	(0 studies)	-	The effect of homeopathy on quality of life in people with headache disorders is unknown
Medication use assessed with: self-reported diary follow-up: 4 months	Two studies do not report sufficient data for inclusion in the meta-analysis, but suggest no difference between homeopathy and placebo groups.^		-	163 (2 RCTs)	⊕◯◯◯ VERY LOW b,c,d,e,h	The evidence is very uncertain about the effects of homeopathy on medication use in people with headache disorders

Homeopathy compared to placebo for Headache disorders

Patient or population: Headache disorders
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

^ One study reported a 52% reduction in medication use per attack from baseline in the homeopathy group compared with a 42% reduction in the placebo group ($p > 0.05$). One study reported a decrease from baseline in the mean daily dose (mg) in both treatment groups across 8 medications ($p = 0.16$).

CI: confidence interval; **MD:** mean difference; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. Two studies contributing results for this outcome were at high risk of bias. Certainty of evidence downgraded.
b. Inconsistency not assessed as studies do not provide sufficient quantitative data for meta-analysis. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in people with chronic headaches or migraine and is directly generalisable to the Australian population with few caveats. Certainty of evidence not downgraded.
d. Very serious imprecision. Inadequate reporting of data for meta-analysis. Certainty of evidence downgraded 2 levels.
e. Publication bias suspected. There is a strong suspicion of non-reporting of results because the *p* value, magnitude or direction of the results generated were considered unfavourable by the study investigators. Certainty of evidence downgraded.
f. Serious risk of bias. Single study contributing 100% of the data for this outcome at high risk of bias. Certainty of evidence downgraded.
g. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.
h. No serious risk of bias. Certainty of evidence not downgraded.

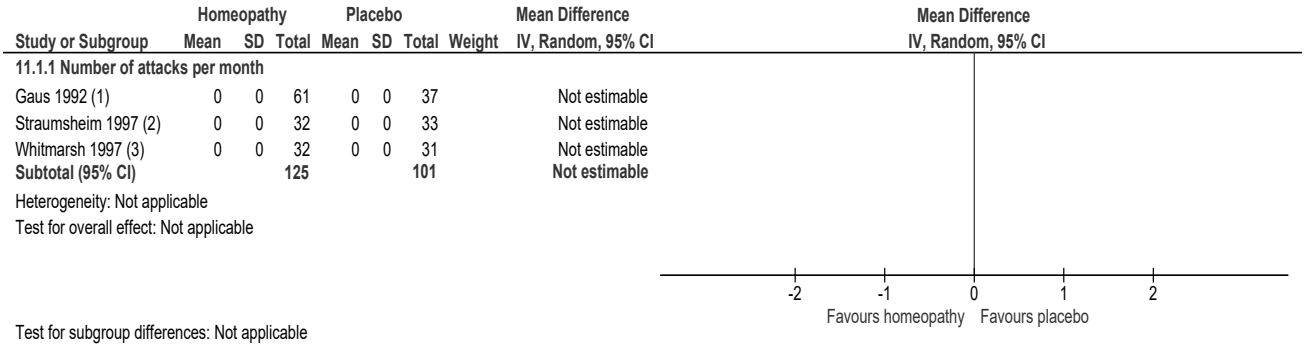
4.10.4.2 Secondary Comparison (vs inactive control)

There were no studies found that compared homeopathy to inactive control (no intervention, usual care or waitlist) in people with headache disorders. The effect of homeopathy compared to inactive control is unknown.

4.10.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with headache disorders are presented in Figure 41 (headache frequency), Figure 42 (headache severity), Figure 43 (headache pain intensity), Figure 44 (headache duration) and Figure 45 (medication use).

Figure 41 Forest plot of primary comparison: Homeopathy vs placebo: Headache disorders – headache frequency



Test for subgroup differences: Not applicable

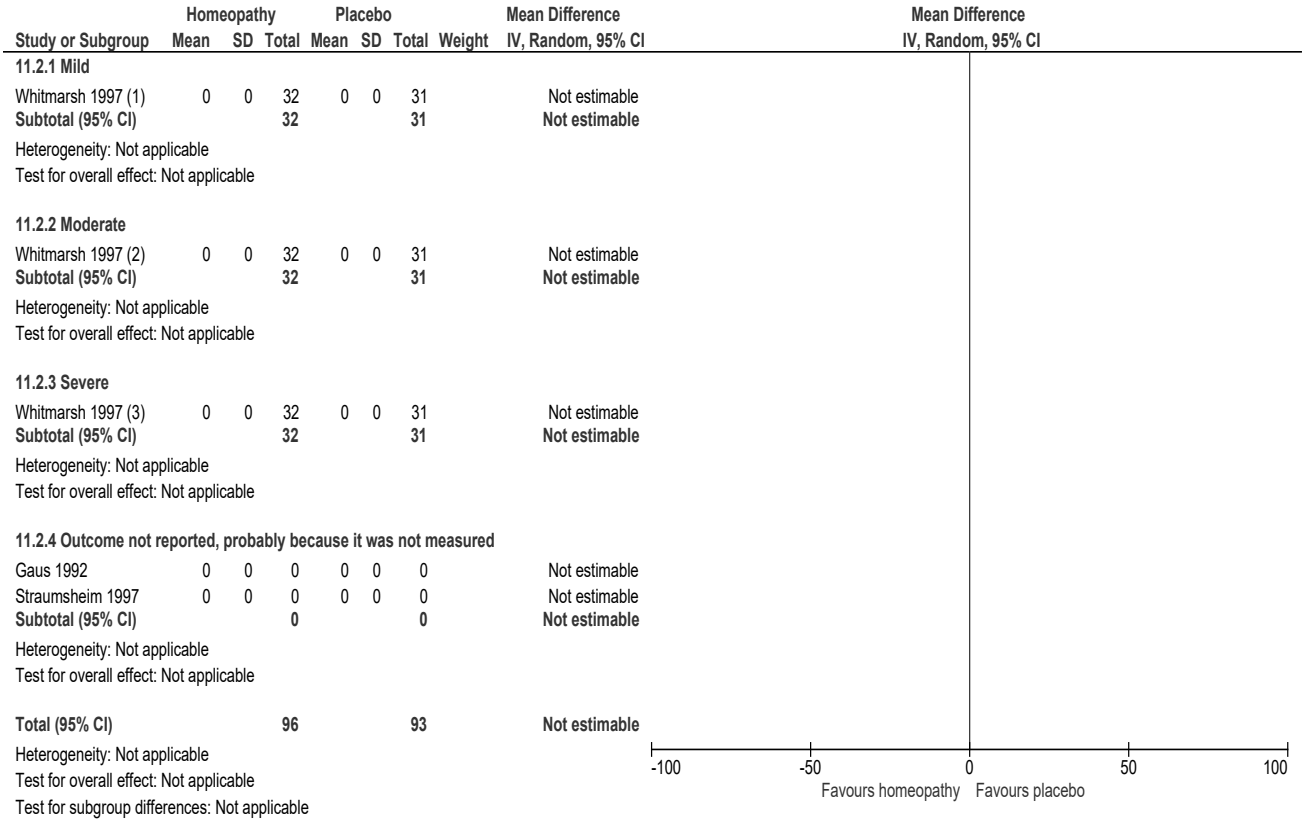
Footnotes

(1) Insufficient data reported for inclusion in the meta-analysis. Study authors did not conduct statistical analysis for comparison but report no difference between groups.

(2) Insufficient data reported for inclusion in the meta-analysis. Study authors report that migraine frequency decreased in both groups, but the difference was not significant (p=0.54).

(3) Insufficient data reported for inclusion in the meta-analysis. Study authors report no significant difference between the homeopathy and placebo arm (p=0.83).

Figure 42 Forest plot of primary comparison: Homeopathy vs placebo: Headache disorders – headache severity



Test for subgroup differences: Not applicable

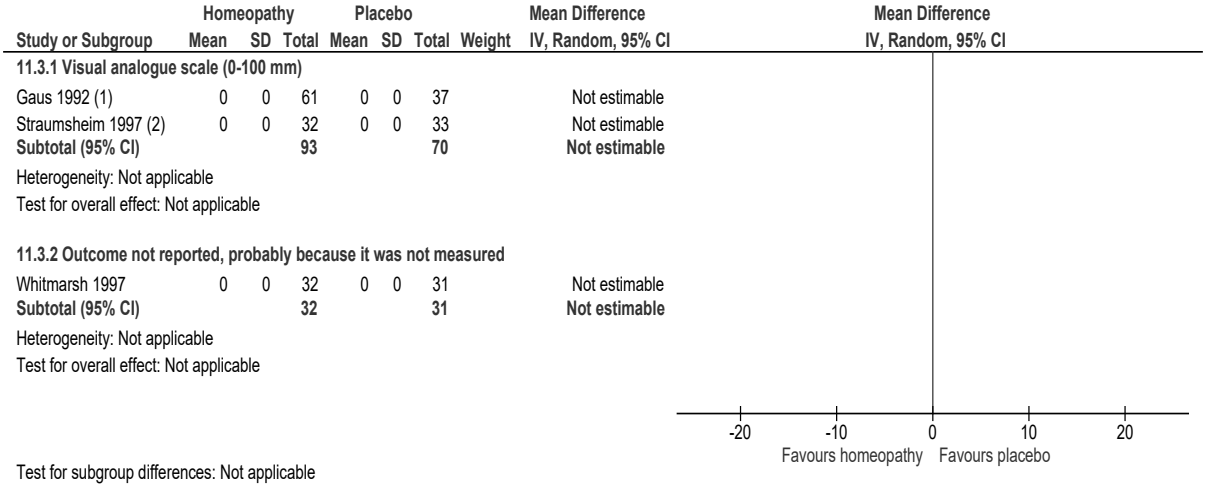
Footnotes

(1) Insufficient data for inclusion in the meta-analysis. Authors note a reduction in frequency of headaches in both groups (18.5% vs 39.3%) comparing homeopathy with placebo.

(2) Insufficient data for inclusion in the meta-analysis. Authors note a reduction in frequency of headaches in both groups (38.2% vs 13.2%) comparing homeopathy with placebo.

(3) Insufficient data for inclusion in the meta-analysis. Authors note a reduction in frequency of headaches in both groups (20.0% vs 13.2%) comparing homeopathy with placebo.

Figure 43 Forest plot of primary comparison: Homeopathy vs placebo: Headache disorders – Pain intensity



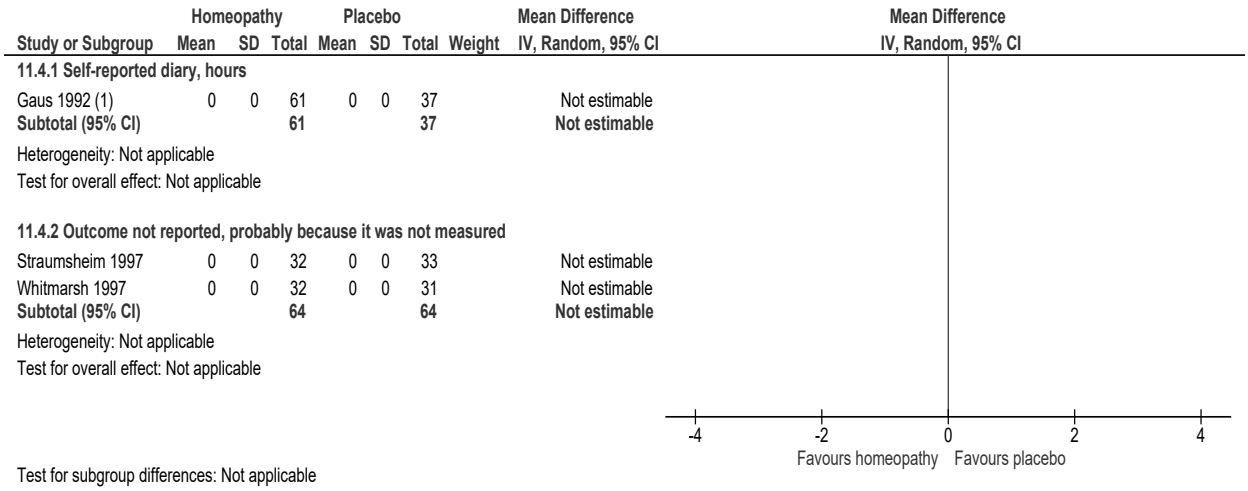
Test for subgroup differences: Not applicable

Footnotes

(1) Insufficient data reported for inclusion in the meta-analysis. Study authors did not conduct statistical analysis for comparison but report no difference between groups.

(2) Insufficient data reported for inclusion in the meta-analysis. Study authors do not report statistical analysis comparing treatment groups.

Figure 44 Forest plot of primary comparison: Homeopathy vs placebo: Headache disorders – headache duration

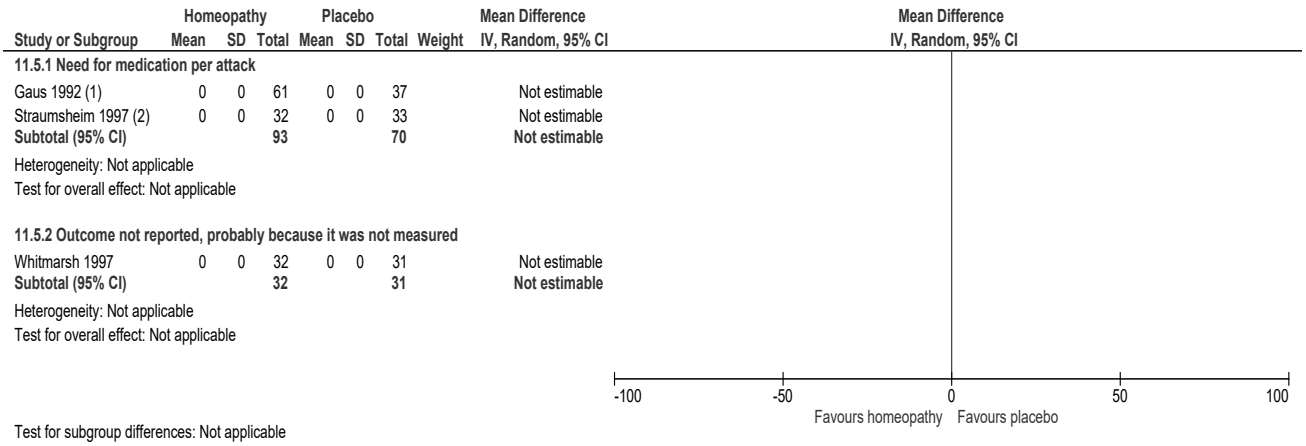


Test for subgroup differences: Not applicable

Footnotes

(1) Insufficient data reported for inclusion in the meta-analysis. Study authors did not conduct statistical analysis for comparison but report no difference between groups.

Figure 45 Forest plot of primary comparison: Homeopathy vs placebo: Headache disorders – medication use



Test for subgroup differences: Not applicable

Footnotes

(1) Insufficient data reported for inclusion in the meta-analysis. Study authors report a non-significant difference between homeopathy and placebo (p=0.16).

(2) Data could not be included in meta-analysis. Medication use reduced in both groups (52% vs 42% reduction from baseline) comapring homeopathy with placebo but the difference was not significant.

4.11 Asthma

4.11.1 Description of the condition

Asthma is a chronic inflammatory condition affecting the airways. The causes of asthma are unknown but are thought to be a combination of genetic and environmental factors (202). An asthma flare up can be triggered by a variety of exposures including dust mites, pollen, air pollution, tobacco smoke, cold air and physical exercise (202). These stimuli cause a widespread narrowing of the airways resulting in symptoms such as wheezing, shortness of breath, chest tightness and fatigue (202). There are 5 common types of asthma, differentiated primarily based on their cause – allergic, non-allergic, occupational, exercise-induced, and nocturnal (203). The effects of asthma can range from mild, intermittent symptoms that cause relatively few problems, to a severe and life-threatening condition, with almost 400 people in Australia dying due to asthma in 2018 (202).

Around 2.7 million Australians (more than one in ten) report being diagnosed with asthma (194). Asthma is the tenth highest contributor to the total burden of disease in Australia (204). The burden is highest among children, with asthma being the leading cause of burden for children aged between 5 and 14 years (204). It has been estimated that the total cost of asthma to Australia in terms of both economic and health costs were $28 billion in 2015 (205).

The key conventional method of managing asthma is through pharmacological intervention, which can be categorised as preventers and relievers, as well as by their pharmacological or chemical classes (206). Alternatively, some people choose to use complementary or alternative therapies such as homeopathy for their symptoms (206).

4.11.2 Description of studies

There were 11 citations (153, 206-216) corresponding to 5 RCTs (Lewith 2002, Qutubuddin 2019, Reilly 1994, Topcu 2010, White 2003) and one quasi RCT (Thompson 2008) identified in the literature search. No additional studies were identified in the Department's public call for evidence. There was one ongoing study and 5 studies awaiting classification, including 2 studies published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D5.1.1.

Four studies were conducted in single outpatient clinics in England (Thompson 2008), Denmark (Topcu 2010), India (Qutubuddin 2019) or Scotland (Reilly 1994) and 2 RCTs (Lewith 2002, White 2003) were conducted in general practice clinics throughout the United Kingdom. All studies enrolled people with asthma, with participants in 2 RCTs (Lewith 2002, Reilly 1994) having flareups associated with allergies and participants in 2 studies (Thompson 2008, White 2003) being children (aged below 15 years). Sample sizes ranged from 28 to 242 (total 626 participants).

Four studies compared an oral homeopathic treatment with placebo. Of these, 3 RCTs (Reilly 1994, Qutubuddin 2019, White 2003) administered individualised homeopathy determined after consultation with a homeopath, with consults ranging between 1 to 12 sessions throughout the study period. The other RCT (Lewith 2002) used non-individualised homeopathy, with participants prescribed an ultramolecular dose of dust mites, taken 3 times orally over 24 hours.

Two studies (Thompson 2008, Topcu 2010) compared individualised homeopathy with an inactive control (no intervention). One study (Topcu 2010) included a third treatment group, being reflexology.

Participants across all included studies continued to receive usual care as a co-intervention. Study durations ranged from 4 to 52 weeks.

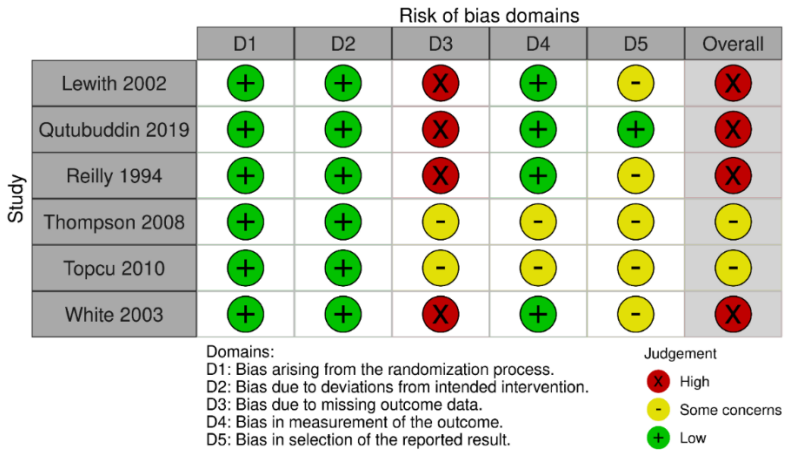
Results for the Primary Comparison: Homeopathy versus placebo and Secondary Comparison: Homeopathy versus control (no intervention, waitlist or usual care) are provided in the Summary of Findings table (see Section 4.11.4). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.11.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for asthma is summarised in Figure 46. Details are provided in Appendix D5.1.2. No studies were judged to be at overall low risk of bias.

Figure 46 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Asthma



4.11.4 Summary of findings and evidence statements

4.11.4.1 Primary Comparison (vs placebo)

Homeopathy compared to Placebo for Asthma

Patient or population: Asthma
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Asthma symptoms assessed with: ACQ or VAS (higher is worse) follow-up: range 4 weeks to 6 months	-	SMD **2.03 SD lower** (3.48 lower to 0.59 lower)	-	168 (2 RCTs) †	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on asthma symptoms in people with asthma **

Homeopathy compared to Placebo for Asthma

Patient or population: Asthma
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Pulmonary function assessed with: FEV_1/FVC ratio (higher is better) follow-up: 6 months	The mean FEV_1/FVC ratio was **82.5%**	MD **5% higher** (8% higher to 1% higher)	-	140 (1 RCT)	⊕⊕◯◯ LOW [a,c,d,e,f]	Homeopathy may have little to no difference on pulmonary function (FEV_1/FVC ratio) in people with asthma [#]
Pulmonary function assessed with: FEV_1 (higher is better) follow-up: range 4 weeks to 6 months	The mean FEV_1 (% predicted) was **67.3%** The mean FEV_1 (L/second) was **0.414**	MD **1.67% higher** (19.71 higher to 16.37 lower) MD **0.28 lower** (0.14 higher to 0.69 lower)	-	410 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c,e,g]	The evidence is very uncertain about the effect of homeopathy on pulmonary function (FEV_1) in people with asthma [##]
Quality of life assessed with: CAQ – active living; ABP (higher is worse) Scale from: 0 to 100 follow-up: 12 months		SMD **0.00 SD** (0.23 lower to 0.23 higher)	-	291 (2 RCTs)	⊕⊕◯◯ LOW [a,c,h,i,j]	Homeopathy may have little to no effect on quality of life in people with asthma **
Hospitalisation – not reported	-	-	-	(0 studies)	-	The effect of homeopathy on hospitalisations in people with asthma is unknown
Medication use assessed with: number of participants with a reduction in inhaler use follow-up: 12 months	391 per 1,000	**376 per 1,000** (266 to 528) ^	**RR 0.96** (0.68 to 1.35)	89 (1 RCT)†	⊕⊕◯◯ LOW [a,c,f,i,k]	Homeopathy may have little to no effect on medication use in people with asthma ***

Homeopathy compared to Placebo for Asthma

Patient or population: Asthma
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				

***The risk in the intervention group (and its 95% confidence interval)** is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** As a rule of thumb, an SMD of 0.2 is considered a small difference, 0.5 is considered medium, and 0.8 is considered large (83).
*** A 25% relative risk reduction was considered important (i.e. RR < 0.75).

^ The ARD is 16 fewer per 1,000 (from 125 fewer to 137 more) i.e. 1.6% reduction.

5% lower than normal is suggestive of airflow obstruction, with normal values typically between 75% to 85% (217).
Changes of 200 mL in adults (or 12%) considered clinically important (217).

† Data from 1 RCT (202 participants) not included here as the study does not report any values, but authors report there is no significant difference between the groups at the end of treatment.

ABP: Asthma bother profile; **ACQ:** Asthma control questionnaire; **ARD:** absolute risk difference; **CAQ:** Childhood asthma questionnaire; **CI:** confidence interval; **FEV1:** forced expiratory volume in first second; **FVC:** forced vital capacity; **MD:** mean difference; **SMD:** standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. RCTs contributing 100% of data were at high risk of bias. Certainty of evidence downgraded.

b. Serious inconsistency. Statistical heterogeneity was high ($I^2 \geq 90\%$) with minimal overlap in point estimates or confidence intervals. Certainty of evidence downgraded.

c. No serious indirectness. The available evidence is in people with asthma (allergic and bronchial) is directly applicable to the Australian population with few caveats. Certainty of evidence not downgraded.

d. No serious imprecision. Certainty of evidence not downgraded.

e. Publication bias suspected. Missing data from at least 2 studies probably because the *p* value, magnitude or direction of the results generated were considered unfavourable by the study investigators. Certainty of evidence downgraded.

f. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

g. Very serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both an important and no important effect). Certainty of evidence downgraded 2 levels.

h. No serious inconsistency. Certainty of evidence not downgraded.

i. Publication bias not suspected. Certainty of evidence not downgraded.

j. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both an important benefit (SMD 0.23 lower) and important harms (SMD 0.23 higher). Certainty of evidence downgraded.

k. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both an important benefit (125 fewer) and important harms (137 more). Certainty of evidence downgraded.

4.11.4.2 Secondary Comparison (vs inactive control)

Homeopathy compared to Inactive control for Asthma

Patient or population: Asthma
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Inactive Control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with control	Risk with Homeopathy				
Asthma symptoms assessed with: ACQ (higher is worse) follow-up: range 16 weeks to 26 weeks	-	SMD **0.21 SD higher** (0.21 lower to 0.64 higher)	-	86 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in symptom severity in people with asthma **
Pulmonary function assessed with: PEFR (L/min) (higher is better) follow-up: 16 weeks	The mean morning PEFR was **282.0** The mean evening PEFR was **289.0**	MD **61.0 lower** (5.24 lower to 116.76 lower) MD **70.0 lower** (16.15 lower to 123.85 lower)	-	35 (1 RCT) †	⊕◯◯◯ VERY LOW [a,c,e,f,g]	The evidence is very uncertain about the effect of homeopathy on pulmonary function in people with asthma # ***
Quality of life – assessed with: AQLQ, PAQLQ (higher is better) follow-up: range 16 weeks to 52 weeks	The mean symptoms score was **5.6** The mean activity limitation score was **5.8** The mean emotional function score was **5.95**	MD **0.05 higher** (0.47 higher to 0.36 lower) MD **0.10 higher** (0.54 higher to 0.34 lower) MD **0.10 lower** (0.27 higher to 0.47 lower)	-	86 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in health-related quality of life in people with asthma ##
Quality of life – environmental stimuli assessed with: AQLQ (higher is better) follow-up: 52 weeks	The mean environmental stimuli score was **6.1**	MD **0.10 lower** (0.45 higher to 0.65 lower)	-	51 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in health-related quality of life in people with asthma ##
Hospitalisation assessed with: number requiring inpatient care follow-up: 16 weeks	118 per 1,000	**125 per 1,000** (20 to 788) ^	**RR 1.06** (0.17 to 6.70)	35 (1 RCT)	⊕⊕◯◯ LOW [a,c,e,g,h]	Homeopathy may result in little to no difference in need for hospitalisation in people with asthma ****

Homeopathy compared to Inactive control for Asthma

Patient or population: Asthma
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Inactive Control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with control	Risk with Homeopathy				
Medication use assessed with: rescue medication use (doses per week) follow-up: 16 weeks	The mean number of doses per week was **66.4**	MD **2.20 fewer** (49.01 fewer to 44.61 more) ^^	-	35 (1 RCT) †	⨁⨁◯◯ LOW [a,b,c,e,i]	Homeopathy may result in little to no difference in medication use in people with asthma ***

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** As a rule of thumb, an SMD of 0.2 is considered a small difference, 0.5 is considered medium, and 0.8 is considered large (83).
*** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).
**** A 25% relative risk reduction was considered important (i.e. RR < 0.75).

^ The ARD is 7 more per 1,000 (from 98 fewer to 671 more) i.e. 0.7% reduction.
^^ SMD –0.03 (95% CI –0.69, 0.63)

An MCID for the PEFR is not established. Changes in peak flow measurements are dependent on the individual. age, weight, height etc. Fifty percent to 80% of personal best suggests airway obstruction. Less than 50% of personal best indicates serious airway obstruction.
A change score of 0.5 is considered the MCID for this outcome measure (218).

† Data from one RCT (51 participants) not included as the data were incomplete. Study authors reported there was no important difference between the homeopathy and control groups at the end of treatment (52 weeks).

ACQ: Asthma control questionnaire; **AQLQ:** Asthma quality of life questionnaire; **CI:** confidence interval; **PAQLQ:** Paediatric asthma quality of life questionnaire; **PEFR:** peak expiratory flow rate; **SMD:** standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.
b. No serious inconsistency. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in adults or children with bronchial asthma is directly applicable to the Australian population with few caveats. Certainty of evidence not downgraded.
d. Very serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both small important benefit [SMD –0.21] and important harms [SMD 0.64]). Certainty of evidence downgraded 2 levels.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. Serious inconsistency. One study suggested an effect that favours the control, and one study suggested no important difference. Certainty of evidence downgraded.

g. Very serious imprecision. Single small study with wide confidence intervals (upper and lower bounds overlap with no important benefit [<10% change in peak flow) and important harms more than 50% change in peak flow). Certainty of evidence downgraded 2 levels.

h. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

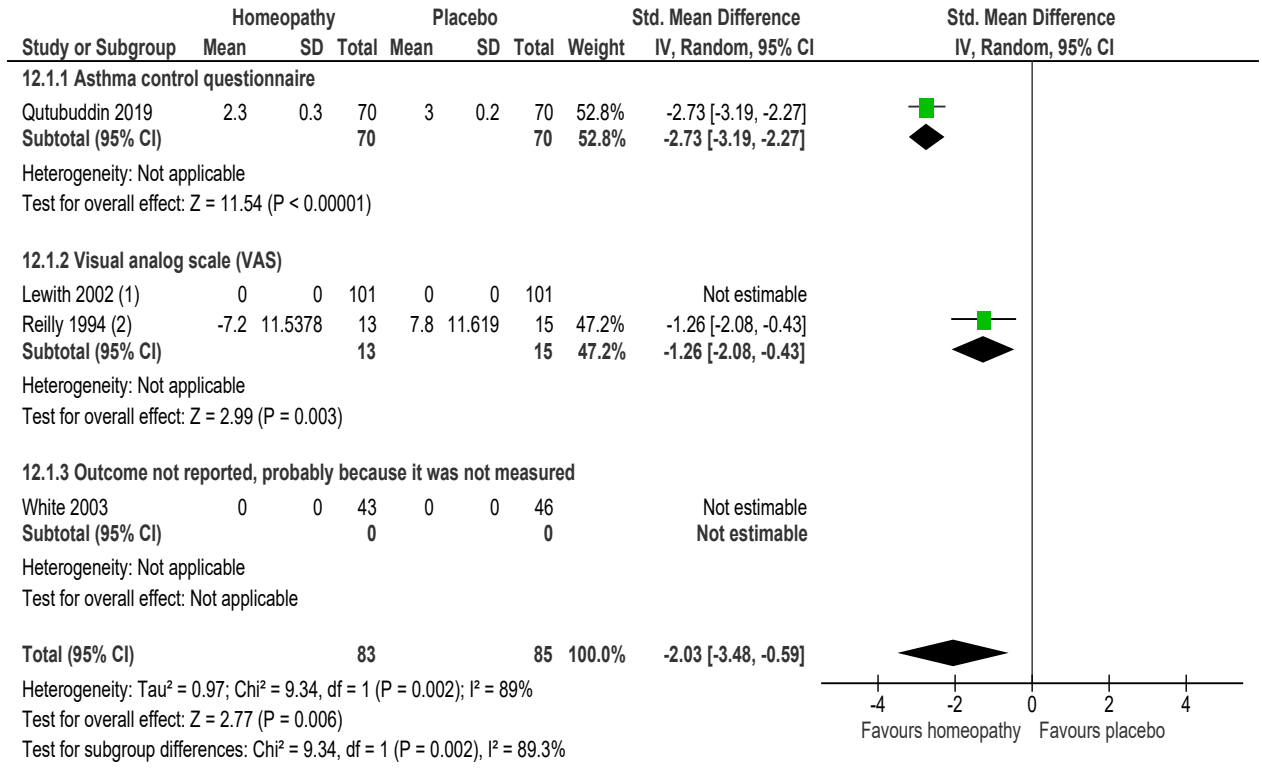
i. Very serious imprecision. Single small study with wide confidence intervals (upper and lower bounds overlap with both an important benefit (49.01 fewer doses or >75% of the mean) and important harms (44..61 more doses or >75% of the mean). Certainty of evidence downgraded 2 levels.

4.11.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with asthma are presented in Figure 47 (asthma symptoms), Figure 48 (pulmonary function - FEV_1), Figure 49 (pulmonary function - PEFR), Figure 50 (quality of life) and Figure 51 (medication use).

Outcome results related to the secondary comparison (homeopathy vs inactive control) in people with asthma are presented in Figure 52 (asthma symptoms), Figure 53 (pulmonary function – PEFR), Figure 54 (quality of life), Figure 55 (hospitalisation) and Figure 56 (medication use).

Figure 47 Forest plot of primary comparison: Homeopathy vs placebo: Asthma – asthma symptoms

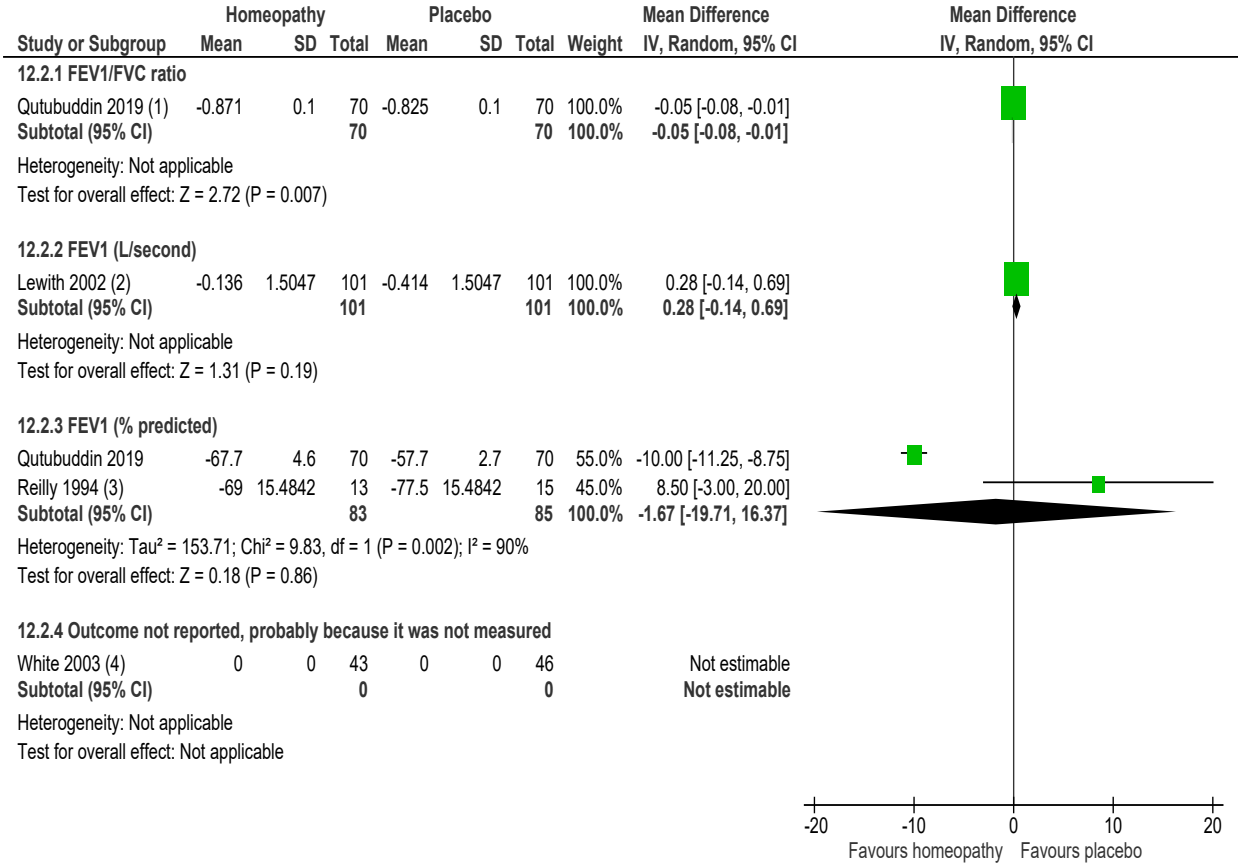


Footnotes

(1) Data presented in figures and not extracted here. The authors note no significant difference between the groups at the end of treatment.

(2) Mean change from baseline.

Figure 48 Forest plot of primary comparison: Homeopathy vs placebo: Asthma – pulmonary function (FEV_1)



Footnotes

(1) Data inverted to ensure consistency in direction of effect

(2) Mean improvement from baseline. Study authors report no significant difference between the homeopathy and placebo group.

(3) Data calculated from reported median and mean % change from baseline.

(4) Peak PEFR reported as a binary outcome.

Figure 49 Forest plot of primary comparison: Homeopathy vs placebo: Asthma – pulmonary function (PEFR)

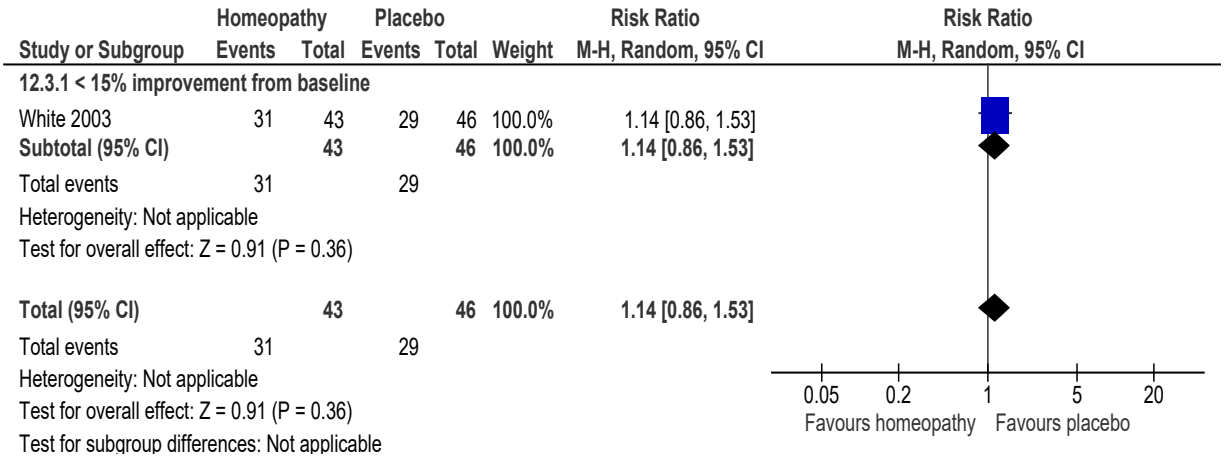
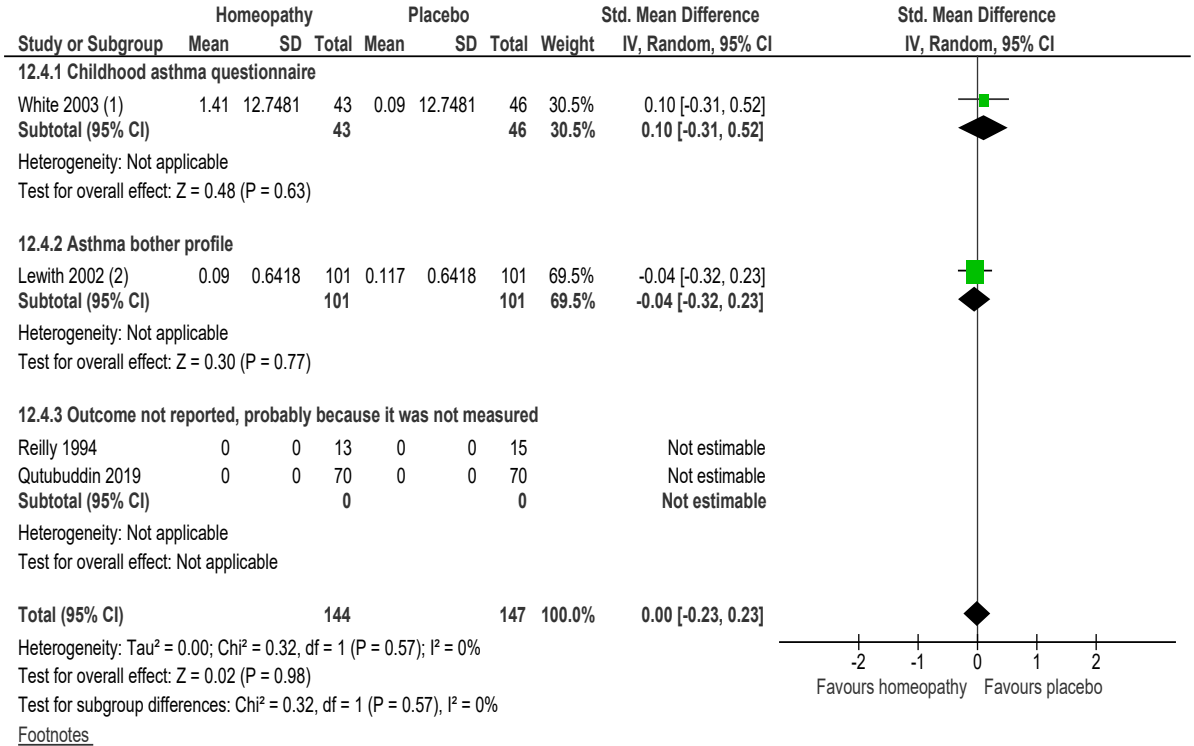


Figure 50 Forest plot of primary comparison: Homeopathy vs placebo: Asthma – quality of life

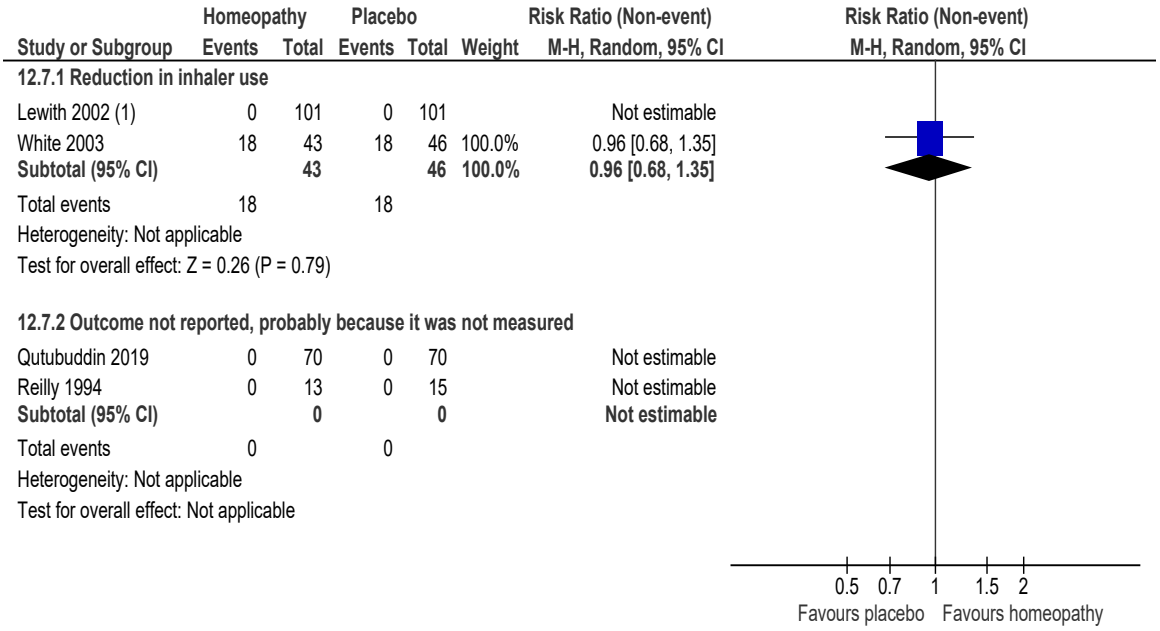


Footnotes

(1) Mean change from baseline. Estimate of treatment effect from reported ANCOVA (95%CI)

(2) Mean change from baseline.

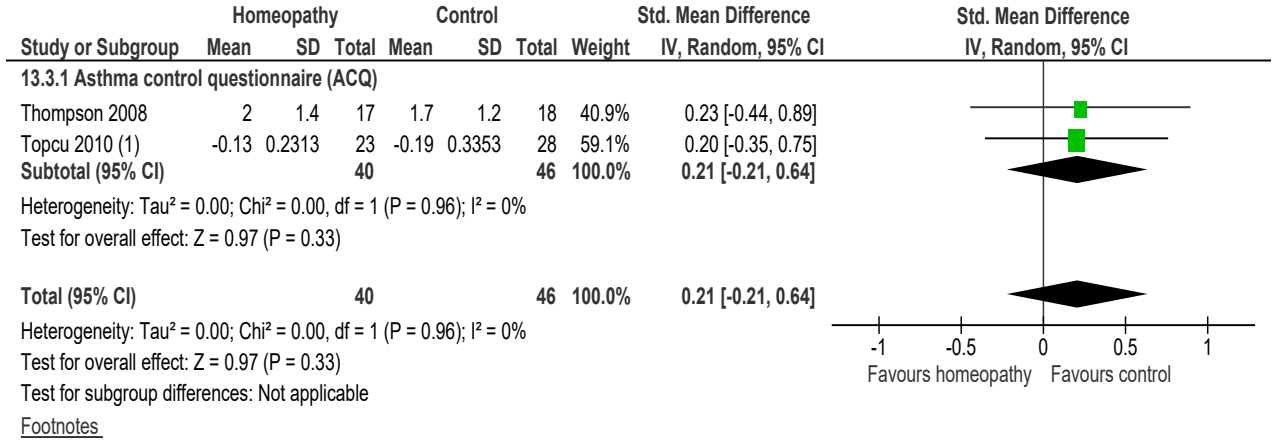
Figure 51 Forest plot of primary comparison: Homeopathy vs placebo: Asthma – medication use



Footnotes

(1) Study did not report any data. Authors reported no difference in inhaler use between the homeopathy group and placebo group (p = not...

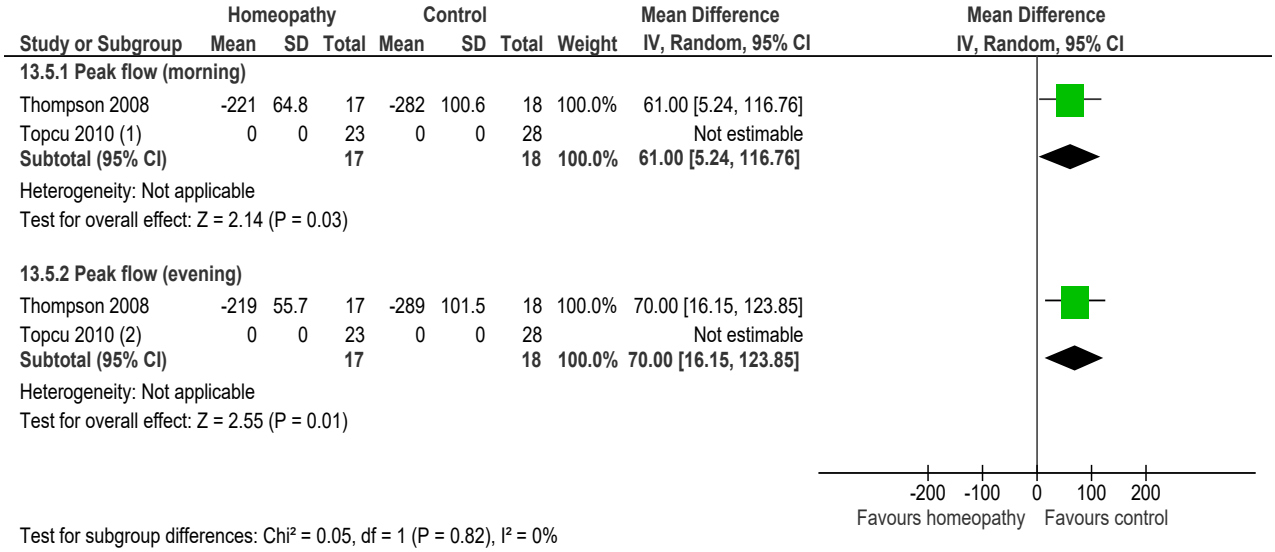
Figure 52 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Asthma – asthma symptoms



Footnotes

(1) Mean change from baseline (95%CI) to mid-treatment (26 weeks). SD calculated as per protocol.

Figure 53 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Asthma – pulmonary function



Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%

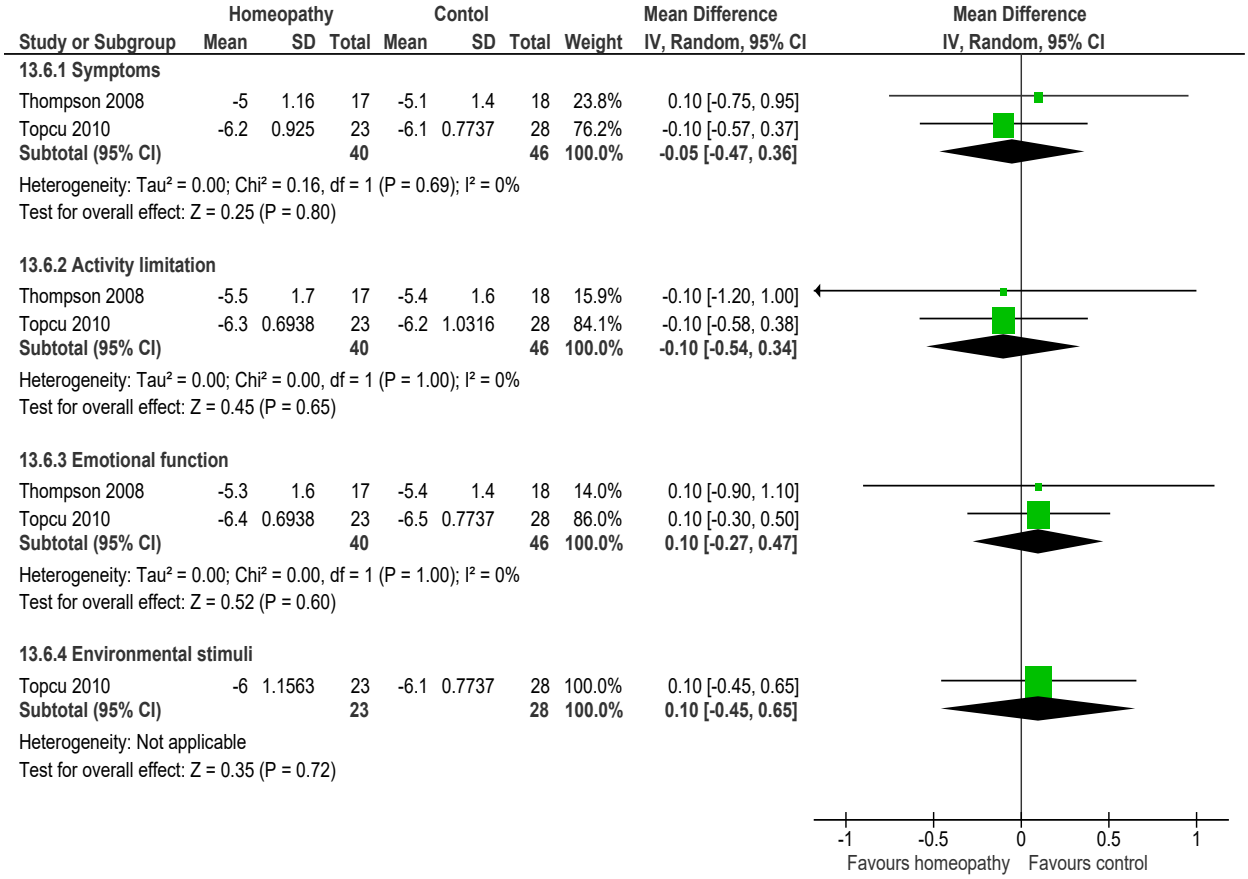
Footnotes

(1) Study does not report usable data. Authors report no difference between the homeopathy and control groups (p = not reported).

(2) Study does not report usable data. Authors report no difference in the change in PEFbetween the homeopathy and control groups (p = not reported).

Note: Data inverted to ensure consistency in direction of effect

Figure 54 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Asthma – quality of life



Note: Data inverted to ensure consistency in direction of effect

Figure 55 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Asthma – hospitalisation

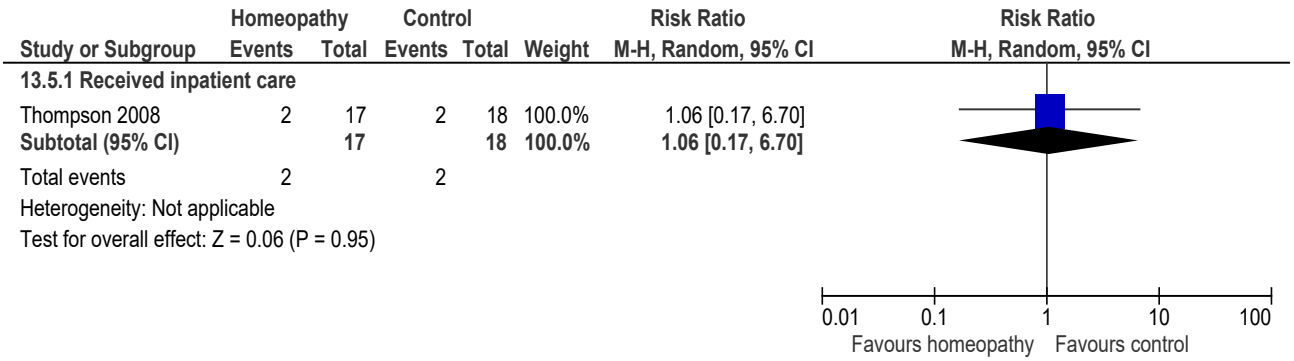
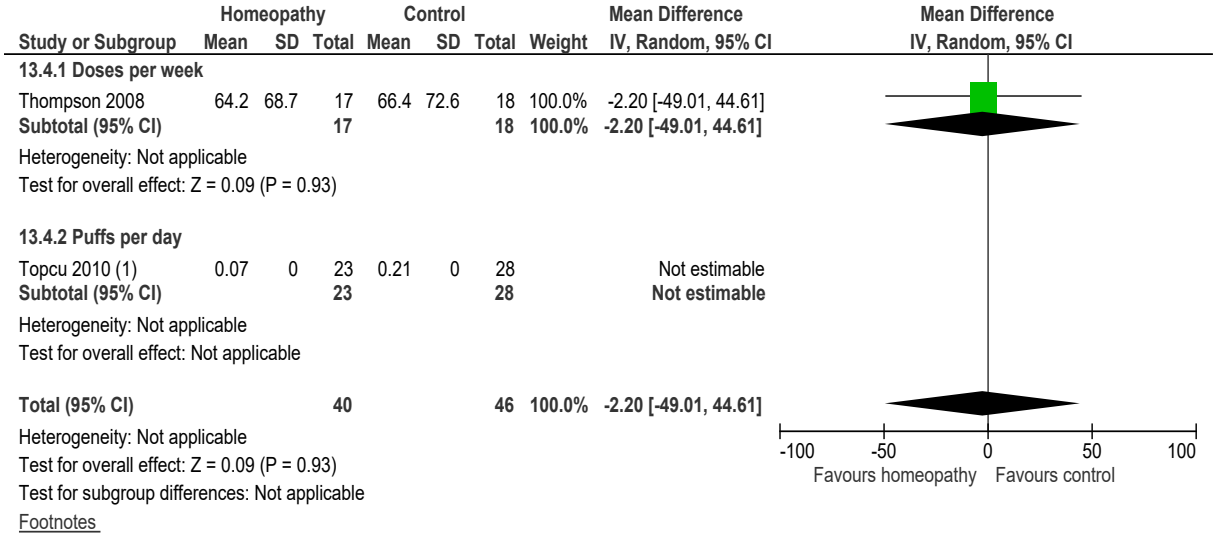


Figure 56 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Asthma – medication use



Footnotes

(1) Authors reported median (min, max) and noted the difference between treatment groups was not statistically significant (p = not reported).

4.12 Diarrhoea

4.12.1 Description of the condition

Diarrhoea (medically referred to as *gastroenteritis*) involves increased frequency and fluidity of stools or bowel movements (219). Acute diarrhoea is typically resolved in less than seven days and is commonly caused by viral pathogens (such as rotavirus or norovirus) transmitted via low quality drinking water, inadequate sanitation, and poor hygiene (219, 220). Abdominal pain, vomiting, fever, loss of appetite, and dehydration are common symptoms of acute diarrhoea (219, 221).

Approximately 17.7 million cases of acute diarrhoea occur in Australia per year, of which 13.9% are in children under 5 years of age (approximately 2.5 million cases) (222). Globally, diarrhoea is the second leading cause of death and leading cause of malnutrition in children under 5 years, but, in Australia, most cases are self-limiting (220). In particular, the inclusion of rotavirus vaccinations in the Australian National Immunisation Program since 2007 has significantly reduced healthcare utilisation relating to acute diarrhoeal episodes (221, 223, 224). Nevertheless, acute diarrhoeal cases continue to be a significant cost burden to the Australian public health system, with some instances requiring interventional therapies like rehydration treatment and other medications, including anti-nausea medicines (219, 221). As such, health care utilisation relating to acute diarrhoea is estimated to cost AUD$419 million per year (inflated for 2022)(224).

4.12.2 Description of studies

There were 3 citations (225-227) corresponding to 2 RCTs (Jacobs 2000, Jacobs 2006) and one quasi RCT (Jacobs 1993) identified in the literature search. One additional quasi RCT (Patel 2010)(228) was found in the Department's public call for evidence. There were no ongoing studies and 2 studies awaiting classification. An overview of the PICO criteria of including studies is provided in Appendix D6.1.1.

Three studies were conducted in community health centres in Nicaragua (Jacobs 1993), Honduras (Jacobs 2006), and India (Patel 2010). One study was carried out in a health clinic in Nepal (Jacobs 2000). Sample size ranged from 34 to 342 participants (803 total participants), with all studies enrolling participants with acute childhood diarrhoea.

Three studies (Jacobs 1993, Jacobs 2000, Patel 2010) used individualised homeopathy which was compared to placebo. One study (Jacobs 2006) used non-individualised homeopathy which was also compared to placebo. In all four studies, participants received rehydration therapy as a co-intervention.

Administration of homeopathic treatment varied between studies. In one study (Jacobs 1993) the intervention was administered twice daily. In 2 studies (Jacobs 2000, Jacobs 2006) the intervention was to be administered after every unformed stool. One study (Patel 2010) did not specify the administration requirements of the intervention as it was individualised with some participants (n=100) receiving treatment for acute symptoms and others (n=100) receiving treatment for acute symptoms followed by constitutional homeopathic treatment that aimed to prevent recurrent attacks. Length of follow up ranged from 5 days (Jacobs 2000) to 2 years (Patel 2010).

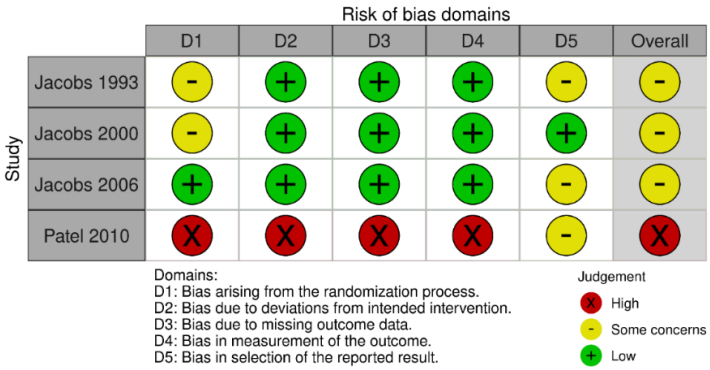
Results for the Primary Comparison: Homeopathy versus placebo are provided in the Summary of Findings table (see Section 4.12.4). There were no studies found for Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) or Tertiary Comparison: Homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.12.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for diarrhoea are summarised in Figure 57. Details are provided in Appendix D6.1.2. No studies were judged to be at overall low risk of bias.

Figure 57 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Diarrhoea



4.12.4 Summary of findings and evidence statements

4.12.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Diarrhoea

Patient or population: Diarrhoea
Setting: Community
Intervention: Homeopathy
Comparison: Placebo (as adjunct to rehydration therapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Symptom severity assessed with: number of loose stools per day (higher is worse) follow-up: up to 7 days	The mean number of stools was **2.8** per day	MD **0.2 fewer** (0.76 fewer to 0.36 more)^	-	292 (1 RCT) †	⊕⊕◯◯ Low [a,b,c,d,e]	Homeopathy may have little to no effect on symptom severity in infants with diarrhoea **
Symptom severity assessed with: Clinical grading (improved) follow-up: 24-hours	180 per 1,000	**661 per 1,000** (271 to 418)^^	**RR 3.67** (2.39 to 5.64)	300 (1 RCT)	⊕◯◯◯ Very Low [c,f,g,h,i]	The evidence is very uncertain about the effect of homeopathy on global improvement in infants with diarrhoea ***

Homeopathy compared to placebo for Diarrhoea

Patient or population: Diarrhoea
Setting: Community
Intervention: Homeopathy
Comparison: Placebo (as adjunct to rehydration therapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Symptom duration assessed with: duration of diarrhoea, days (higher is worse) follow-up: up to 7 days	Two studies reported no difference in symptom duration between homeopathy and placebo. One study reported improvement in favour of homeopathy.		-	448 (3 RCTs)	⨁⨁◯◯ LOW [a,b,c,d,e]	Homeopathy may have little to no effect on symptom duration in infants with diarrhoea
Hospitalisation – not reported	-	-	-	(0 studies)	-	The effect of homeopathy on hospitalisation in infants with diarrhoea is unknown

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI)
** As a rule of thumb, an SMD of 0.2 is considered a small difference, 0.5 is considered medium, and 0.8 is considered large (83).
*** A 25% relative risk reduction was considered important (i.e. RR < 0.75).
**Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

^ SMD –0.08 (95% CI –0.31, 0.15).
^^ The ARD is 481 more per 1000 (from 250 more to 835 more) i.e. 48.1% more with symptom relief.

† Data from 2 studies were incomplete and not able to be included in the data synthesis. One study (123 participants) suggested there was no difference between groups and the other study (33 participants) suggested improvements favoured the homeopathy group (see Appendix D6.1.3.1).

ARD: absolute risk difference; **CI:** confidence interval

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.
b. Serious inconsistency. Two studies reported no difference between homeopathy and placebo groups and one study suggested an effect in favour of homeopathy. Certainty of evidence downgraded.
c. Serious indirectness. Studies were conducted in settings that are likely to be substantially different from the Australian healthcare context (Honduras, Nicaragua, India and Nepal). The evidence is not directly generalisable. Certainty of evidence downgraded.
d. No serious imprecision. Certainty of evidence not downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. Serious risk of bias. One study contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.

g. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

h. Serious imprecision. Single study with wide confidence interval. Certainty of evidence downgraded.

i. Publication bias suspected. The is a strong suspicion of non-reporting of results because the *p* value, magnitude or direction of the results generated were considered unfavourable by the study investigators. Certainty of evidence downgraded.

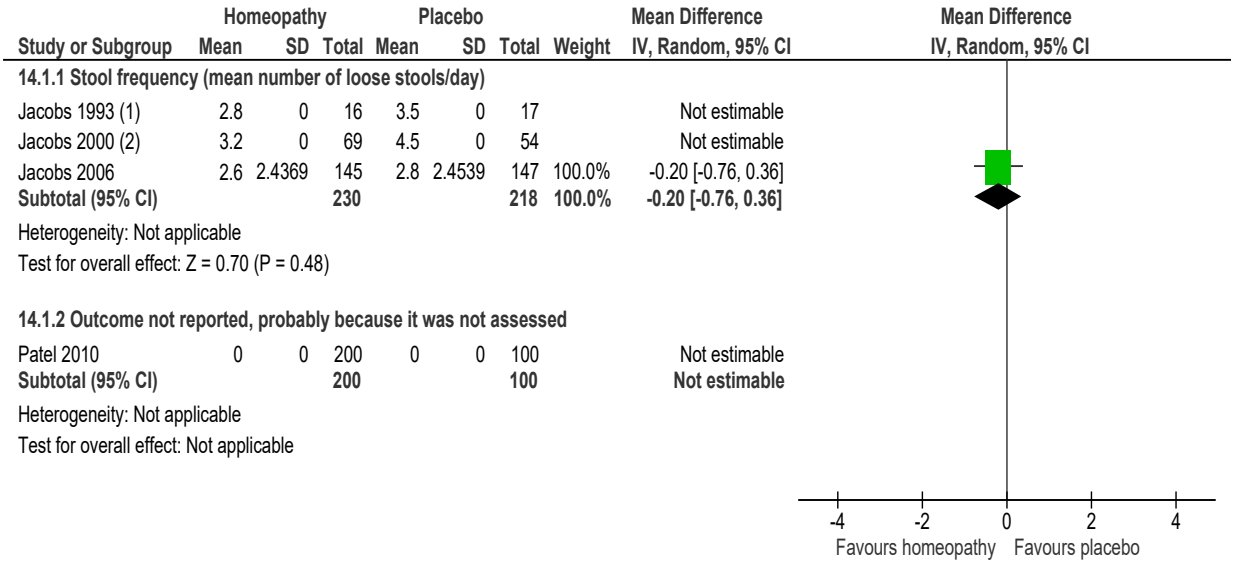
4.12.4.2 Secondary Comparison (vs inactive control)

There were no studies comparing homeopathy with inactive control in digestive disorders (diarrhoea).

4.12.5 Forest plots

Outcome results relating to the primary comparison (homeopathy vs placebo) in children with diarrhoea are presented in Figure 58 (symptom severity – number of stools/day), Figure 59 (symptom duration) and Figure 60 (symptom severity – global improvement).

Figure 58 Forest plot of primary comparison: Homeopathy vs placebo: Diarrhoea – symptom severity, number of stools/day



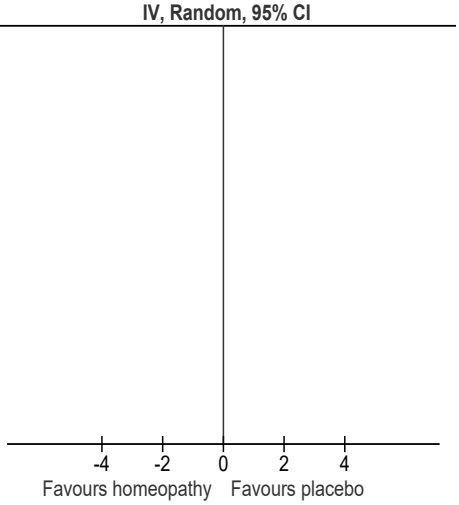
Footnotes

(1) Missing data. Study could not be included in meta-analysis. Authors report no difference between homeopathy and placebo groups (p=0.57).

(2) Missing data. Study could not be included in meta-analysis. Authors report a difference between groups that favours homeopathy (p=0.023).

Figure 59 Forest plot of primary comparison: Homeopathy vs placebo: Diarrhoea – symptom duration

Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
14.3.1 mean/median duration (days)								
Jacobs 1993 (1)	2.4	0	16	3	0	17		Not estimable
Jacobs 2000 (2)	0	0	69	0	0	54		Not estimable
Jacobs 2006 (3)	0	0	145	0	0	147		Not estimable
Subtotal (95% CI)			**230**			**218**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
14.3.2 Outcome not reported, probably because it was not assessed								
Patel 2010	0	0	200	0	0	100		Not estimable
Subtotal (95% CI)			**200**			**100**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Footnotes

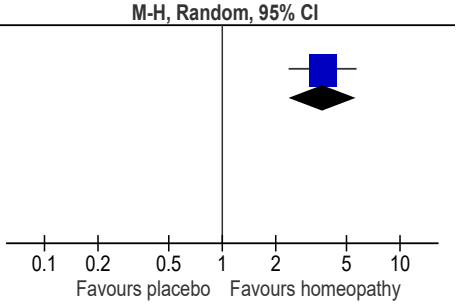
(1) Missing data. Study could not be included in meta-analysis. Authors report no difference between homeopathy and placebo groups (p=0.28).

(2) Study authors report that the homeopathy group are significantly more likely to be symptom free after 5 days compared to the placebo group...

(3) Authors report median (95% CI) values and not included here. Authors suggest no difference between homeopathy and placebo groups.

Figure 60 Forest plot of primary comparison: Homeopathy vs placebo: Diarrhoea – symptom severity, global improvement

Study or Subgroup	Homeopathy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
14.2.1 Improvement (clinician rated)						
Patel 2010 (1)	132	200	18	100	100.0%	3.67 [2.39, 5.64]
Subtotal (95% CI)		**200**		**100**	**100.0%**	**3.67 [2.39, 5.64]**
Total events	132		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.92 (P < 0.00001)						



Footnotes

(1) Number of participants rated with "amelioration"

4.13 Infantile colic and other digestive disorders

4.13.1 Description of the conditions

4.13.1.1 Infantile colic

Infantile colic describes excessive crying, fussing, and sleeping problems that cannot be otherwise explained (229). Colic is estimated to affect up to 28% of infants and is one of the most common presentations in primary health settings (229, 230). Although many cases are self-resolving in the first six months of life, the burden of infantile colic is significant. It is strongly associated with post-natal depression, early breastfeeding cessation, family dysfunction, and development delay (229, 230).

In the absence of a single cause for infantile colic, management of infantile colic is often guided by exclusion of possible causes (e.g. milk allergy, lactose intolerance, gastroesophageal reflux disease (GERD) (229); with the effectiveness of pharmaceutical and non-pharmaceutical treatment options, such as probiotics and hydrolysed formula, somewhat limited (229, 230). Complementary therapies, such as homeopathy, acupuncture and herbal medicines, are therefore commonly sought to alleviate symptoms (229).

4.13.1.2 Gastroesophageal reflux disease (GERD)

Gastroesophageal reflux disease (GERD) is a condition where the acidic contents of the stomach is regurgitated into the oesophagus, caused by a weakened or malfunctioning valve between the stomach and oesophagus (231). Symptoms of GERD include recurrent vomiting, dysphagia, weight loss, and gastrointestinal blood loss leading to iron deficiency or anaemia (231). In Australia, GERD affects between 10 and 15% of the population and is expected to increase over the coming years (231).

Management of GERD involves both modifying lifestyle factors and medicines to suppress acute symptoms, including over-the-counter antacids (231). However, between 20% to 30% of people living with GERD experience persistent symptoms (231). In this instance, clinical guidance suggests further medical and surgical management to review the diagnosis (231). Some complementary or alternative therapies such as homeopathy, acupuncture and Western herbal medicines (e.g. ginger, chamomile) may also be considered for GERD symptoms (232).

4.13.1.3 Functional dyspepsia

Functional dyspepsia (or indigestion) is characterised by chronic upper-gastrointestinal symptoms, including early satiety, postprandial fullness, and epigastric pain and discomfort (233). In Australia, dyspepsia affects 10% of the population (233). Although dyspepsia has no long-term effects on mortality, living with the condition has been shown to significantly impact a person's quality of life (233, 234). As such, treatment is orientated toward managing symptoms and minimising discomfort. Clinical guidance suggests both pharmacological and non-pharmacological interventions are effective, including medication to supress acid secretion (e.g. proton-pump inhibitors), and diet modification (233). Complementary or alternative therapies are also commonly sought to help symptoms, including homeopathy, Western herbal medicines (e.g. peppermint) and relaxation techniques (235, 236).

4.13.2 Description of studies

There were 5 citations (237-240), corresponding to 3 RCTs (Dossett 2015, Paterson 2003, Raak 2019) identified in the literature search. No studies were identified in the Department's public call for evidence. There were 2 ongoing studies and one study awaiting classification that was published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D6.2.1.

One RCT (Paterson 2003) was conducted at a general practice clinic in the United Kingdom and enrolled people who were on repeat prescriptions for dyspepsia. One RCT (Dossett 2015) was conducted at a clinical research centre in the United States and enrolled adults with gastroesophageal reflux disease (GERD). One RCT (Raak 2019) was carried out across 3 medical centres in Russia and enrolled infants with colic. Sample sizes ranged from 24 to 125 (total 209 participants).

One RCT (Dossett 2015) compared homeopathy with placebo. The study had 4 intervention groups, with participants randomised to receive either a standard or expanded length consultation, and either non-individualised homeopathy (Acidil) or placebo. One study (Paterson 2003) compared individualised homeopathy to usual general practitioner care. Details about the interventions or care prescribed for the control group were not provided. One study (Raak 2019) compared non-individualised homeopathic intervention to active control (simethicone). Administration of homeopathic intervention varied between studies, as did the duration of the study, which ranged from 10 days to 6 months.

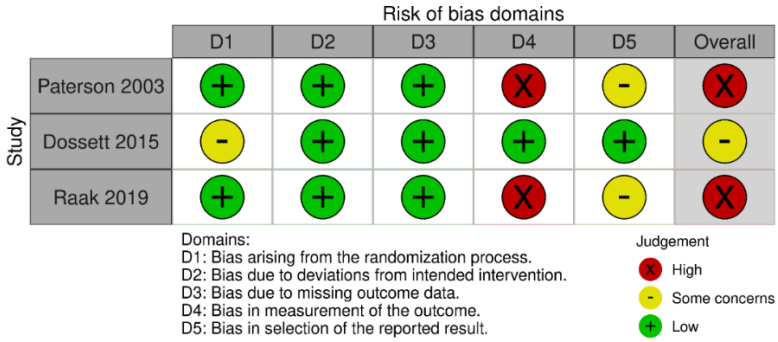
Results for the Primary Comparison: Homeopathy versus placebo and Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist, or usual care) are provided in the Summary of Findings table (see Section 4.13.4). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.13.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for infantile colic and other digestive disorders are summarised in Figure 61. Details are provided in Appendix D6.2.2. No studies were judged to be at overall low risk of bias.

Figure 61 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Infantile colic and other digestive disorders



4.13.4 Summary of findings and evidence statements

4.13.4.1 Primary Comparison (vs placebo)

There were no studies identified comparing homeopathy to placebo in infants with colic. The effect of homeopathy compared to placebo is unknown.

Homeopathy compared to placebo for Other digestive disorders

Patient or population: Other digestive disorders
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Symptom severity assessed with: symptom diary score – GERD symptoms (higher is worse) Scale from: 0 to 12 Follow-up: 2 weeks	The mean symptom severity score was **1.85**	MD **1.1 higher** (0.56 lower to 2.76 higher)	-	24 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on symptoms of GERD in people with digestive disorders **
Symptom severity assessed with: symptom diary score – dyspepsia symptoms (higher is worse) Scale from: 0 to 24 Follow-up: 2 weeks	The mean symptom severity score was **3.5**	MD **0.30 higher** (1.86 lower to 2.46 higher)	-	24 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on symptoms of dyspepsia in people with digestive disorders **
Quality of life assessed with: GERD-HRQL (higher is worse) Scale from: 0 to 75 Follow-up: 2 weeks	The mean HRQL score was **17.95**	MD **4.35 higher** (0.51 lower to 9.21 higher)	-	24 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on quality of life in people with digestive disorders **

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

CI: confidence interval; **GERD:** gastroesophageal reflux disease; **GERD-HRQL:** GERD-Health-Related Quality of Life Instrument; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in a people with GERD and is directly generalisable to the Australian healthcare context with few caveats. Certainty of evidence not downgraded.

d. Very serious imprecision. One small study with wide confidence intervals (upper and lower bound include both meaningful benefit and meaningful harm). Certainty of evidence downgraded 2 levels.

e. Publication bias suspected. The available evidence is limited to one small study. There is a strong suspicion of non-reporting of results because the *p* value, magnitude or direction of the results generated were considered unfavourable by the study investigators. Certainty of evidence downgraded.

4.13.4.2 Secondary Comparison (vs inactive control)

There were no studies identified comparing homeopathy to inactive control in infants with colic. The effect of homeopathy compared to inactive control is unknown.

Homeopathy compared to inactive control for Other digestive disorders

Patient or population: Other digestive disorders
Setting: Community
Intervention: Homeopathy
Comparison: inactive control (usual care)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Symptom severity assessed with: MYMOP Scale from: 0 to 6	The mean change score was **0.53**	MD **0.09 lower** (1.08 lower to 0.90 higher)	-	40 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effect of homeopathy on symptom severity in people with digestive disorders **
Quality of life assessed with: SF-36 health survey Scale from: 0 to 100	-	-	-	(0 studies)	-	The effect of homeopathy on quality of life in people with digestive disorders is unknown

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

CI: confidence interval; **MYMOP:** Measure Yourself Medical Outcome Profile

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One study contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with dyspepsia and is directly generalisable to the Australian healthcare context with few caveats. Certainty of evidence not downgraded.

d. Very serious imprecision. Single study with wide confidence intervals (upper and lower bounds overlap with both meaningful benefit and harm). Certainty of evidence downgraded 2 levels.

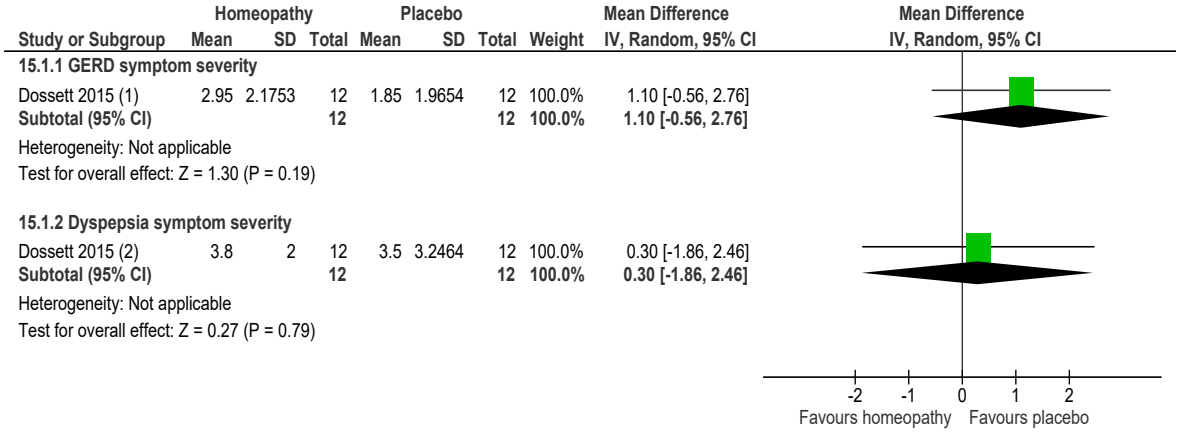
e. Publication bias suspected. The available evidence is limited to one small study. There is a strong suspicion of non-reporting of results because the *p* value, magnitude or direction of the results generated were considered unfavourable by the study investigators. Certainty of evidence downgraded.

4.13.5 Forest plots

Outcome results relating to the primary comparison (homeopathy vs placebo) in people with digestive disorders are presented in Figure 62 (symptom severity) and Figure 63 (quality of life).

Outcome results related to the secondary comparison (homeopathy vs inactive control) in people with digestive disorders are presented in Figure 64 (symptom severity).

Figure 62 Forest plot of primary comparison: Homeopathy vs placebo: Digestive disorders – symptom severity

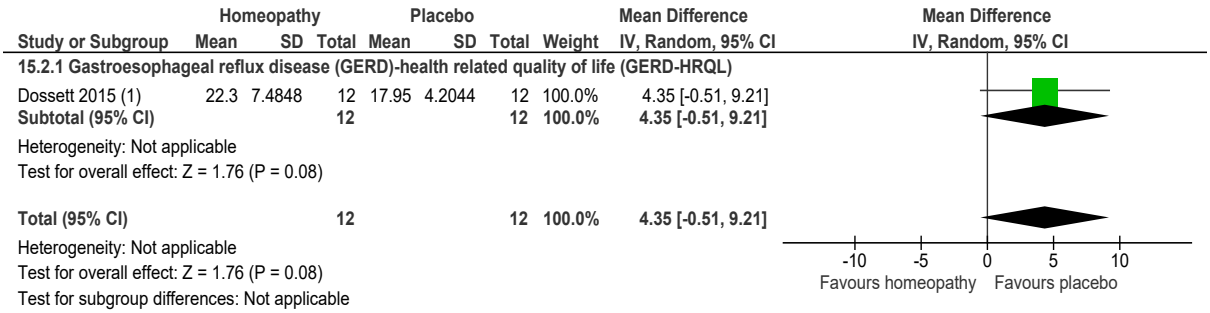


Footnotes

(1) Data combined for standard and expanded length interview

(2) Data combined for standard and expanded length interview

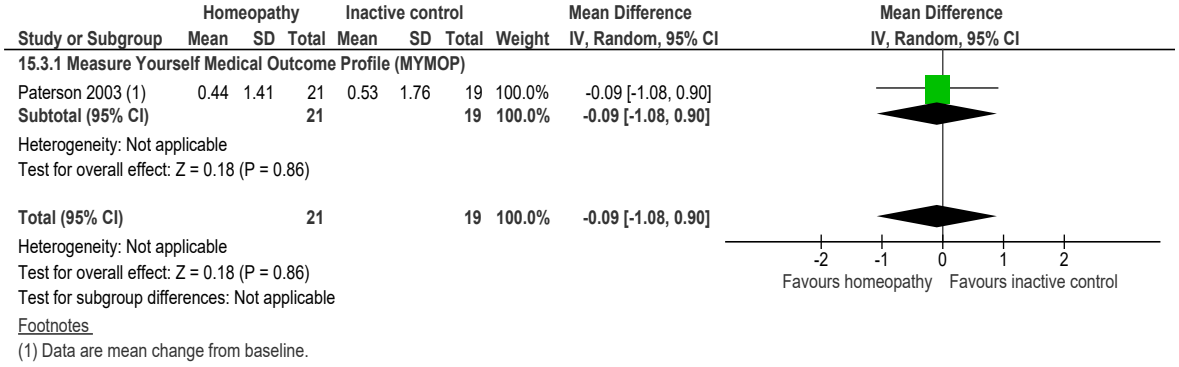
Figure 63 Forest plot of primary comparison: Homeopathy vs placebo: Digestive disorders – quality of life



Footnotes

(1) Data combined for standard and expanded length interview.

Figure 64 Forest plot of secondary comparison: Homeopathy vs inactive control: Digestive disorders – symptom severity



4.14 Irritable bowel syndrome

4.14.1 Description of the condition

Irritable bowel syndrome (IBS) is a group of conditions whose symptoms include abdominal pain, bloating and changes in bowel movements, either constipation, diarrhoea or both (241). These symptoms occur without any visible sign of damage to the digestive tract but have a substantial impact on a person's quality of life (241, 242). The exact cause of IBS is not known; with symptoms tending to be triggered by diet, stress, infection and medications (241, 242).

IBS is estimated to affect one in five Australians at some time (243). There are no medications specifically designed to treat IBS. Often, a dietary change that focuses on moderating the intake of gas-producing foods (e.g. fructose, lactose, sorbitol) is sufficient to improve symptoms (244). Other treatments include lifestyle changes, exercise, probiotics and medication such as laxatives, antidiarrhea medication or antispasmodics (245). In the absence of definitive treatments, complementary and alternative therapies, including homeopathy and Western herbal medicines are routinely sought among people with IBS (245, 246).

4.14.2 Description of studies

Two citations (247, 248) corresponding to one quasi RCT (Peckham 2012) were identified in the literature search. No additional studies were identified in the Department's public call for evidence. There were 2 ongoing studies, and 3 studies awaiting classification. An overview of the PICO criteria of included studies is provided in Appendix D6.3.1.

The study (Peckham 2012) was conducted in a community setting in the UK, with participants being referred from primary or secondary care. The study enrolled 94 people with irritable bowel syndrome aged 18 years and above.

The study compared homeopathy with an inactive control (no intervention). Participants received individualised homeopathy in the form of 5x 1-hour sessions over a 6-month period. There were no limitations on the type, potency or dosage of homeopathic product prescribed. There were two comparator arms: one included 5x 1-hour sessions of supportive listening over a 6-month period, the other was no intervention. All participants continued to receive usual care.

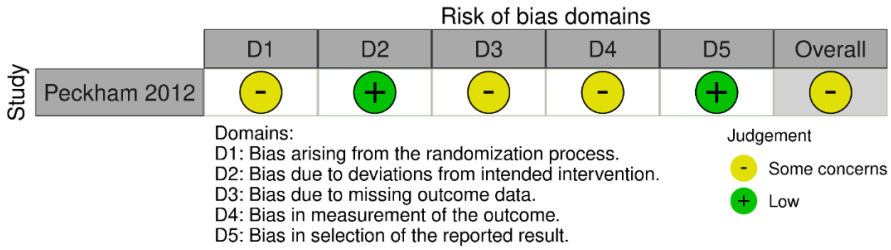
There were no studies found for the Primary Comparison: Homeopathy versus placebo. Results for the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings table (see Section 4.14.4). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.14.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for IBS are summarised in Figure 65. Details are provided in Appendix D6.3.2. No studies were judged to be at overall low risk of bias.

Figure 65 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Irritable bowel syndrome



4.14.4 Summary of findings and evidence statements

4.14.4.1 Primary Comparison (vs placebo)

There were no studies identified comparing homeopathy to placebo in people with IBS. The effect of homeopathy compared to placebo is unknown.

4.14.4.2 Secondary Comparison (vs inactive control)

Homeopathy compared to inactive control for irritable bowel syndrome

Patient or population: Irritable bowel syndrome
Setting: Community
Intervention: Homeopathy
Comparison: inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with control	Risk with homeopathy				
Symptom severity assessed with: IBS Symptom Severity Scale (higher is worse) Scale from: 0 to 500 follow-up: 26 weeks	The mean global improvement score was **237.3 points**	MD **26.86 points lower** (88.59 lower to 34.87 higher)	-	76 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in symptom severity in people with IBS [#]
Pain – not reported	-	-	-	(0 studies)	-	The effect of homeopathy on pain in people with IBS is unknown
Quality of life assessed with: EQ-5D VAS (higher is better) Scale from: 0 to 100 follow-up: 26 weeks	The mean quality of life was **63.41 points**	MD **5.66 points higher** (4.69 lower to 16.01 higher)	-	76 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in quality of life in people with IBS [##]

Homeopathy compared to inactive control for irritable bowel syndrome

Patient or population: Irritable bowel syndrome
Setting: Community
Intervention: Homeopathy
Comparison: inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence Statement
	Risk with control	Risk with homeopathy				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

A 50-point change in scores is considered clinically relevant (249).
The MCID is estimated to be around 10 points (250).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with IBS and is directly applicable to the Australian population with few caveats. Certainty of evidence not downgraded.

d. Very serious imprecision. One small study that did not reach optimal information size, with wide confidence intervals (upper and lower bounds overlap with both an important an no important difference). Certainty of evidence downgraded 2 levels.

e. Publication bias not suspected. Certainty of evidence not downgraded.

4.14.5 Forest plots

Outcome results related to the secondary comparison (homeopathy vs control) in people with IBS are presented in Figure 66 (symptom severity) and Figure 67 (quality of life).

Figure 66 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention, waitlist or usual care): IBS – symptom severity

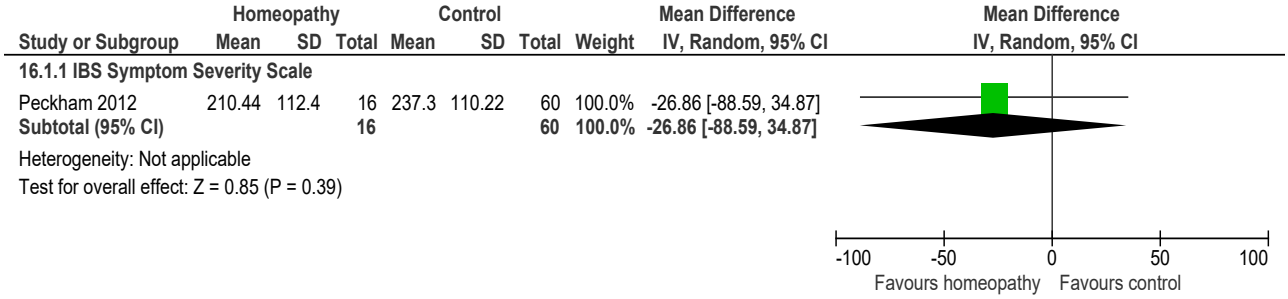
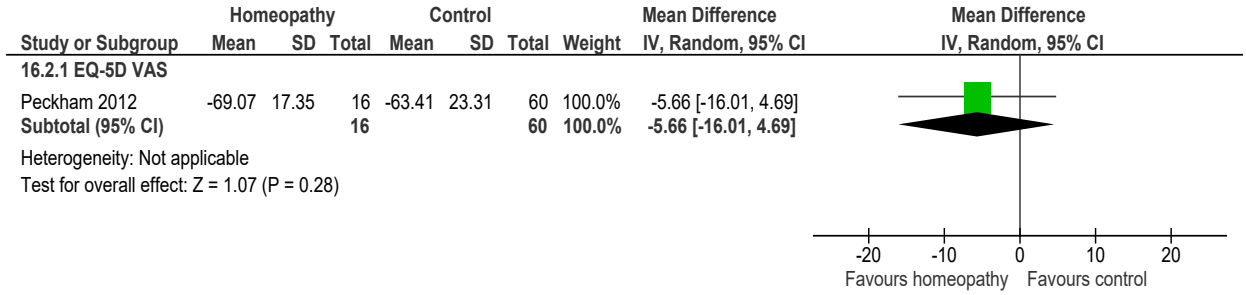


Figure 67 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention, waitlist or usual care): IBS – quality of life



4.15 Psoriasis

4.15.1 Description of the condition

Psoriasis is a chronic, non-communicable, inflammatory skin disease that affects over 100 million people worldwide (251, 252). It is characterised by skin lesions spread throughout the body or localised to one area, including the face, palms, soles of feet and genitalia (253). The lesions can cause itching, stinging, and pain, and can significantly impact a person's quality of life (252).

In Australia, it is estimated 2.5% of people are living with psoriasis (254). Treatment is typically multi-faceted and can include topical therapy, oral systematic therapies, and interventional therapies, such as phototherapy (253). The need for such treatment is usually lifelong, with the aim of treatment being to stop skin cells from growing so quickly, to remove scales, and to optimise symptom management (252). The success of treatment is variable, and different combinations are usually required. As such, up to 51% of people with psoriasis report the use of complementary and alternative medicine (255); this includes acupuncture, herbal medicines, and homeopathy.

4.15.2 Description of studies

Two citations (256, 257), corresponding to 2 quasi RCTs (Bernstein 2006, Wiesenauer 1992) were identified in the literature search. There were no studies identified in the Department's public call for evidence. There was one ongoing studies, and one study awaiting classification. An overview of the PICO criteria of included studies is provided in Appendix D7.1.1.

One study (Bernstein 2006) was carried out across six sites in the United States and Canada. The other study (Wiesenauer 1992) was conducted at family physician and dermatology clinics in Germany. Sample sizes ranged from 82 to 200 (total 282 participants). One study (Bernstein 2006) included people with mild to moderate psoriasis covering less than 10-15% of the body, and the other study (Wiesenauer 1992) enrolled participants with psoriasis of any degree of severity.

Both studies (Bernstein 2006, Wiesenauer 1992) compared non-individualised, topical homeopathic intervention to placebo. Administration of the intervention and duration of the study varied, with the intervention being applied twice daily for 12 weeks in one study (Bernstein 2006); and administered 2 to 3 times a day and then again at night with smeared bandages in the study reported by Wiesenauer 1992. Here, the length of treatment was individually assigned by the treating physician, although 8 weeks was suggested by the study coordinators.

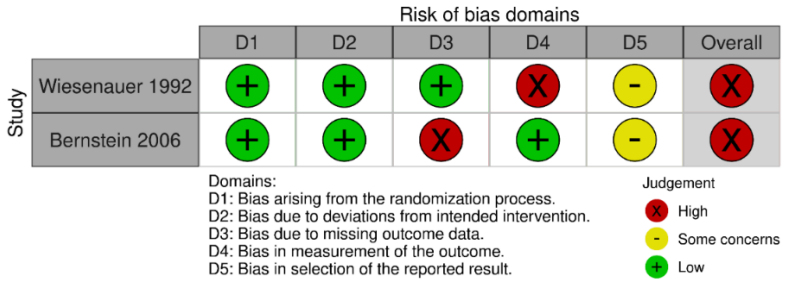
Results for the Primary Comparison: Homeopathy versus placebo are provided in the Summary of Findings table (see Section 4.15.4). There were no studies found for the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) or Tertiary Comparison: Homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.15.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for psoriasis are summarised in Figure 68. Details are provided in Appendix D7.1.2. No studies were judged to be at overall low risk of bias.

Figure 68 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Psoriasis



4.15.4 Summary of findings and evidence statements

4.15.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Psoriasis

Patient or population: Psoriasis
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Disease severity assessed with: Psoriasis Area Severity Index (PASI) (higher is worse) Scale from: 0 to 100 follow-up: 12 weeks	Mean reduction in PASI score was **0.09 points**	MD **3.30 more** (2.12 more to 4.48 more)	-	200 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no improvement in disease severity in people with psoriasis [#]
Symptoms severity assessed with: improvement or resolution – clinician assessed follow-up: median 4 weeks	450 per 1,000	**725 per 1,000** (491 to 1,000) ^	**RR 1.61** (1.09 to 2.38)	80 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,e,f,g]	The evidence is very uncertain about the effect of homeopathy on symptom improvement people with psoriasis **
Quality of life assessed with: Quality of life index (higher is worse) Scale from: 0 to 120 follow-up: 12 weeks	Mean QLI improved by **15.1 points**	MD **10.40 more** (3.21 more to 17.59)	-	200 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,e,f]	The evidence is very uncertain about the effect of homeopathy on quality of life in people with psoriasis ***

Homeopathy compared to placebo for Psoriasis

Patient or population: Psoriasis
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Itching – not measured	-	-	-	(0 studies)	-	The effect homeopathy on itching in people with psoriasis is unknown
Skin condition – not measured	-	-	-	(0 studies)	-	The effect homeopathy on skin condition in people with psoriasis is unknown
Medication use – not measured	-	-	-	(0 studies)	-	The effect homeopathy on medication use in people with psoriasis is unknown

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** A 25% relative risk improvement was considered important (i.e. RR > 1.25).
*** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

^ The ARD is 275 more per 1000 (from 41 more to 61 more) i.e. 27.5% increase.
# A 50% reduction in the PASI score is considered clinically meaningful (258).

CI: confidence interval **MD:** mean difference; **QLI:** Quality of life index

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One study contributing 100% was at high risk of bias. Certainty of evidence downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. Serious indirectness. The available evidence is in people with mild to moderate psoriasis covering less than 10-15% of the body and may not be generalisable to people with severe psoriasis (but could be sensibly applied). The study also uses a topical homeopathic intervention (*M. aquifolium* 10%) so applicability to other modes of administration may be limited. Certainty of evidence downgraded.

d. No serious imprecision. Certainty of evidence not downgraded.

e. Publication bias not suspected. Certainty of evidence not downgraded.

f. Serious imprecision. Single study with wide confidence intervals (upper and lower bounds overlap with important and no important difference). Certainty of evidence downgraded.

g. Serious indirectness. The available evidence is applicable to the Australian population with some caveats. The study uses a topical homeopathic intervention (*M. aquifolium* 10%) so applicability to other modes of administration may be limited. Certainty of evidence downgraded.

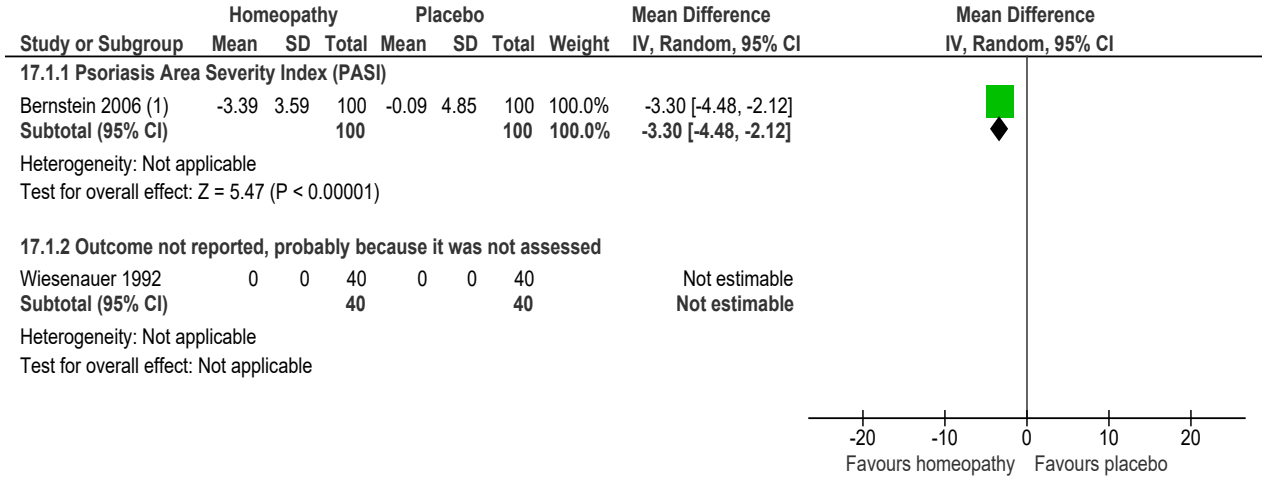
4.15.4.2 Secondary Comparison (vs inactive control)

There were no studies identified which compared homeopathy to inactive control (no intervention, usual care, or waitlist) in people with psoriasis.

4.15.5 Forest plots

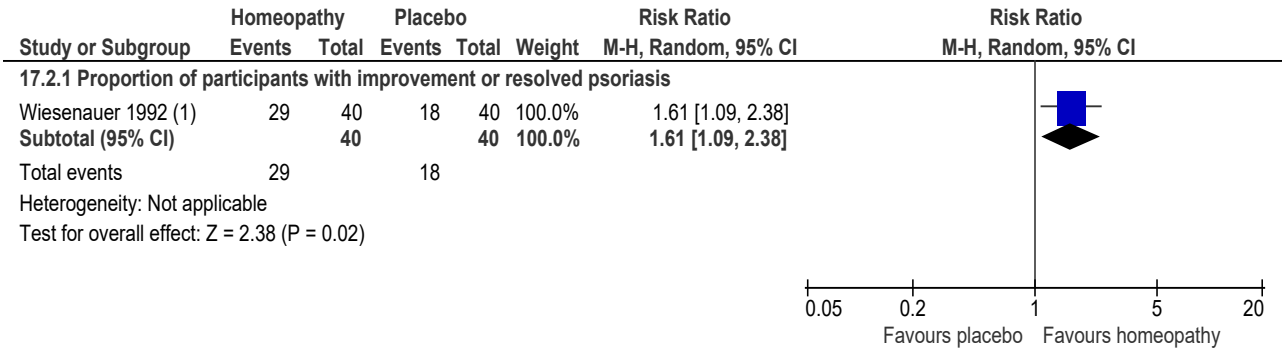
Outcome results related to the primary comparison (homeopathy vs placebo) in people living with psoriasis are presented in Figure 69 (disease severity), Figure 70 (symptom improvement) and Figure 71 (quality of life).

Figure 69 Forest plot of primary comparison: Homeopathy vs placebo: Psoriasis – disease severity



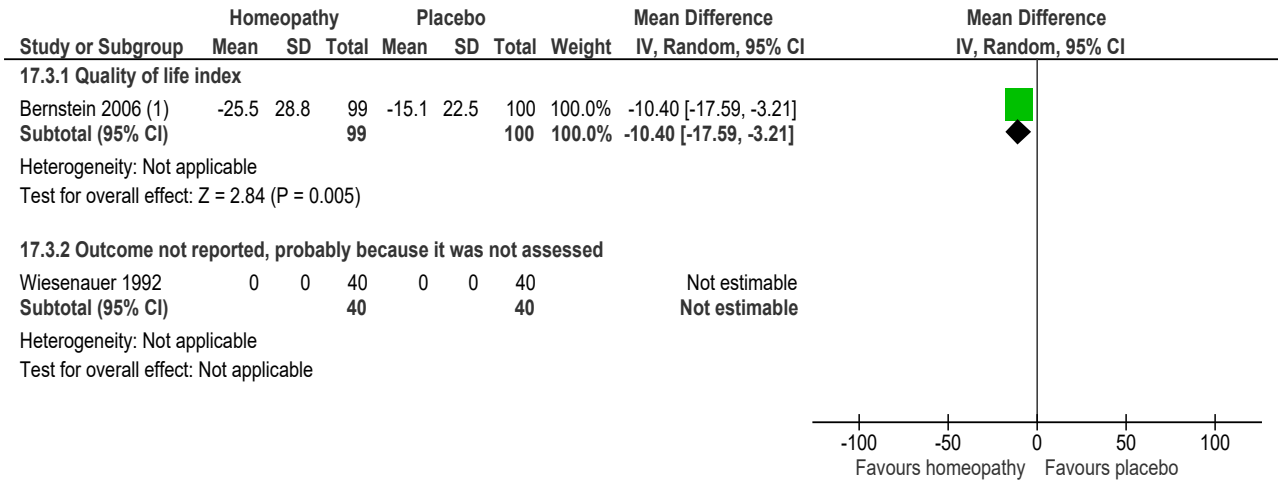
Footnotes
(1) Reported as change from baseline.

Figure 70 Forest plot of primary comparison: Homeopathy vs placebo: Psoriasis – symptom improvement



Footnotes
(1) Clinician assessment

Figure 71 Forest plot of primary comparison: Homeopathy vs placebo: Psoriasis – quality of life



Footnotes

(1) Mean change from baseline.

4.16 Arthropathies

4.16.1 Description of the condition

4.16.1.1 Osteoarthritis

Osteoarthritis (OA) is a chronic disease that primarily impacts the articular cartilage and the subchondral bone of a synovial joint, eventually resulting in joint failure (259). Individuals with OA experience joint pain, stiffness and swelling that mainly affects the hands, knees and hips (260). As OA progresses it can impact a person's quality of life as it becomes difficult to perform everyday tasks (260).

OA is the most common form of arthritis in Australia, with a 2017-18 survey suggesting an estimated 2.2 million (9.3%) Australians are living with OA (259-261). There is no specific known cause for OA, however several factors contribute to the onset and progression of disease, including being female, overweight or obese. Although younger people can be affected, it most frequently occurs in people aged over 55 years with over one third of all adults aged 75 years or older experiencing this condition (260, 261). There is no cure for OA (261), with recommended treatments focused on relieving pain and improving joint function. Australian guidelines (260) strongly recommend regular land based exercise such as muscle strengthening exercises, Pilates, walking and Tai Chi. Other complementary and alternative therapies used among people with OA include vitamins and mineral supplements and herbal medicines (262, 263).

4.16.1.2 Inflammatory arthropathies

Inflammatory arthropathies are a group of related conditions where joint inflammation and pain are caused by a chronic autoimmune reaction (203). Inflammatory arthropathies include conditions such as rheumatoid arthritis (RA), psoriatic arthritis, and juvenile idiopathic arthritis. RA is the most common inflammatory arthropathy in Australia (203) and is characterised by joint swelling, tenderness, and destruction of synovial joints (264). Instead of producing nourishing and lubricating fluid, the synovial membrane that lines affected joints is attacked by the immune system and becomes thick and inflamed. This results in unwanted tissue growth, bone erosion, and irreversible joint damage (265). RA typically affects hand joints and both sides of the body at the same time (265).

The estimated prevalence of RA in Australia is 1.9%, or around 456,000 people (265). RA is more common in females than in males, and occurs most commonly in people over age 75 (265). In 2017 to 2018, there were 12,045 hospitalisations for RA (265). Several pharmacological options are indicated for the management of inflammatory arthropathies. Disease-modifying anti-rheumatic drugs (DMARDs), biologic disease-modifying anti-rheumatic drugs (bDMARDs), and corticosteroids can slow disease progression (265). If initiated early, these medications can help prevent irreversible damage and disability (265). Complementary therapies including homeopathy are widely used among people with rheumatoid arthritis (263, 266).

4.16.2 Description of studies

There were 9 citations (15, 267-274) corresponding to 3 RCTs (Brien 2004, Koley 2015, van Haselen 2000) and 4 quasi RCTs (Fisher 2001, Shealy 1998, Shipley 1983, Strosser 2000) identified in the literature search. Three additional studies (Ibrahim 2015, Khitrov 2009, Widrig 2007) were identified in the Department's public call for evidence (275-277). There were 14 ongoing studies, and 7 studies awaiting classification including 4 studies published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D8.1.1.

The studies were predominantly conducted in community or outpatient settings in Germany (Strosser 2000), Egypt (Ibrahim 2015), India (Koley 2015), Russia (Khitrov 2009), Switzerland (Widrig 2007), the United Kingdom (Brien 2004, Fisher 2001, Shipley 1983, van Haselen 2000), the United States (Shealy 1998). Three studies (Brien 2004, Strosser 2000, Widrig 2007) were conducted across multiple centres.

Five studies included participants with OA of the knee (Ibrahim 2015, Koley 2015, Strosser 2000, van Haselen 2000, Shealy 1998), the other studies were in people with OA of the hand (Widrig 2007) or hip and/or knee (Shipley 1983). Two studies (Brien 2004, Fisher 2001) included participants with rheumatoid arthritis and one study (Khitrov 2009) included participants with periarthritis of the shoulder. The sample sizes ranged between 35 and 204 (total 924 participants).

Eight studies (Fisher 2001, Ibrahim 2015, Khitrov 2007, Shealy 1998, Shipley 1983, Strosser 2000, van Haselen 2000, Widrig 2007) evaluated non-individualised homeopathic medicinal products, commonly including *Rhus toxicodenderon* and Arnica. One study (Koley 2015) evaluated individualised homeopathy. One study (Brien 2004) included three homeopathic treatment arms including individualised homeopathy and non-individualised homeopathy both with and without a homeopathic consultation.

Four studies (Shipley 1983, Koley 2015, Brien 2004, Fisher 2001) compared homeopathy to placebo. The remaining studies compared homeopathy to an active control, typically pharmacotherapy with non-steroidal anti-inflammatory drugs, with one study (Ibrahim 2015) also comparing homeopathy with acupuncture.

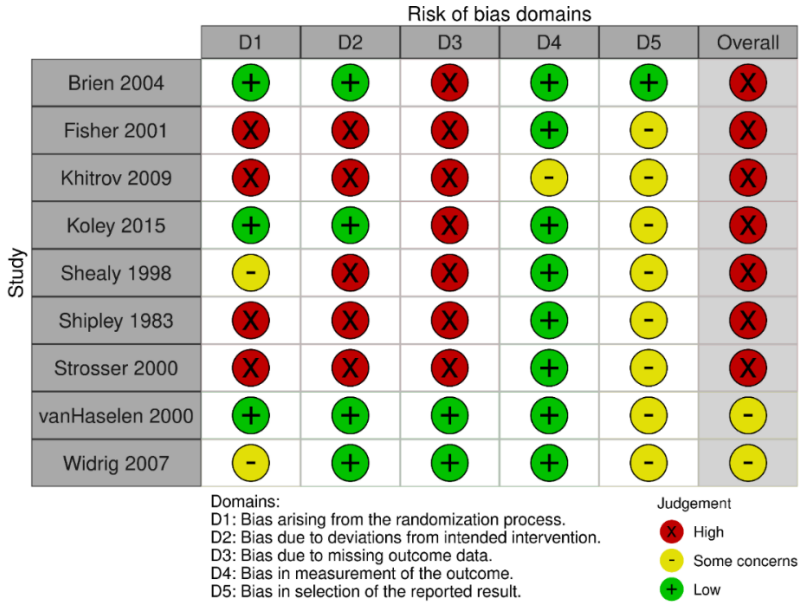
Results for Primary Comparison: Homeopathy versus placebo are provided in the Summary of Findings table (see Section 4.16.4.1). There were no studies found for Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.16.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for arthropathies are summarised in Figure 72. Details are provided in Appendix D8.1.2. No studies were judged to be at overall low risk of bias.

Figure 72 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Arthropathies



4.16.4 Summary of findings and evidence statements

4.16.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Arthropathies

Patient or population: Arthropathies
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Pain intensity assessed with: VAS (higher is worse) Scale from: 0 to 100 follow-up: range 2 weeks to 24 weeks	-	SMD **0.01 SD lower** (0.36 lower to 0.39 higher)	-	112 (2 RCTs) †	⨁◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on pain intensity in people with arthritis **
Physical functioning/ disability assessed with: HAQ, VAS (higher is worse) Scale from: 0 to 100 follow-up: 2 weeks	-	SMD **0.05 SD lower** (0.42 lower to 0.32 higher)	-	114 (2 RCTs)	⨁◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on physical function/disability in people with arthritis **

Homeopathy compared to placebo for Arthropathies

Patient or population: Arthropathies
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Disease severity assessed with: DAS-28 follow-up: 24 weeks	The mean change in DAS-28 score was **0.6548**	MD **0.06 more** (0.57 less to 0.68 more)	-	53 (1 RCT)	⨁◯◯◯ VERY LOW [d,e,f,g,h]	The evidence is very uncertain about the effect of homeopathy on disease severity in people with arthritis #
Health related quality of life assessed with: VAS (higher is better) Scale from: 0 to 100 follow-up: 24 weeks	The mean change in VAS was **17.45**	MD **4.96 less** (18.7 less to 8.78 more)	-	54 (1 RCT)	⨁◯◯◯ VERY LOW [c,d,e,f,g]	The evidence is very uncertain about the effect of homeopathy on health-related quality of life in people with arthritis ***
Medication use - not reported	-	-	-	(0 studies) ‡	-	The effect of homeopathy on medication use in people with arthritis is unknown

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** As a rule of thumb, an SMD of 0.2 is considered a small difference, 0.5 is considered medium, and 0.8 is considered large (83).
*** Effect estimates were to be considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Data from 2 crossover studies (148 participants) not included in the meta-analysis as study authors do not report results prior to treatment crossover.
‡ Data from one crossover study (36 participants) not included in the meta-analysis as study authors do not report results prior to treatment crossover.

A decrease of 1.2 points is considered clinically meaningful, a decrease of less than 0.6 points is considered a non-response (278)

CI: confidence interval; **MD:** mean difference; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. Two studies contributing 100% of the data for this outcome were judged at high risk of bias. Certainty of evidence downgraded.

b. No serious inconsistency. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with rheumatoid arthritis or knee osteoarthritis and is directly applicable to the Australian population with few caveats. Certainty of evidence not downgraded.

d. Serious imprecision. Wide confidence intervals that include the possibility of both harm and benefit. Certainty of evidence downgraded.

e. Publication bias strongly suspected. Data from several studies listed as awaiting classification or ongoing (see Appendix C6) not reported, probably because the *p* value, magnitude or direction of the results generated were considered unfavourable by the study investigators. Certainty of evidence downgraded.

f. Serious risk of bias. One study contributing 100% of the data for this outcome was judged at high risk of bias. Certainty of evidence downgraded.

g. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

h. No serious indirectness. The available evidence is in people with rheumatoid arthritis and is directly applicable to the Australian population with few caveats. Certainty of evidence not downgraded.

4.16.4.2 Secondary Comparison (vs inactive control)

There were no studies identified that compared homeopathy to inactive control in people with arthropathies; therefore, the effect of homeopathy for this comparison is unknown.

4.16.5 Forest plots

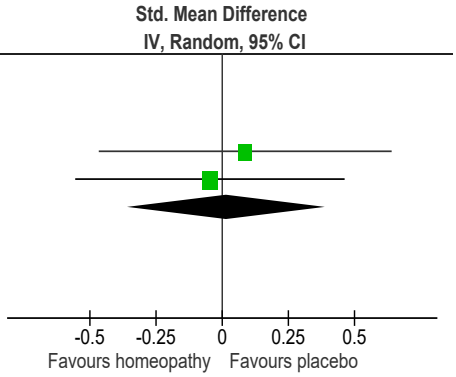
Outcome results related to the primary comparison (homeopathy vs placebo) in people with arthritis are presented in Figure 73 (pain intensity), Figure 74 (physical function), Figure 75 (disease severity) and Figure 76 (quality of life).

Figure 73 Forest plot of primary comparison: Homeopathy vs placebo: Arthritis – pain intensity

	Homeopathy			Placebo				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
18.1.1 Visual analogue scale								
Fisher 2001 (1)	0	0	56	0	0	56		Not estimable
Shipley 1983 (2)	0	0	15	0	0	21		Not estimable
Brien 2004 (3)	-5.499	22.1931	30	-7.7	28.293	22	45.8%	0.09 [-0.46, 0.64]
Koley 2015	56.6	26.9	30	58	32.5	30	54.2%	-0.05 [-0.55, 0.46]
Subtotal (95% CI)			**60**			**52**	**100.0%**	**0.01 [-0.36, 0.39]**

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

Test for overall effect: Z = 0.08 (P = 0.94)



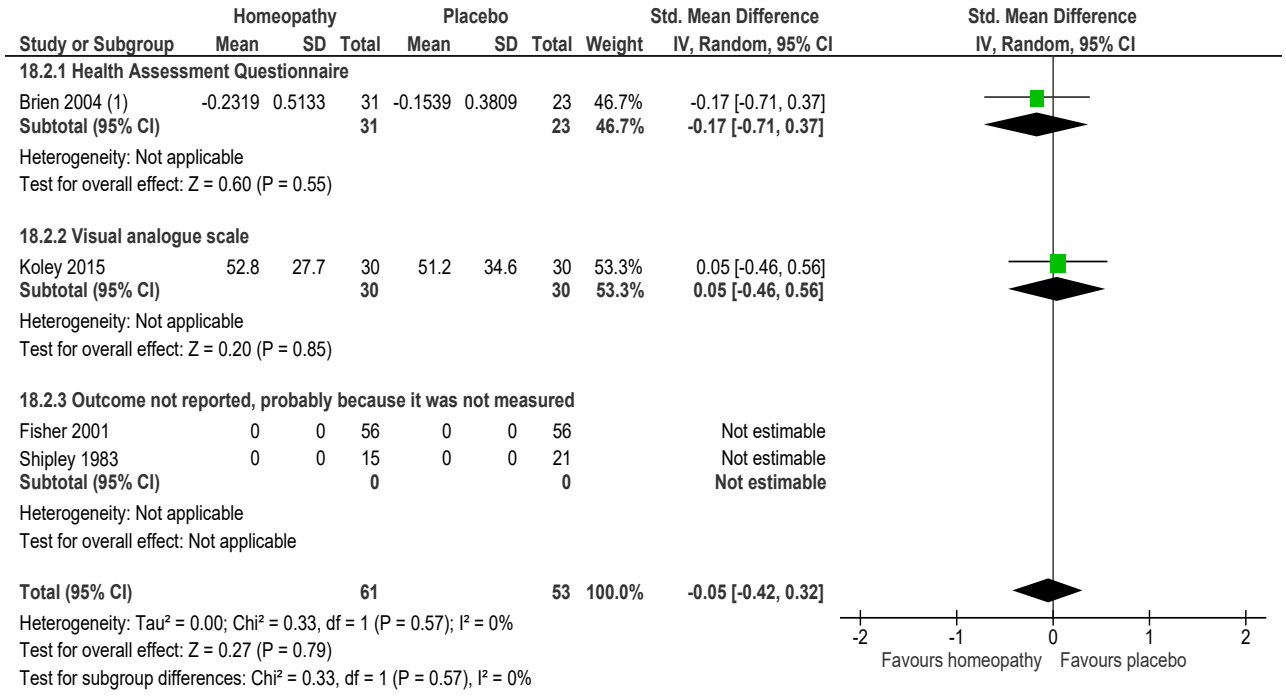
Footnotes

(1) Study does not report results prior to crossover therefore not included here. Study authors report a significant difference in favour of placebo.

(2) Study does not report results prior to crossover therefore not included here. Study authors report no difference between homeopathy and placebo.

(3) Study reports results as change from baseline to end of treatment. Results from 5 treatment arms (3 homeopathy, 2 placebo) combined (as per protocol).

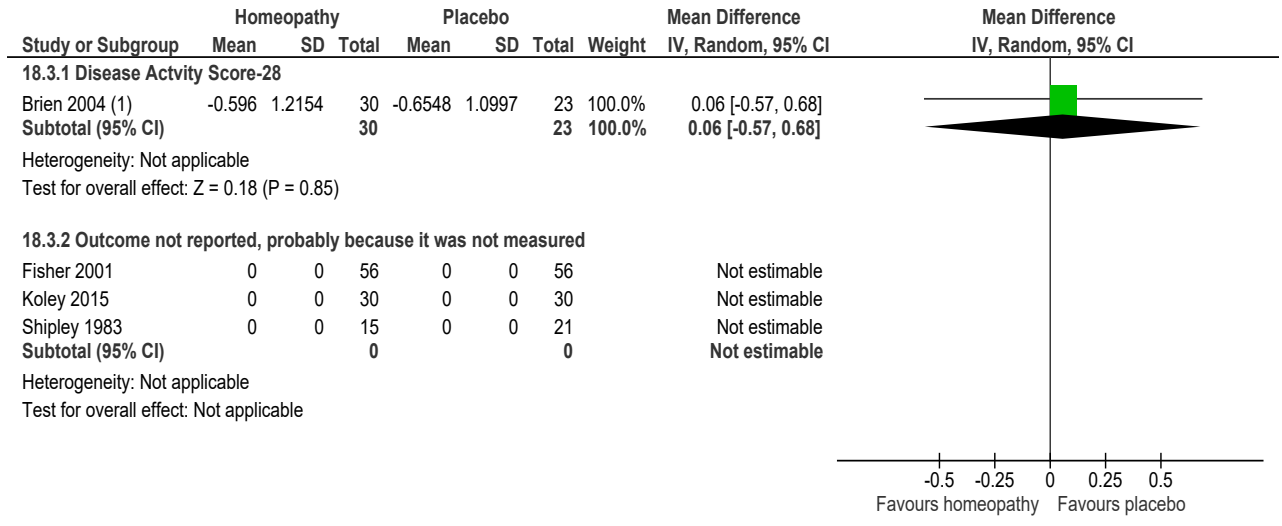
Figure 74 Forest plot of primary comparison: Homeopathy vs placebo: Arthritis – physical function



Footnotes

(1) Study reports results as change from baseline to end of treatment. Results from 5 treatment arms (3 homeopathy, 2 placebo) combined (as per protocol).

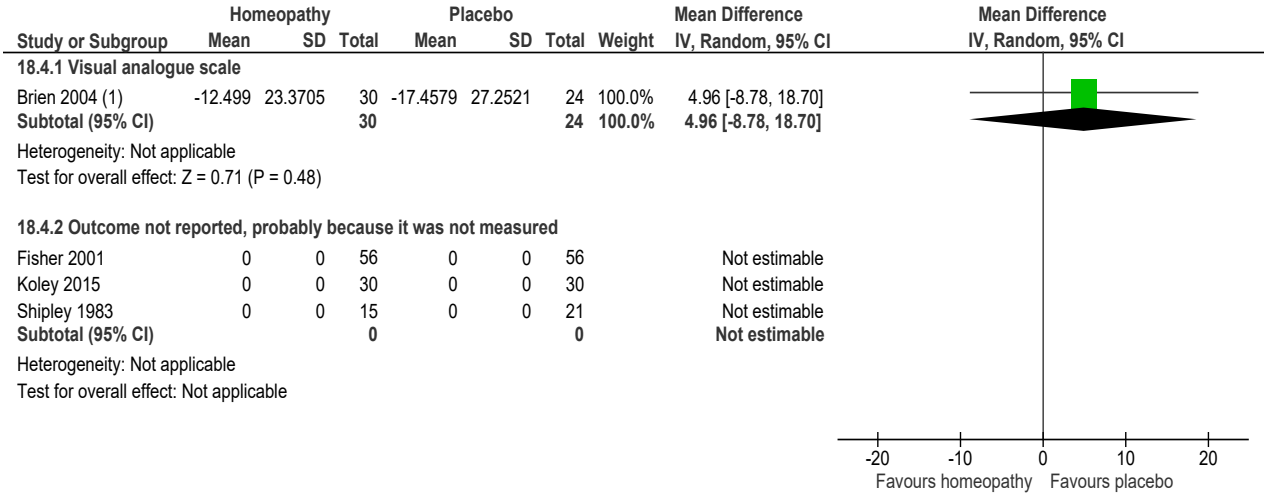
Figure 75 Forest plot of primary comparison: Homeopathy vs placebo: Arthritis – disease severity



Footnotes

(1) Study reports results as change from baseline to end of treatment. Results from 5 treatment arms (3 homeopathy, 2 placebo) combined (as per protocol).

Figure 76 Forest plot of primary comparison: Homeopathy vs placebo: Arthritis – quality of life



Footnotes

(1) Study reports results as change from baseline to end of treatment. Results from 5 treatment arms (3 homeopathy, 2 placebo) combined (as per protocol).

4.17 Back or neck pain

4.17.1 Description of the condition

Back and neck pain occurs when the bones, joints, connective tissues, muscles, and nerves of the central musculoskeletal system are inflamed (279). Such inflammation can have many causes, including conditions such as arthritis, spondylitis, osteoporosis or injuries relating to work or sport. In most cases there is no specific cause; risk factors include genetics, previous episode of back or neck pain, poor posture, physically demanding tasks and lack of physical activity (279, 280). When mismanaged, back and neck pain can affect a person's quality of life, and can lead to psychological distress, bodily pain, and disability (279, 280).

Low back pain (LBP) is the most encountered musculoskeletal problem in general practice in Australia and the leading cause of disability globally (281-283). In Australia, approximately 16% of the population are living with back and neck pain, contributing to 4.2% of Australia's total disease burden (284). While LBP is generally benign and self-limiting, approximately 10-40% with acute LBP develop persistent and debilitating chronic LBP that continues for more than 3 months (282). Direct and indirect costs of LBP are reportedly $1 billion and $8 billion, respectively (285). In 2019-2022, healthcare utilisation related to back and neck pain cost the Australian Government $3.2 billion (279).

International guidelines consistently recommend people with neck or back pain remain active and return to normal activities as soon as possible (281, 282). Treatment typically differs between chronic and acute presentations, however, often involves multidisciplinary care, including guidance from General Practitioners, physiotherapists, and other specialists (284), but no one approach appears superior to another (281). Various nonpharmacological and complementary therapies may be used for back and neck pain include exercise therapy, mind-body interventions (286) and homeopathy (287).

4.17.2 Description of studies

Three citations (288-290) corresponding to 3 RCTs (Gupta 2020, Morris 2016, Stam 2001) were identified in the literature search. No additional studies were identified in the Department's public call for evidence. There were 4 ongoing studies, and 5 studies awaiting classification including 3 studies published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D8.2.1.

One RCT was conducted in a single private physiotherapy clinic in South Africa (Morris 2016). The other 2 RCTs were conducted across multiple research centres in India (Gupta 2020) or multiple general practice clinics in the United Kingdom (Stam 2001). Sample size ranged from 30 to 161 (total 327 participants). One study (Gupta 2020) enrolled participants with neck pain associated with spondylosis. The other 2 studies enrolled participants with low back pain, with one study being in people with chronic pain secondary to OA of the lumbar spine (Morris 2016) and one study being in people with an acute occurrence of pain (Stam 2001).

Two studies (Gupta 2020, Morris 2016) compared homeopathy with placebo. Participants in Gupta 2020 received individualised homeopathy, given as an oral intervention. Participants in Morris 2016 received a non-individualised oral combination product, with both groups also receiving fortnightly physiotherapy as a co-intervention. One study (Stam 2001) compared a topical homeopathic product with another topical intervention, both of which were delivered as an adjunct to usual care (paracetamol).

Administration of the homeopathic intervention varied between studies. In one study (Gupta 2020) the intervention was administered 3 times daily at 6-hour intervals. In one study (Morris 2016) the intervention was administered twice daily 20 minutes before meals. One study (Stam 2001) required the intervention to be applied 3 times daily to the affected area. Length of follow up ranged from 7 days (Stam 2001) to 6 weeks (Morris 2016).

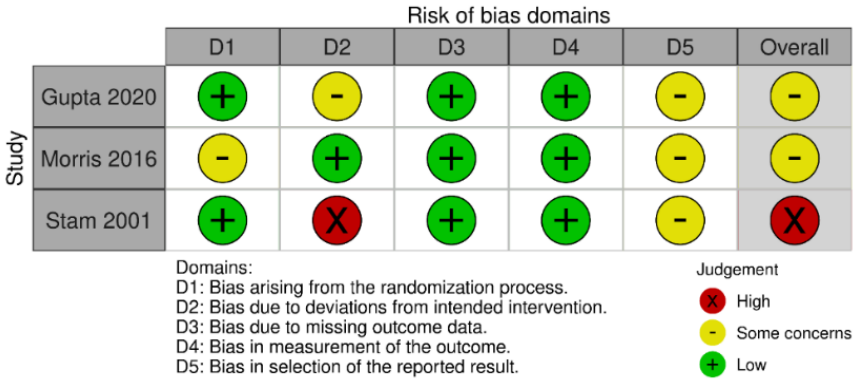
Results for the Primary Comparison: Homeopathy versus placebo are provided in the Summary of Findings table (see Section 4.17.4). There were no studies found for the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care). Results of studies that compared homeopathy with another comparator (Tertiary Comparison) are presented in Appendix F2.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.17.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for back and neck pain are summarised in Figure 77. Details are provided in Appendix D8.2.2. No studies were judged to be at overall low risk of bias.

Figure 77 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: back and neck pain



4.17.4 Summary of findings and evidence statements

4.17.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Back and neck pain

Patient or population: Back and neck pain
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Pain intensity assessed with: VAS Scale from: 0 to 10 (higher is worse) follow-up: 8 days	The mean VAS score was **4.0 cm**	MD **0.74 higher** (1.87 higher to 0.39 lower)	-	134 (1 RCT) †	⨁⨁◯◯ LOW [a,b,c,d,e]	Homeopathy may result in a little to no difference in pain intensity in people with neck pain #
Mobility (stiffness) assessed with: VAS Scale from: 0 to 10 (higher is worse) follow-up: 8 days	The mean VAS score was **3.28**	MD **0.36 lower** (1.48 lower to 0.76 higher)	-	134 (1 RCT) †	⨁⨁◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in stiffness or range of motion in people with neck pain **
Disability assessed with: ODI Scale from: 0 to 100 (higher is worse) follow-up: 6 weeks	The median ODI score was **19**	The median ODI score was **12**	-	30 (1 RCT) †	⨁◯◯◯ VERY LOW [b,e,f,g,h]	The evidence is very uncertain about the effect of homeopathy on disability in people with back pain **

Homeopathy compared to placebo for Back and neck pain

Patient or population: Back and neck pain
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Quality of life assessed with: Patient's Global Impression of Change Scale Scale from: 0 to 10 (higher is worse) follow-up: 8 days	The mean quality of life was **2.93**	MD **0.64 lower** (1.35 lower to 0.07 higher)	-	134 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in quality of life in people with neck pain **
Medication use assessed with: tablets per week (higher is worse) follow-up: 6 weeks	The median number of tablets was **18**	The median number of tablets was **10**	-	30 (1 RCT) †	⊕◯◯◯ VERY LOW [b,e,f,g,h]	The evidence is very uncertain about the effect of homeopathy on medication use in people with back pain

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Data from one RCT were incomplete (30 participants) and could not be included in the data synthesis.
# The MCID for pain with chronic back or neck pain is estimated to be 2.0 cm (291-293).

CI: confidence interval; **MD:** mean difference; **ODI:** Oswestry disability index; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. Serious indirectness. The available evidence is in people with cervical spondylosis and may not be applicable to people with chronic nonspecific low back or neck pain. Certainty of evidence downgraded.

d. Serious imprecision. Single study with wide confidence intervals (upper and lower bounds overlap with both important and no important benefit). Certainty of evidence downgraded.

e. Publication bias not suspected. Certainty of evidence not downgraded.

f. Serious risk of bias. One study contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.

g. Serious indirectness. The available evidence is in people with low back pain secondary to osteoarthritis of the lumbar spine and may not be applicable to people with chronic nonspecific low back or neck pain. Certainty of evidence downgraded.

h. Very serious imprecision. Small pilot study. Baseline data showed abnormal distribution, with median values reported. Certainty of evidence downgraded 2 levels.

4.17.4.2 Secondary Comparison (vs inactive control)

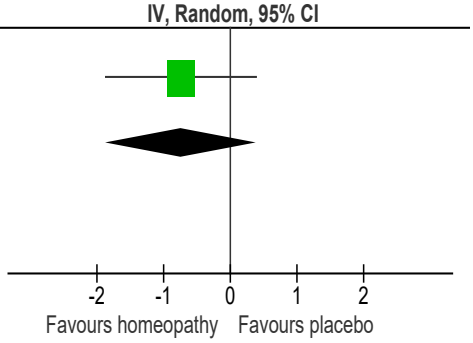
There were no studies identified which compared homeopathy to inactive control (no intervention, usual care, or waitlist) in people living with back or neck pain.

4.17.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with back or neck pain are presented in Figure 78 (pain intensity), Figure 79 (mobility), Figure 80 (disability) and Figure 81 (quality of life).

Figure 78 Forest plot of primary comparison: Homeopathy vs placebo: Back or neck pain – pain intensity

	Homeopathy			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
19.1.1 Visual Analogue Scale (VAS)								
Gupta 2020	3.26	3.29	67	4	3.42	69	100.0%	-0.74 [-1.87, 0.39]
Morris 2016 (1)	4	0	15	6	0	15		Not estimable
Subtotal (95% CI)			**82**			**84**	**100.0%**	**-0.74 [-1.87, 0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								

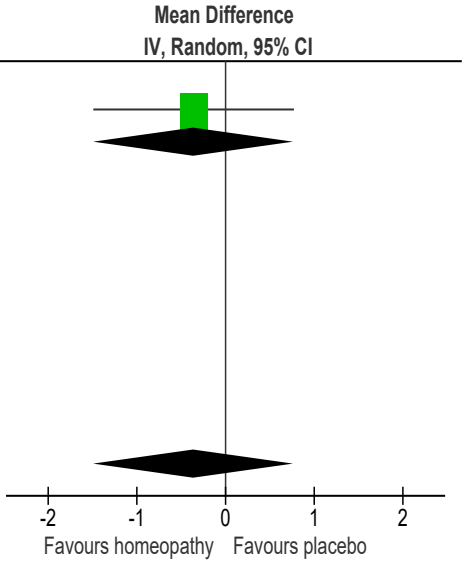


Footnotes

(1) Median value (with palpatation). Authors do not report mean or SD etc.

Figure 79 Forest plot of primary comparison: Homeopathy vs placebo: Back or neck pain – mobility

	Homeopathy			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
19.2.1 Visual Analogue Scale (VAS)								
Gupta 2020 (1)	2.92	3.32	66	3.28	3.31	68	100.0%	-0.36 [-1.48, 0.76]
Subtotal (95% CI)			**66**			**68**	**100.0%**	**-0.36 [-1.48, 0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.63 (P = 0.53)								
19.2.2 Outcome not reported, probably because it was not assessed								
Morris 2016	0	0	15	0	0	15		Not estimable
Subtotal (95% CI)			**15**			**15**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**81**			**83**	**100.0%**	**-0.36 [-1.48, 0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.63 (P = 0.53)								
Test for subgroup differences: Not applicable								

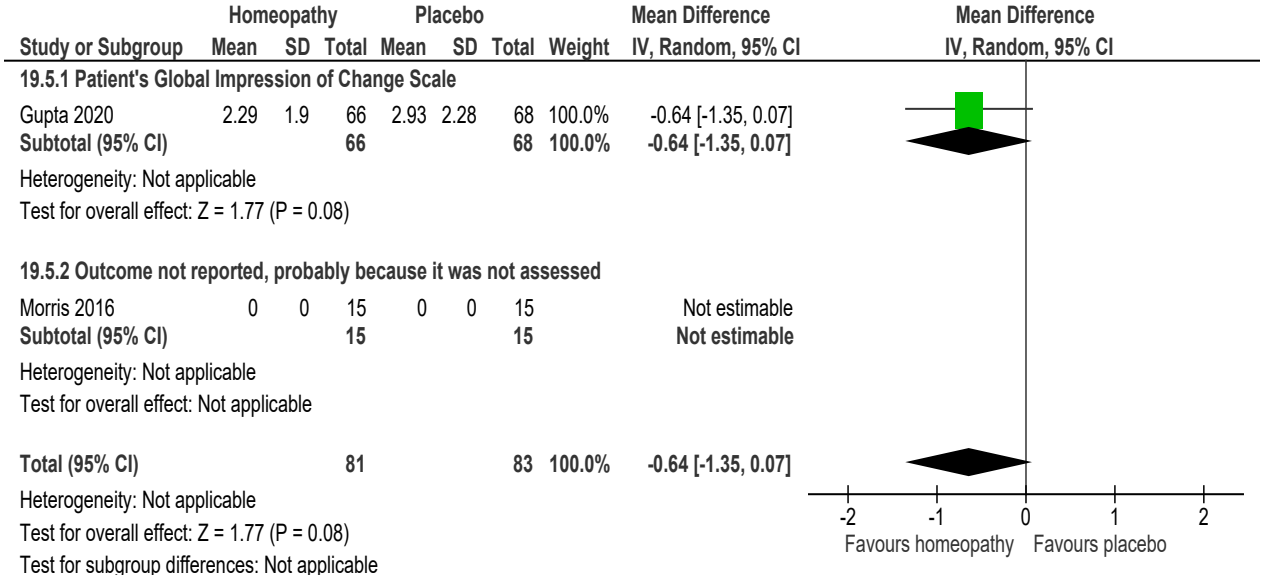


Footnotes

(1) Measured as change from baseline in stiffness. Study authors report significant difference between groups in favour of homeopathy (p=0.0001).

Figure 80 Forest plot of primary comparison: Homeopathy vs placebo: Back or neck pain – disability

Figure 81 Forest plot of primary comparison: Homeopathy vs placebo: Back or neck pain – quality of life



4.18 Menopausal symptoms or complaints

4.18.1 Description of the condition

Natural menopause is defined as the permanent cessation of menses and is a normal process of ageing that is typically confirmed after menstrual periods have been absent for 12 months (294-297). Symptoms of menopause are characterised by the pathological changes that occur during the transition period (perimenopause) and are related to the gradual loss of ovarian follicular function and decline in circulating blood oestrogen levels (295-297). Perimenopause is estimated to last around 4 years and is the period when bothersome symptoms such as hot flushes, headache, sleep disturbance, lack of concentration, depressed mood, atrophic genital changes and bone loss can begin, with females who experience a longer transition period more likely to seek help (294).

Females with artificial menopause, induced after the surgical removal of ovaries, or through interventions such as chemotherapy or radiation therapy, are also more likely to experience bothersome or disabling symptoms of menopause (295); as are females who experience premature (before 40 years of age) or early menopause (aged between 40 and 45 years) (297).

Natural menopause is estimated to occur between the ages of 47 and 53 years, with education, lifestyle factors (such as smoking, high physical activity), and ethnicity reported to play a role (297-299). Globally, between 2% and 3.7% of females are estimated to experience premature menopause and between 7.6% and 12.2% of females are estimated to undergo early menopause (299, 300), which places them at increased risk of chronic conditions later in life. In Australia, natural menopause is estimated to occur at a mean age of 52 years (298), with about 1.2% of females undergoing premature menopause and 5.8% experiencing early menopause (299).

Treatment and management of troublesome and disruptive symptoms associated with menopause centre on minimising the effects of declining oestrogen levels through hormone replacement therapy (296, 301-303). Other treatments may focus on managing or preventing specific symptoms such as localised oestrogen cream for vaginal atrophy, blood pressure medications for hot flushes, antidepressants for mood changes, or calcium and Vitamin D for bone loss (301, 303-305). Given the risks associated with long-term hormone replacement therapy (e.g. thromboembolic or coronary events, breast cancer) (295, 301, 303, 306), and the variability of symptom severity, females experiencing mild or moderate symptoms of menopause may seek lifestyle and other alternative therapies such as homeopathy.

4.18.2 Description of studies

There were 8 citations (307-314) corresponding to 5 RCTs (Andrade 2019, Colau 2012, Jacobs 2005, Relton 2012, von Hagens 2012) identified in the literature search. One additional study (Gupta 2019) (315) was identified in the Department's public call for evidence. There were 2 ongoing studies and 2 studies awaiting classification. An overview of the PICO criteria of included studies is provided in Appendix D9.1.1.

Five studies were conducted in single outpatient clinics across Brazil (Andrade 2019), France (Colau 2012), Germany (von Hagens 2012), the United Kingdom (Relton 2012) and the United States (Jacobs 2005). One study (Gupta 2019) was conducted in multiple research centres across India.

Five studies (Andrade 2019, Colau 2012, Gupta 2019, Relton 2012, von Hagens 2012) enrolled peri and/or postmenopausal females experiencing symptoms of menopause, 3 of which (Andrade 2019, Colau 2012, Relton 2012) were focused on females with hot flushes. Sample sizes ranged from 40 to 108 participants (total 408). One study (Jacobs 2005) enrolled breast cancer survivors with menopausal symptoms (total 83 participants).

Five studies (Andrade 2019, Colau 2012, Gupta 2019, Jacobs 2005, von Hagens 2012) compared homeopathy with placebo. Of these, 4 studies (Andrade 2019, Colau 2012, Gupta 2019, von Hagens 2012) used various non-individualised homeopathic treatments. One study (Jacobs 2005) had two intervention groups consisting of individualised homeopathy and non-individualised homeopathy.

One study (Relton 2012) compared individualised homeopathy with an inactive control. Participants in the homeopathy treatment group attended up to five consultations with a homeopath and were prescribed individualised treatment, whilst those in the control group received no intervention.

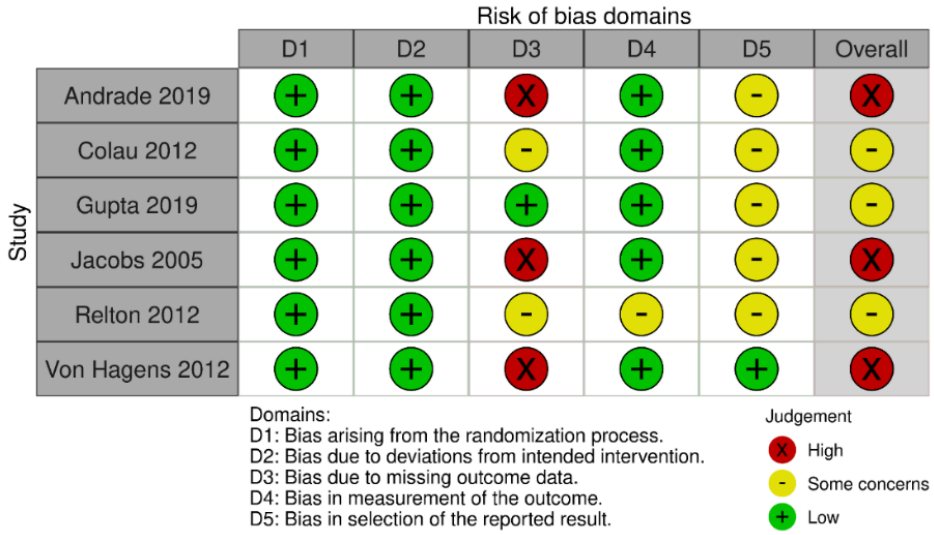
Results for the Primary Comparison: Homeopathy versus placebo and the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings table (see Section 4.18.4). There were no studies found for Tertiary Comparison: Homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.18.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for menopausal symptoms or complaints is summarised in Figure 82. Details are provided in Appendix D9.1.2. No studies were judged to be at overall low risk of bias.

Figure 82 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Menopausal symptoms or complaints



4.18.4 Summary of findings and evidence statements

4.18.4.1 Primary Comparison (vs placebo)

Homeopathy compared to Placebo for Menopausal symptoms or complaints

Patient or population: Menopausal symptoms or complaints
Setting: Community (outpatient clinics)
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				
Symptom severity assessed with MRS or GCS follow-up: from 12 weeks to 6 months	-	SMD **0.07 lower** (0.71 lower to 0.57 higher)	-	290 (3 RCTs) †	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on symptom severity in people with menopausal symptoms or complaints. **
Hot flush severity assessed with: hot flush severity score Scale from: NR (higher is worse) follow-up: 12 weeks	The mean hot flush severity score was **113**	MD **30.7 lower** (57.66 lower to 3.74 lower)	-	108 (1 RCT) ††	⊕◯◯◯ VERY LOW c,f,g,h,i	The evidence is very uncertain about the effect of homeopathy on hot flush severity in in people with menopausal symptoms or complaints. #
Health-related quality of life assessed with: HFRDIS Scale from: 0 to 10 (higher is worse) follow-up: 12 weeks	The mean change in HFRDIS was **2.0**	MD **0.30 lower** (0.65 lower to 1.25 higher)	-	108 (1 RCT) ‡	⊕⊕◯◯ LOW c,d,f,g,i	Homeopathy may result in little to no difference in quality of life in people with menopausal symptoms or complaints. ##
Hot flush frequency – not reported	-	-	-	(0 studies)	-	The effect of homeopathy on hot flush frequency in people with menopausal symptoms or complaints is unknown
Night sweat frequency – not reported	-	-	-	(0 studies)	-	The effect of homeopathy on night sweat frequency in people with menopausal symptoms or complaints is unknown

Homeopathy compared to Placebo for Menopausal symptoms or complaints

Patient or population: Menopausal symptoms or complaints
Setting: Community (outpatient clinics)
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with Homeopathy				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** As a rule of thumb, an SMD of 0.2 is considered a small difference, 0.5 is considered medium, and 0.8 is considered large (83).
† Data from one RCT (83 participants) not able to be included in the meta-analysis. Study authors suggest no difference in symptom severity in the homeopathy groups compared with placebo (p = 0.1).
†† Missing data from 2 RCTs (total 123 participants) as the data were incomplete. Study authors report no difference in hot flush severity between the homeopathy and placebo groups.
‡ Data from one RCT (83 participants) not able to be included in the meta-analysis. It is not known whether missing data would meaningfully change the result.

The MCID for HFS in people with menopausal symptoms is estimated to be a weekly reduction of 25 hot flushes (316)
The MCID for HFRDIS is estimated to be a reduction of 1.66 points (317).

CI: confidence interval; **GCS:** Greene climacteric scale; **HFRDIS:** hot flush related daily interference scale; **MD:** mean difference; **MRS:** menopausal rating scale; **SMD:** standardised mean difference.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One study contributing 33% of data was at high risk of bias. Certainty of evidence downgraded.
b. Serious inconsistency. Point estimates varied and some confidence intervals do not overlap. Statistical heterogeneity was high (I^2 > 86%). Certainty of evidence downgraded.
c. No serious indirectness. The available evidence is in perimenopausal and menopausal women experiencing hot flushes and is generalisable to the Australian population with few caveats. Certainty of evidence not downgraded.
d. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both important and no important difference). Certainty of evidence downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. No serious risk of bias. Certainty of evidence not downgraded.
g. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.
h. Very serious imprecision. Single study with wide confidence intervals (upper and lower bounds overlap with both important and no important difference). Certainty of evidence downgraded 2 levels.
i. Publication bias suspected. There is a strong suspicion of non-reporting of results related to p value, magnitude or direction of the results being considered unfavourable by the study investigators. Certainty of evidence downgraded.

4.18.4.2 Secondary Comparison (vs inactive control)

One study (43 participants) comparing individualised homeopathy with control (no intervention) was eligible for this comparison. Results from this study contribute to two outcomes (symptom severity, hot flush severity).

Homeopathy compared to inactive control for Menopausal symptoms or complaints

Patient or population: Menopausal symptoms or complaints
Setting: Community (outpatient clinics)
Intervention: Homeopathy
Comparison: inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with Homeopathy				
Symptom severity assessed with: Greene Climateric Scale Scale from: 0 to 36 (higher is worse) follow up: 36 weeks	The mean symptom severity was **1.83**	MD **3.78 lower** (7.81 lower to 0.25 higher)	-	43 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effect of homeopathy on symptom severity in people with menopausal symptoms or complaints **
Hot flush severity assessed with: Hot flush frequency severity score Scale from: 0 to 36 (higher is worse) follow up: 36 weeks	The mean hot flush severity was **-1.16**	MD **5.73 lower** (11.94 lower to 0.48 higher)	-	43 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effect of homeopathy on hot flush severity in people with menopausal symptoms or complaints **
Health-related quality of life - not reported	-	-	-	-	-	The effect of homeopathy on quality of life in people with menopausal symptoms or complaints is unknown
Hot flush frequency - not reported	-	-	-	-	-	The effect of homeopathy on hot flush frequency in people with menopausal symptoms or complaints is unknown
Night sweat frequency - not reported	-	-	-	-	-	The effect of homeopathy on night sweat frequency in people with menopausal symptoms or complaints is unknown

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Effect estimates were to be considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

CI: confidence interval; **MD:** mean difference

Homeopathy compared to inactive control for Menopausal symptoms or complaints

Patient or population: Menopausal symptoms or complaints
Setting: Community (outpatient clinics)
Intervention: Homeopathy
Comparison: inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control	Risk with Homeopathy				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence in perimenopausal and menopausal women experiencing hot flushes and is generalisable to the Australian population with a few caveats. Certainty of evidence not downgraded.

d. Very serious imprecision. Single study with wide confidence intervals (upper and lower bounds overlap with both important benefits and no important difference). Certainty of evidence downgraded 2 levels.

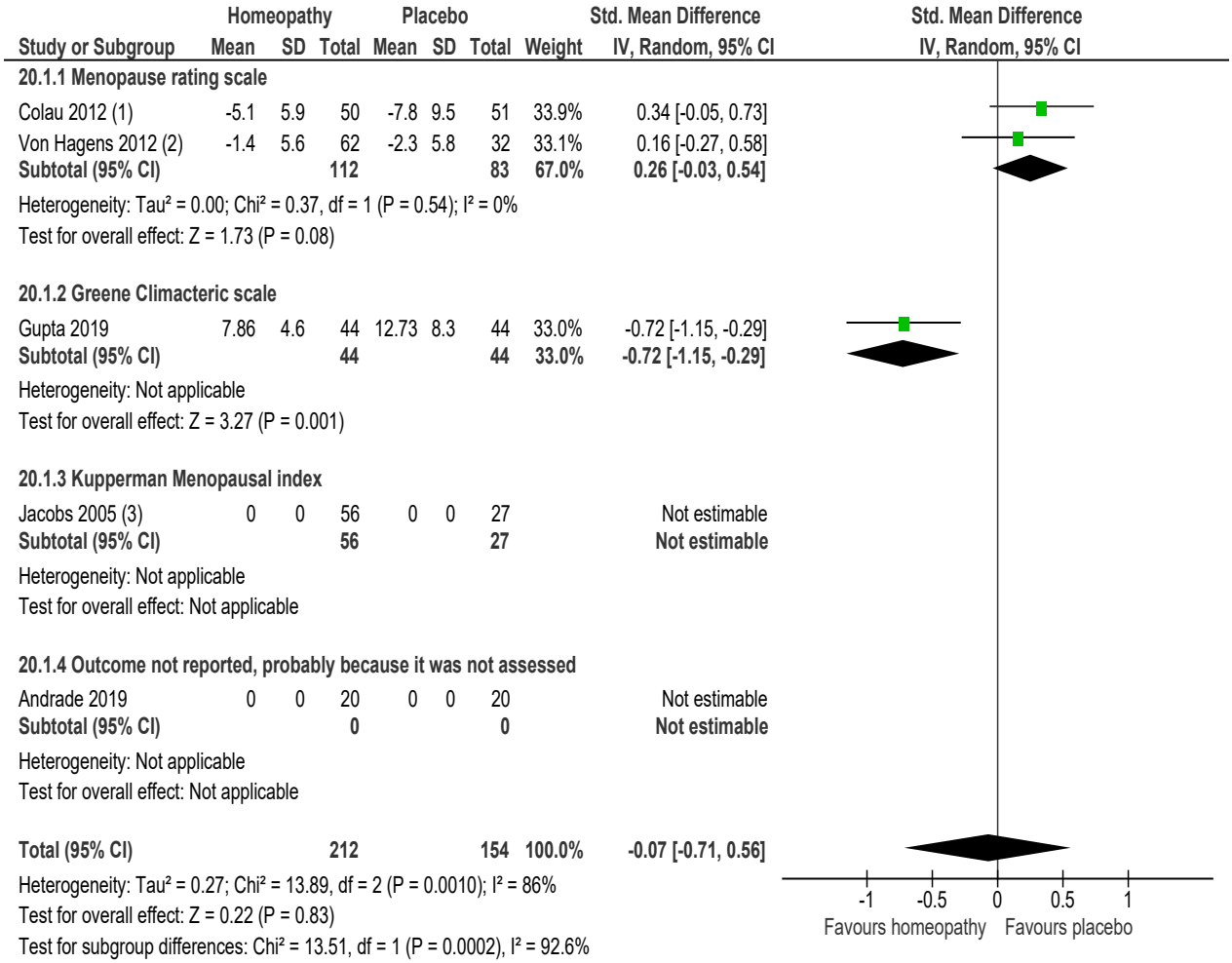
e. Publication bias suspected. Evidence is limited to 1 small study. There is a strong suspicion of non-reporting of results related to p value, magnitude or direction of the results being considered unfavourable by the study investigators. Certainty of evidence downgraded.

4.18.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with menopausal symptoms or complaints are presented in Figure 83 (symptom severity), Figure 84 (hot flush severity), and Figure 85 (health-related quality of life).

Outcome results related to the secondary comparison (homeopathy vs inactive control) in people with menopausal symptoms or complaints are presented in Figure 86 (symptom severity), Figure 87 (hot flush severity),

Figure 83 Forest plot of primary comparison: Homeopathy vs placebo: Menopausal symptoms – symptom severity



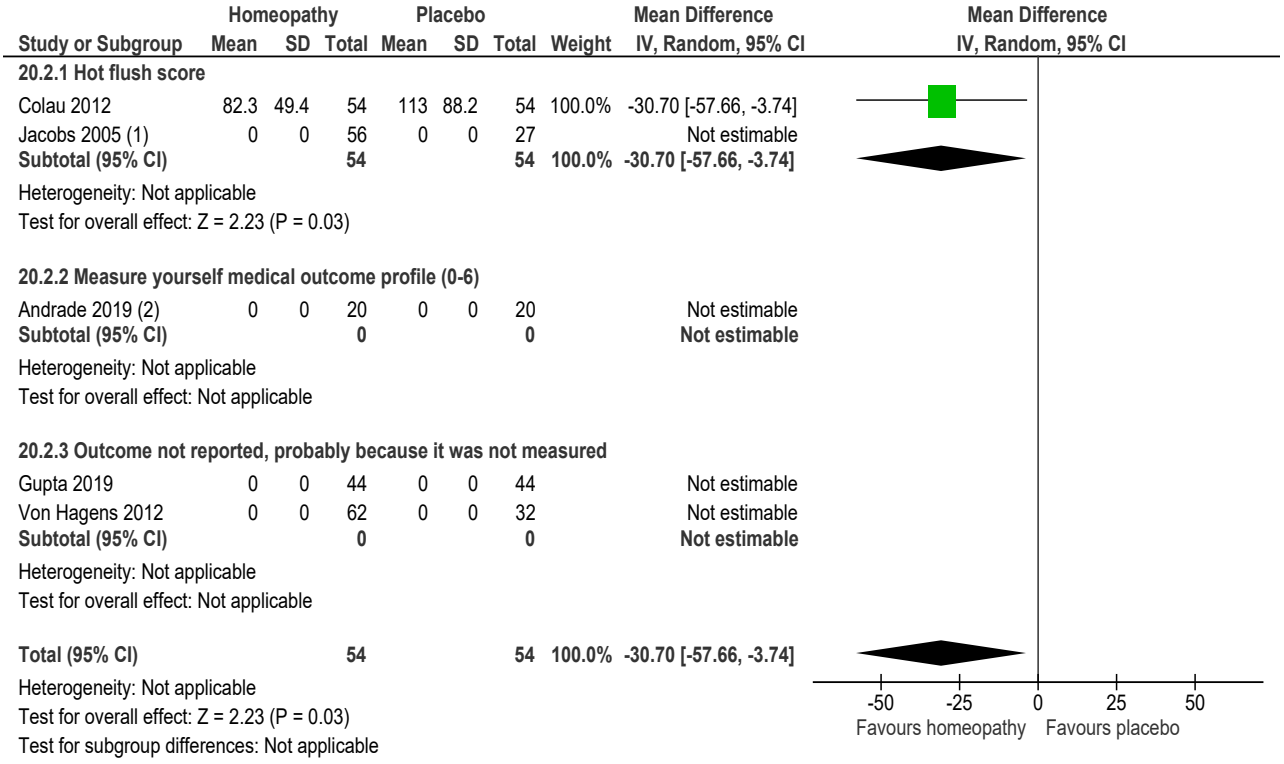
Footnotes

(1) Mean change from baseline. Data inverted to ensure consistency in direction of effect.

(2) Mean change from baseline. Data inverted to ensure consistency in direction of effect.

(3) Data were incomplete and not able to be included in the data synthesis. There was no significant difference between treatment groups at 12 mth...

Figure 84 Forest plot of primary comparison: Homeopathy vs placebo: Menopausal symptoms – hot flush severity



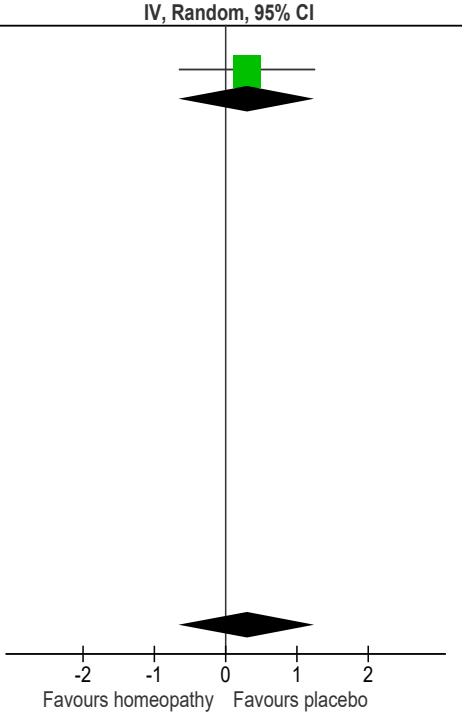
Footnotes

(1) No difference between groups: individualised (MD -12.0; 95%CI -34.3, 10.30; p=0.3) and non-individualised (MD -0.4; 95%CI -22.3, 10.3; p=1.0)

(2) Study reports no difference between the homeopathy and placebo groups (MD –0.06; 95% CI –0.66, 1.86; p = 0.07)

Figure 85 Forest plot of primary comparison: Homeopathy vs placebo: Menopausal symptoms – health-related quality of life

Study or Subgroup	Homeopathy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
20.3.1 Hot flush related daily interference scale								
Colau 2012 (1)	2.3	2.3	54	2	2.7	54	100.0%	0.30 [-0.65, 1.25]
Subtotal (95% CI)			**54**			**54**	**100.0%**	**0.30 [-0.65, 1.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
20.3.2 SF-36								
Jacobs 2005 (2)	0	0	56	0	0	27		Not estimable
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
20.3.3 Outcome not reported, probably because it was not measured								
Andrade 2019	0	0	20	0	0	20		Not estimable
Gupta 2019	0	0	44	0	0	44		Not estimable
Von Hagens 2012	0	0	62	0	0	32		Not estimable
Subtotal (95% CI)			**0**			**0**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**54**			**54**	**100.0%**	**0.30 [-0.65, 1.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Mean change from baseline. Data inverted to ensure consistency in direction of effect

(2) Data were incomplete and not able to be included in the data synthesis.

Figure 86 Forest plot of secondary comparison: Homeopathy vs inactive control: Menopausal symptoms – symptom severity

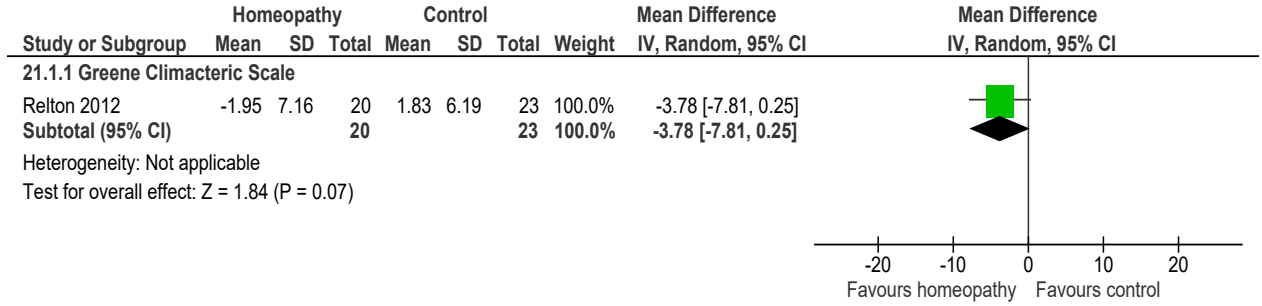
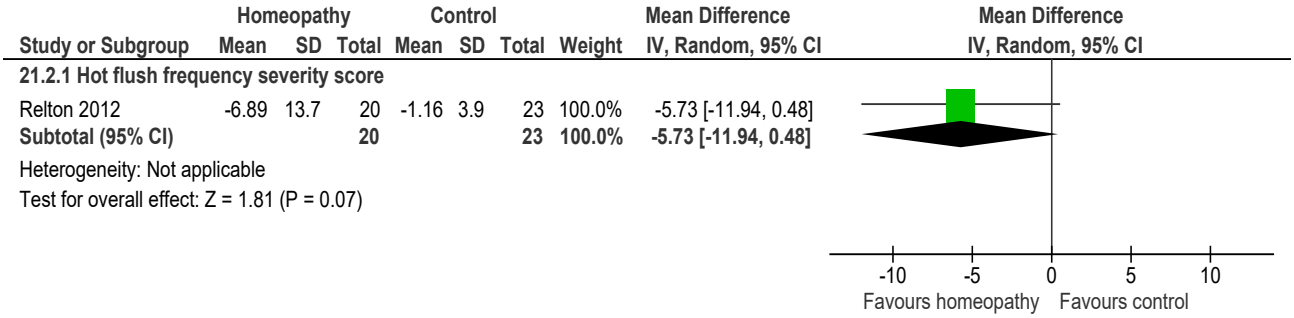


Figure 87 Forest plot of secondary comparison: Homeopathy vs inactive control: Menopausal symptoms – hot flush severity



4.19 Menstrual disorders

4.19.1 Description of the condition

Menstrual disorders refer to conditions relating to the menstrual cycle, and in this review includes amenorrhea, dysmenorrhea, heavy bleeding, endometriosis, and premenstrual syndrome (PMS). Endometriosis is a chronic inflammatory condition characterised by abnormal growth of endometrial-like tissue outside the uterine cavity (318). Primary dysmenorrhoea describes painful menstrual bleeding, commonly experienced by 50-90% of people with menstrual cycles. Secondary dysmenorrhoea is attributed to underlying pelvic conditions such as endometriosis or fibroids in females who have menstruated previously (319). Amenorrhoea is the absence of menstruation, commonly due to a lack of hormonal function in the ovaries, which may result in infertility (320). PMS is a complex condition referring to the physical and emotional symptoms that may be experienced 1-2 weeks prior to menstruation (321).

Endometriosis affects 10-15% of all females of reproductive age and 70% of females with chronic pelvic pain (322). Typically, the diagnosis of endometriosis is often delayed, impairing the quality of life for many females, and resulting in unnecessary pain and, in some cases, infertility. The prevalence of dysmenorrhoea is estimated to affect 16.8% to 81% of females of reproductive age, although some evidence reports rates high as 90% (323). At the same time, amenorrhoea not due to pregnancy, lactation or menopause affects between 3-4% of females (324). The prevalence of PMS has a broad range in the literature, with estimates as high as 90% of females of reproductive age, most experiencing only mild symptoms (325).

Lifestyle, dietary patterns, environment and genetic factors may influence the risk of menstrual disorders. However, there is no known aetiology behind endometriosis. Dysmenorrhoea has several underlying causes that can be classified as either primary or secondary (319). The most common causes of amenorrhoea include polycystic ovarian syndrome, hypothalamic amenorrhoea, ovarian failure and hyperprolactinemia (324). Therapeutic options for most menstrual conditions include nonsteroidal anti-inflammatory drugs and hormonal contraceptives (319). The primary aim of treatment is to provide symptomatic relief and improve quality of life by reducing pain and discomfort, which is where alternative therapies such as homeopathy may be considered.

4.19.2 Description of studies

There were 13 citations (326-338) corresponding to 6 RCTs (Charandabi 2016, Klein-Laansma 2017, Singh 2020, Teixeira 2016, Yakir 1994, Yakir 2019) identified in the literature search. No additional studies were identified in the Department's public call for evidence. There were 8 ongoing studies, and 5 studies awaiting classification including one study published in a language other than English. An overview of the PICO criteria of included studies is provided in Appendix D9.2.1.

Five RCTs were conducted in single settings, being either a university hospital in Brazil (Teixeira 2016), a university centre in Iran (Charandabi 2016), a homeopathic hospital and research centre in India (Singh 2020), or an outpatient clinic in Israel (Yakir 1994, Yakir 2019). One study was conducted across multiple homeopathic practices in the Netherlands, Sweden and Germany.

Three studies (Klein-Laansma 2017, Yakir 1994, Yakir 2019) enrolled females with PMS, with sample sizes ranging from 23 to 105 (total 188 participants). In 2 studies (Charandabi 2016, Singh 2020) the participants had primary dysmenorrhea (total 199 participants) and in one study (Teixeira 2016) the participants had been diagnosed with endometriosis (total 50 participants).

Five studies (Charandabi 2016, Singh 2020, Teixeira 2016, Yakir 1994, Yakir 2019) compared homeopathy with a placebo. Of these, 4 studies (Charandabi 2016, Singh 2020, Yakir 1994, Yakir 2019) used individualised homeopathic treatments that were prescribed during consultations with a homeopath. One study (Teixeria 2016) used a non-individualised homeopathic treatment, which consisted of potentised oestrogen that was administered orally in increasing potencies over the course of 12 weeks.

One study (Klein-Laansma 2017) compared individualised homeopathy with an inactive control (no intervention). Participants were prescribed a homeopathic treatment based on a predetermined patient questionnaire. Both groups received usual care.

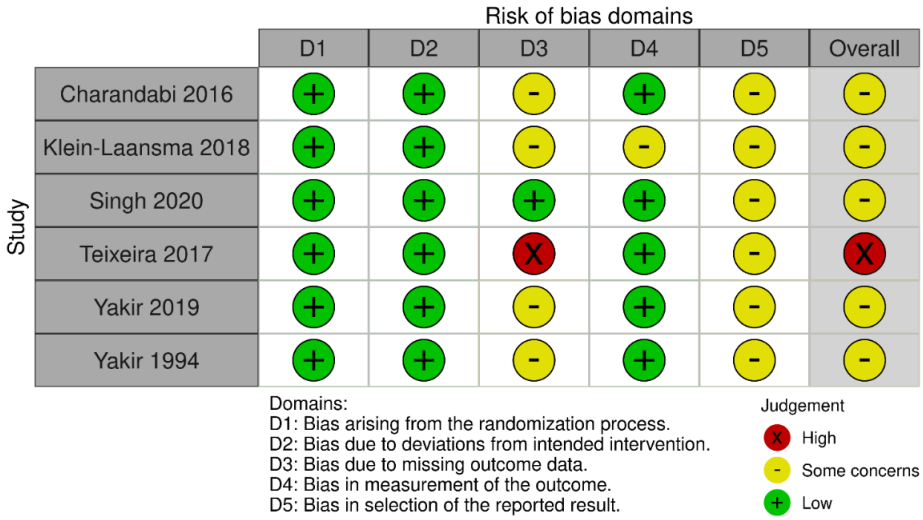
Results for the Primary Comparison: Homeopathy versus placebo and the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings table (see Section 4.19.4). There were no studies found for Tertiary Comparison: Homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.19.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for menstrual disorders is summarised in Figure 88. Details are provided in Appendix D9.2.2. No studies were judged to be at overall low risk of bias.

Figure 88 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: menstrual disorders



4.19.4 Summary of findings and evidence statements

4.19.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Menstrual disorders

Patient or population: Menstrual disorders
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI) Risk with Placebo	Risk with Homeopathy	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Pain intensity assessed with: VAS Scale from: 0 to 100 (higher is worse) follow-up: range 3 months to 6 months	The mean pain score was **47.325**	MD **15.25 lower** (36.49 lower to 5.98 higher)	-	112 (2 RCTs) †	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on pain intensity in people with menstrual disorders. #
Symptom severity assessed with: MDQ range: 0 to 4 (higher is worse) follow-up: 3 months	The mean MDQ score was **0.34**	MD **0.1 lower** (0.25 lower to 0.04 higher)	-	115 (2 RCTs) †	⊕◯◯◯ VERY LOW a,d,e,f,g	The evidence is very uncertain about the effect of homeopathy on symptom severity in people with menstrual disorders.
Depression assessed with BDI Range: 0 to 63 (higher is worse) follow-up: 3 months	-	-	-	(0 studies) †	-	The effect of homeopathy on depression in people with menstrual disorders is unknown
Anxiety assessed with: BAI Range: 0 to 63 (higher is worse) follow-up: 3 months	-	-	-	(0 studies) ††	-	The effect of homeopathy on anxiety in people with menstrual disorders is unknown
Health-related quality of life assessed with: SF-36 Range: 0 to 100 (higher is better) follow-up: 3 months	The mean physical component score was **78.2**	MD **0.50 higher** (7.05 lower to 8.05 higher)		47 (1 RCT) †††	⊕◯◯◯ VERY LOW a,c,e,h,i	The evidence is very uncertain about the effect of homeopathy on health-related quality of life in people with menstrual disorders. ##
	The mean mental component score was **75.7**	MD **4.60 lower** (12.70 lower to 3.50 higher)				
Medication use assessed with: Number of additional medications used follow-up: 3 months	-	SMD **0.24 lower** (0.57 lower to 0.09 higher)	-	143 (2 RCTs) ‡	⊕◯◯◯ VERY LOW a,d,e,g,j,	The evidence is very uncertain about the effect of homeopathy on medication use in people with menstrual disorders. **

Homeopathy compared to placebo for Menstrual disorders

Patient or population: Menstrual disorders
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI) Risk with Placebo	Risk with Homeopathy	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (83)
*** Effect estimates were to be considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Missing data from 1 RCT (50 participants). Study authors suggest a reduction in non-cyclic pelvic pain, global symptom severity, and depression that favours the homeopathy group, but data for the placebo group are incomplete and not able to be included in the data synthesis.
†† Missing data from 1 RCT (50 participants). Study authors suggest there is no difference between treatment groups for anxiety.
††† Missing data from 1 RCT (50 participants). Study authors suggest a reduction in bodily pain, vitality and mental health that favours the homeopathy group, but data for the placebo group are incomplete and information on other SF-36 domains are not reported.
‡ Missing data from 1 RCT (23 participants). Study authors suggest there is no difference between treatment groups for number of medications consumed during the 7-day period prior to menstruation.

The MCID for the VAS is estimated to be 20 mm (291).
The MCID for the SF-36 is estimated to be around 2 to 4 points for the general population (339).

BAI: Beck anxiety inventory; **BDI:** Beck depression inventory; **CI:** confidence interval; **MD:** mean difference; **MDQ:** Moos menstrual distress questionnaire; **SF-36**: 36-item short form; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Serious inconsistency. Point estimates vary and no overlap of confidence intervals. Certainty of evidence downgraded.

c. No serious indirectness. The available evidence is in people with dysmenorrhoea and is generalisable to the Australian population with some caveats. Applicability to people with premenstrual syndrome or endometriosis may be limited. Certainty of evidence not downgraded.

d. Very serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both important benefit and important harms). Certainty of evidence downgraded 2 levels.

e. Publication bias suspected. Several studies awaiting classification or ongoing (292+ participants) that were judged likely to be missing (not reported) because the *p*-value, magnitude or direction of the results generated were considered unfavourable by the study investigators. Certainty of evidence downgraded.

f. No serious inconsistency. Certainty of evidence not downgraded.

g. No serious indirectness. The available evidence is in people with premenstrual syndrome and is generalisable to the Australian population with some caveats. Applicability to people with dysmenorrhoea or endometriosis may be limited. Certainty of evidence not downgraded.

h. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

i. Very serious imprecision. Single study with wide confidence intervals (upper and lower bounds overlap with both important benefit and harms). Certainty of evidence downgraded 2 levels.

j. No serious inconsistency. Certainty of evidence not downgraded.

4.19.4.2 Secondary Comparison (vs inactive control)

Homeopathy compared to inactive control for menstrual disorders

Patient or population: Menstrual disorders
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control (no intervention)	Risk with homeopathy				
Pain intensity assessed with: PMTS-VAS Range: 0 to 100 (higher is worse) Follow up: 4 months	-	-	-	(0 studies) †		The effect of homeopathy on pain in people with menstrual disorders is unknown
Symptom severity assessed with: DRSP Range: 168 to 1008 (higher is worse) Follow up: 4 months	The mean DRSP score was **414**	MD **125 lower** (198.26 lower to 51.74 lower)	-	60 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Compared with no intervention, homeopathy may result in a reduction in symptom severity in people with menstrual disorders **
Depression - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on depression in people with menstrual disorders is unknown
Anxiety - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on anxiety in people with menstrual disorders is unknown
Health-related quality of life - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on health-related quality of life in people with menstrual disorders is unknown
Medication use - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on medication use in people with menstrual disorders is unknown

Homeopathy compared to inactive control for menstrual disorders

Patient or population: Menstrual disorders
Setting: Outpatient clinics
Intervention: Homeopathy
Comparison: Inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control (no intervention)	Risk with homeopathy				

***The risk in the intervention group (and its 95% confidence interval)** is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** Effect estimates were to be considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Missing data from 1 study (60 participants). Study authors suggest there is no difference between groups.

CI: confidence interval; **DRSP:** daily record of severity of problems; **MD**: mean difference; PMTS-VAS: premenstrual tension syndrome self-rating visual analogue scale

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Single study inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with premenstrual syndrome and is generalisable to the Australian population with some caveats. Applicability to people with dysmenorrhoea or endometriosis may be limited. Certainty of evidence not downgraded.

d. Very serious imprecision. Single study with wide confidence intervals (upper and lower bounds overlap with both important and no important benefit. Certainty of evidence downgraded 2 levels.

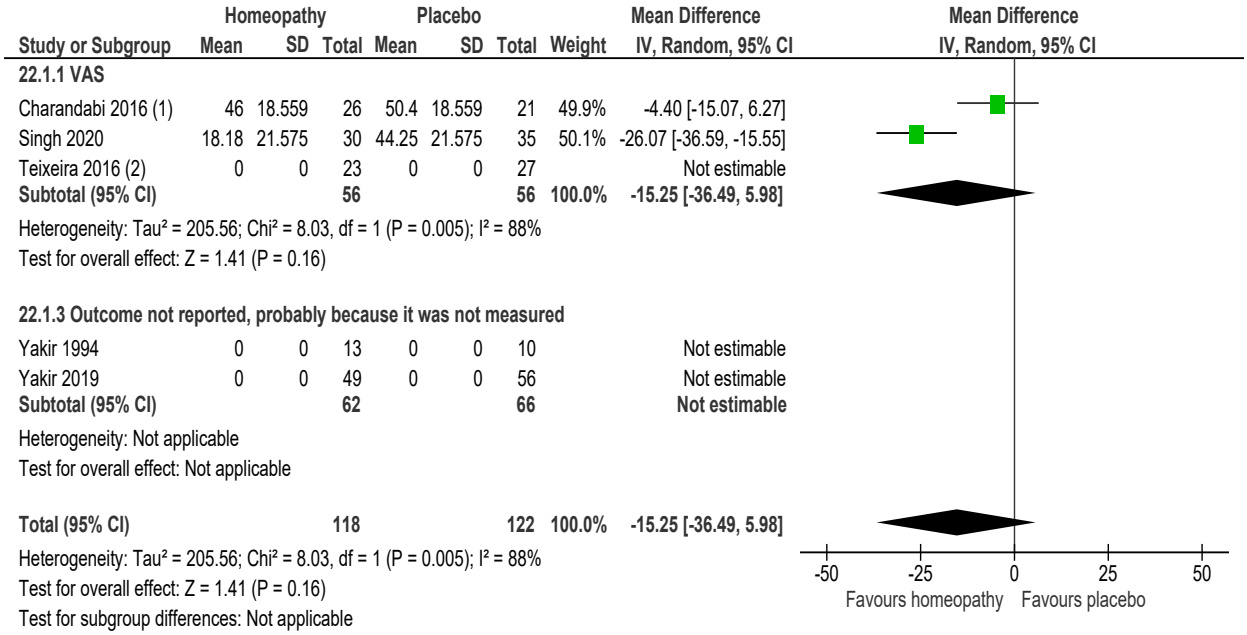
e. Publication bias not suspected. Certainty of evidence not downgraded.

4.19.5 Forest plots

Outcome results related to Primary Comparison (homeopathy vs placebo) in people with menstrual disorders are presented in Figure 89 (pain intensity), Figure 90 (symptom severity), Figure 91 (health-related quality of life) and Figure 92 (medication use).

Outcome results related to Secondary Comparison (homeopathy vs inactive control) in people with menstrual disorders are presented in Figure 93 (symptom severity).

Figure 89 Forest plot of primary comparison: Homeopathy vs placebo: Menstrual disorders – pain intensity

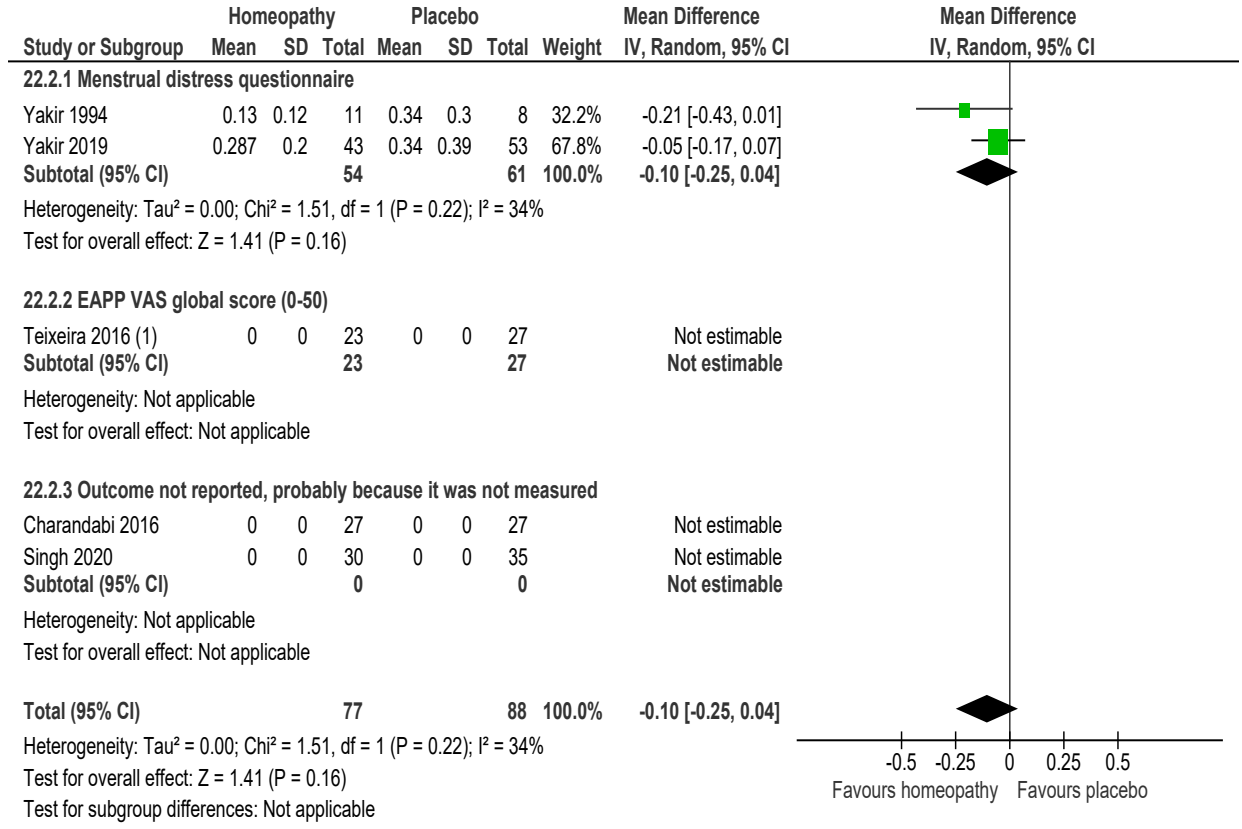


Footnotes

(1) Data adjusted for the baseline values by trialists using ANCOVA.

(2) Trialists reported change from baseline for the intervention group only. Result could not be included and are uninterpretable due to confounding.

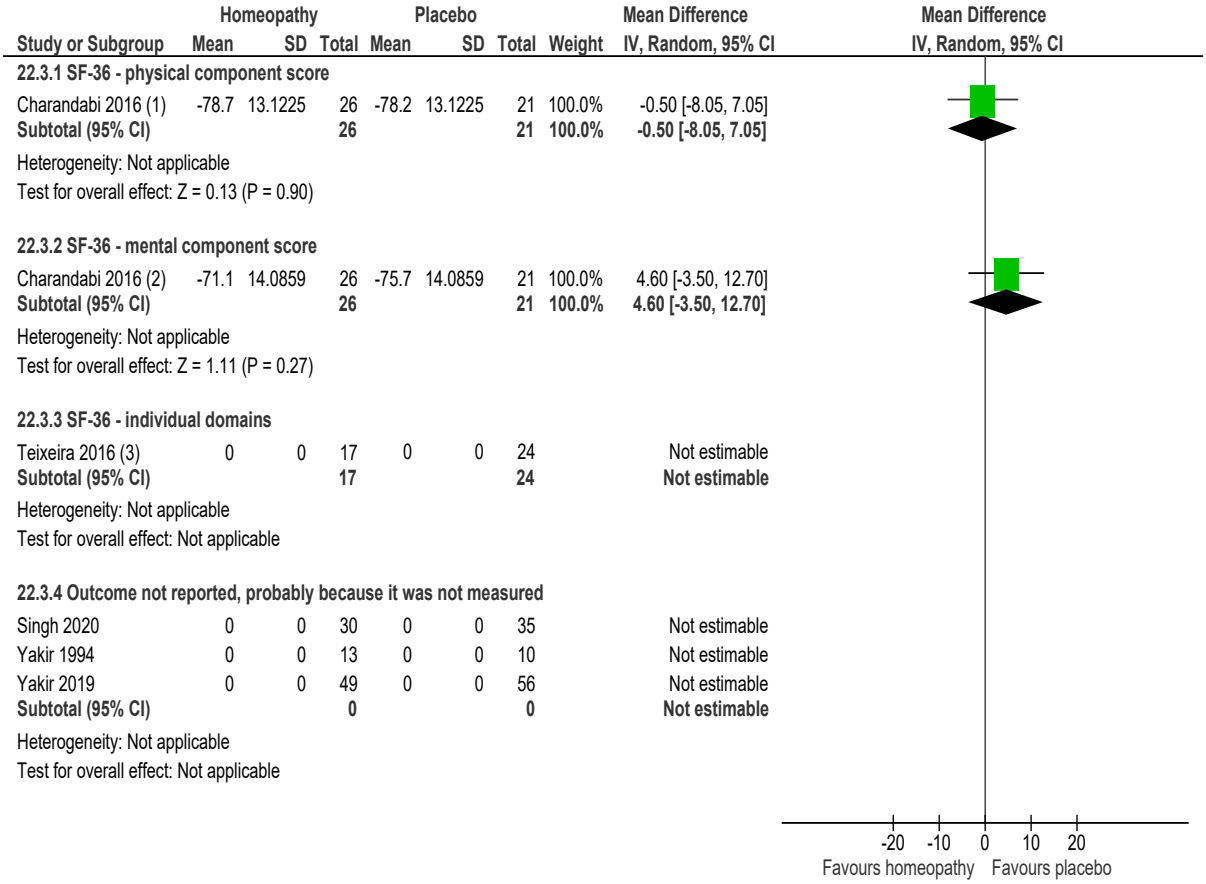
Figure 90 Forest plot of primary comparison: Homeopathy vs placebo: Menstrual disorders – symptom severity



Footnotes

(1) Trialists reported change from baseline for the intervention group only. Result could not be included and are uninterpretable due to confounding.

Figure 91 Forest plot of primary comparison: Homeopathy vs placebo: Menstrual disorders – health-related quality of life



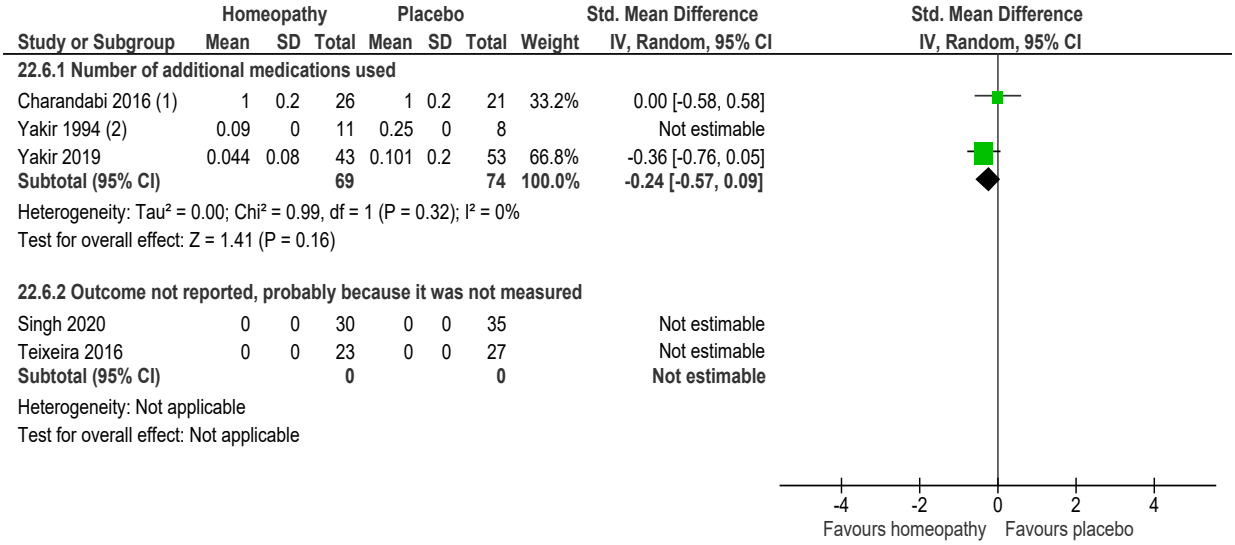
Footnotes

(1) Direction of effect standardised (i.e.higher is worse). Data adjusted for the baseline values by trialists using ANCOVA

(2) Direction of effect standardised (i.e.higher is worse). Data adjusted for the baseline values by trialists using ANCOVA

(3) Trialists reported change from baseline for the intervention group only. Result could not be included and are uninterpretable due to confounding.

Figure 92 Forest plot of primary comparison: Homeopathy vs placebo: Menstrual disorders – medication use

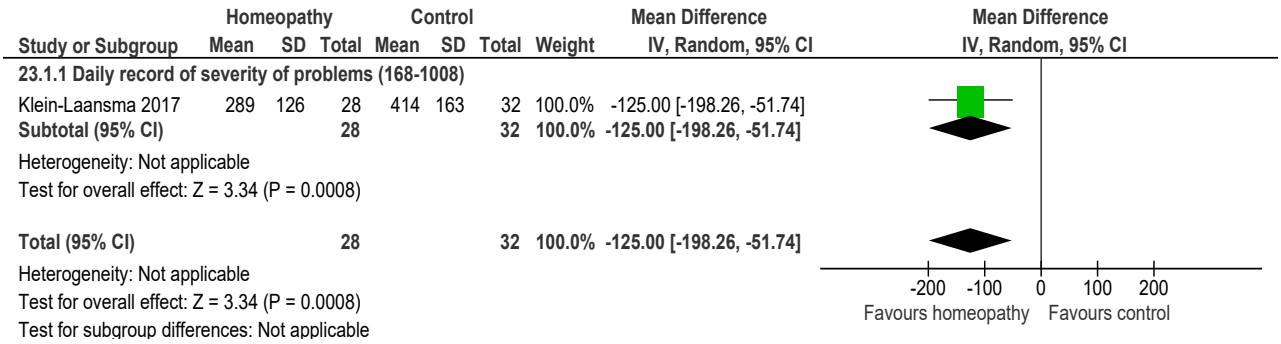


Footnotes

(1) non-steroidal anti-inflammatory drugs

(2) Study authors suggest no difference between groups (p=NR) but no other data provided.

Figure 93 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Menstrual disorders – symptom severity



4.20 Fatigue conditions

4.20.1 Description of the condition

Fatigue conditions encompass a range of diagnoses whose symptoms present as recurrent, persistent fatigue that limit a person's ability to carry out ordinary daily activities and impair cognitive function (340). Fatigue conditions include post-viral fatigue and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), among others. Post-viral fatigue refers to symptoms of fatigue which persist for an extended period of time following a viral infection. Viruses associated with post-viral fatigue include Epstein-Barr virus (which causes Glandular fever), human herpes virus 6, and SARS-CoV-2 (COVID-19) (341, 342).

ME/CFS is a complex condition, characterised by recurrent fatigue and post-exertional malaise that does not go away with rest (343). ME/CFS involves dysregulation of the central nervous system, immune system, cellular energy metabolism and ion transport (344). Diagnostic criteria for chronic fatigue vary, leading to a wide range of prevalence estimates depending on the criterion used. Australian studies estimate that there are over 20,000 people in Australia living with ME/CFS (343).

Treatment for fatigue conditions centre on symptoms management and include rest, diet and the gradual re-introduction to daily routines (345). Many complementary and alternative therapies, including homeopathy, yoga, meditation, massage therapy, and acupuncture are also used by people with ME/CFS or post-viral fatigue.

4.20.2 Description of studies

There were 4 citations (346-349) corresponding to one RCT (McKendrick 1999) identified in the literature search. No additional studies were identified in the Department's public call for evidence. There were 3 ongoing studies (total 197 participants) and no studies awaiting classification. An overview of the PICO criteria of included studies is provided in Appendix D10.1.1.

One RCT (McKendrick 1999) was conducted in the United Kingdom, and enrolled participants from outpatient departments with chronic fatigue syndrome. A total of 103 participants were randomised to individualised homeopathy or placebo. All participants received monthly consultations with a homeopath for 6 months. There were no limitations of the product, dosage or patency prescribed.

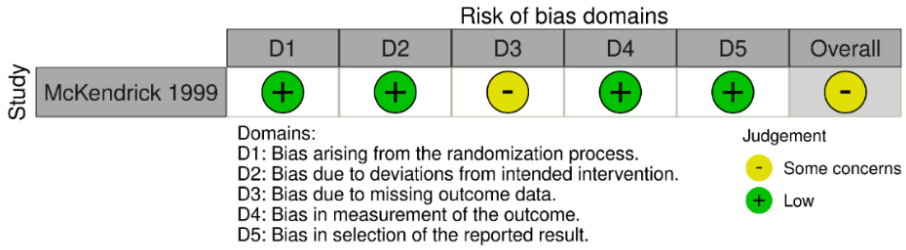
Results for the Primary Comparison: Homeopathy versus placebo are provided in the Summary of Findings table (see 4.20.4.1). There were no studies found for the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) or the Tertiary Comparison: Homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.20.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for fatigue conditions is summarised in Figure 94. Details are provided in Appendix D10.1.2. No studies were judged to be a low risk of bias.

Figure 94 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Fatigue conditions



4.20.4 Summary of findings and evidence statements

4.20.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Fatigue conditions

Patient or population: Fatigue conditions
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Fatigue assessed with: Multidimensional Fatigue Inventory Scale from: 4 to 20 (higher is worse) follow-up: 6 months	Little (to no) effect on any of the 5 domains of the Multidimensional Fatigue Inventory (see Figure 98).		-	86 (1 RCT)	⊕⊕◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in fatigue in people with fatigue conditions. **
Quality of life assessed with: Functional Limitations Profile Scale from: 0 to 100 (higher is worse) follow-up: 6 months	The mean change in physical score was **2.72**	MD **2.39 lower** (6.03 lower to 1.25 higher)	-	86 (1 RCT)	⊕⊕◯◯ LOW [a,b c,d,e]	Homeopathy may result in little to no difference in quality of life in people with fatigue conditions. **
	The mean change in psychosocial score was **6.76**	MD **3.05 lower** (8.36 lower to 2.26 higher)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

CI: confidence interval; **MD:** mean difference

Homeopathy compared to placebo for Fatigue conditions

Patient or population: Fatigue conditions
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with chronic fatigue syndrome and is applicable to the Australian population with few caveats. Certainty of evidence not downgraded.

d. Very serious imprecision. One small study (sample size not optimal) with wide confidence intervals (upper and lower bounds overlap with both important and no important benefit). Certainty of evidence downgraded 2 levels.

b. Publication bias not suspected. Certainty of evidence not downgraded.

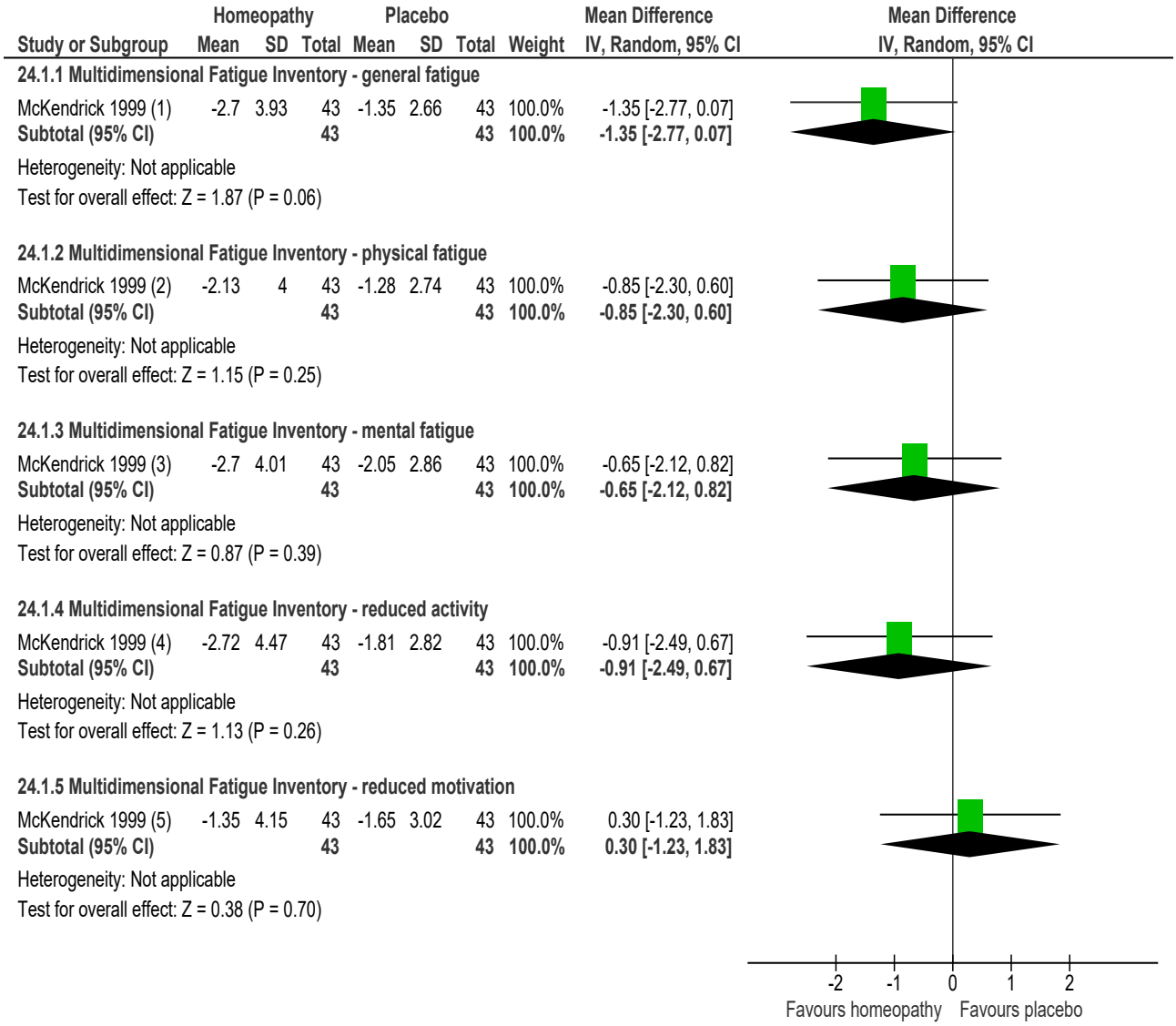
4.20.4.2 Secondary Comparison (vs inactive control)

There were no studies identified which compared homeopathy to inactive control in people with fatigue conditions. The effect of homeopathy compared to inactive control is unknown.

4.20.5 Forest plots

Outcome results related to the primary comparison: Homeopathy vs placebo in people with fatigue conditions are presented in Figure 95 (fatigue) and Figure 96 (quality of life).

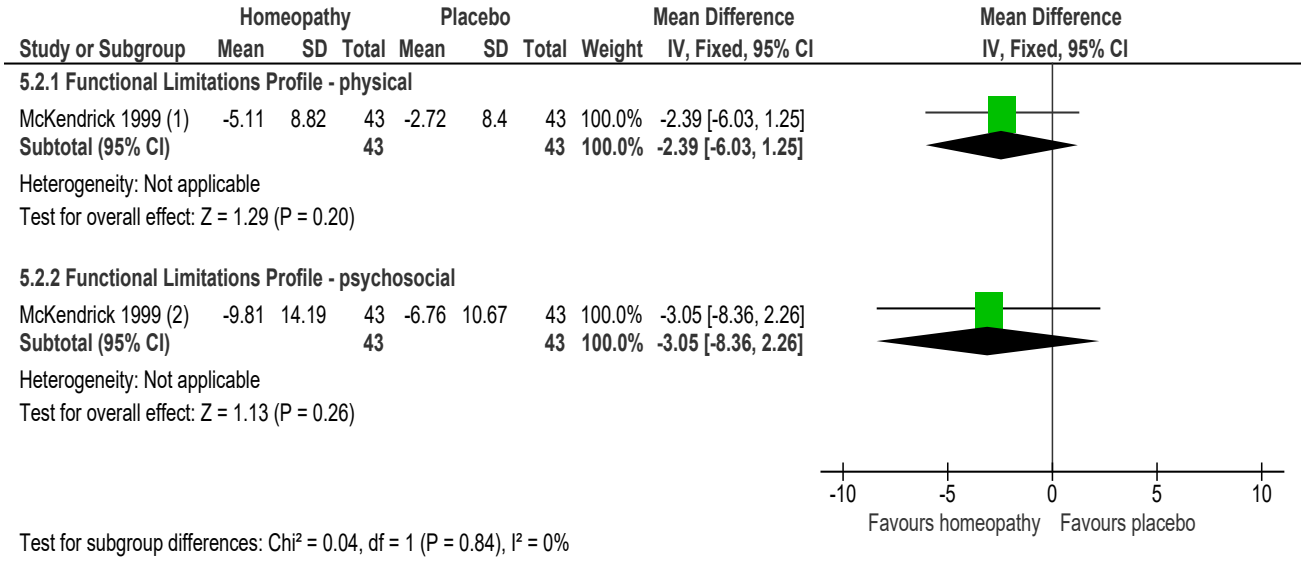
Figure 95 Forest plot of primary comparison: Homeopathy vs placebo (no intervention, waitlist or usual care): Fatigue conditions – fatigue



Footnotes

(1) Study reports mean change from baseline
(2) Study reports mean change from baseline
(3) Study reports mean change from baseline
(4) Study reports mean change from baseline
(5) Study reports mean change from baseline

Figure 96 Forest plot of primary comparison: Homeopathy vs placebo (no intervention, waitlist or usual care): Fatigue conditions – quality of life



Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² = 0%

Footnotes

(1) Study reports mean change from baseline

(2) Study reports mean change from baseline

4.21 Fibromyalgia

4.21.1 Description of the condition

Fibromyalgia is a chronic condition defined as widespread and prolonged pain persisting for more than three months with pain on at least 11 of 18 specified tender points on the body when palpated (350). People diagnosed with fibromyalgia not only experience widespread pain but also experience poor sleep quality, fatigue, extreme sensitivity, irritable bowel (diarrhoea, stomach pain) and headaches (351). Fibromyalgia can be difficult to diagnose as there is no single diagnostic test, symptoms may fluctuate from day to day, and it often co-exists with other chronic illnesses such as arthritis, depression, or sleep apnoea (352). In a North American survey, approximately half of the participants surveyed had consulted three to six healthcare professionals before receiving their diagnosis (353).

Fibromyalgia is a disabling condition that can affect all aspects of life, including work, family, and leisure (354). In Australia, fibromyalgia is estimated to affect approximately 3-5% of the population, equating to as many as 1 million Australians, and although it can affect people of all ages, it has a significantly higher prevalence in females (355).

For those who are successfully diagnosed, management of symptoms is the mainstay of treatment, with various drug and non-drug treatments playing a supportive role in managing pain, promoting sleep and reducing stress. The complex nature of fibromyalgia symptoms can lead people to seek complementary or alternative medicines such as homeopathy (356).

4.21.2 Description of studies

Seven citations (357-363) corresponding to 2 RCTs (Bell 2004, Relton 2009) and one quasi RCT (Fisher 1988) were identified in the literature. Seven citations (357-363) corresponding to 2 RCTs (Bell 2004, Relton 2009) and one quasi RCT (Fisher 1988) were identified in the literature. No additional studies were identified in the Department's public call for evidence. There were no ongoing studies and 2 studies awaiting classification (total 92 participants). An overview of the PICO criteria of included studies is provided in Appendix D10.2.1.

One study was conducted in an outpatient Rheumatology clinic in the United Kingdom (Fisher 1988). The other 2 studies were conducted in community settings, one in the United Kingdom (Relton 2009) and one in the United States (Bell 2004). All studies consisted of participants who met the diagnostic criteria for fibromyalgia, with sample sizes ranging from 30 to 62 (total 139 participants).

Two studies (Bell 2004, Fisher 1988) compared homeopathy with a placebo. In one study (Bell 2004) treatment was individualised and taken orally for a period of 4 months. In this study, visits to the homeopath were completed by both the treatment and placebo group at 2-month intervals. In the other study (Fisher 1988) participants received a non-individualised homeopathic product consisting of *R. toxicodendron* 6c in the form of an oral tablet sucked three times daily over a one-month period.

One study (Relton 2009) compared individualised homeopathy treatment with an inactive control. In this study, participants completed an initial interview with a homeopath and up to 4 follow-up interviews over a period of 4 to 6 weeks. All participants were allowed to continue with their usual care, which consisted of one or more of the following: physiotherapy, aerobic exercise, analgesics, non-steroidal anti-inflammatory drugs, or anti-depressants.

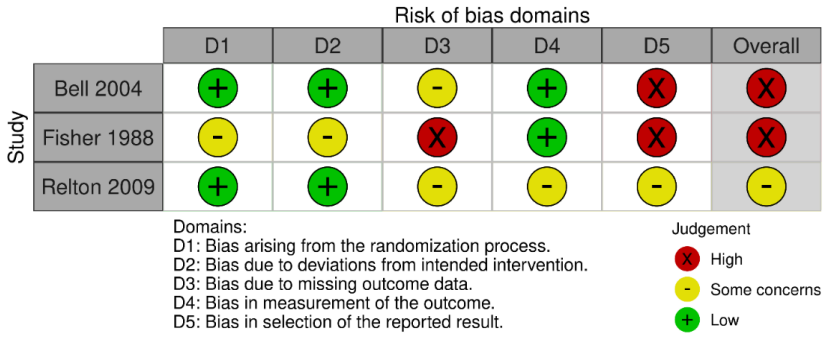
Results for the Primary Comparison: Homeopathy versus placebo and for the Secondary Comparison: Homeopathy versus inactive control (no intervention, waitlist or usual care) are provided in the Summary of Findings table (see 4.21.4). There were no studies found for Tertiary Comparison: Homeopathy versus another comparator.

We did not stratify according to the intervention (individualised or non-individualised) as there were too few studies per comparison that also included studies with a different mode of intervention.

4.21.3 Risk of bias – summary assessment across studies

The risk of bias for each item in the included RCTs for fibromyalgia is summarised in Figure 97. Details are provided in Appendix D10.2.2. No studies were judged to be at overall low risk of bias.

Figure 97 Risk of bias summary: review authors' judgement about each risk of bias item for each included study: Fibromyalgia



4.21.4 Summary of findings and evidence statements

4.21.4.1 Primary Comparison (vs placebo)

Homeopathy compared to placebo for Fibromyalgia

Patient or population: Fibromyalgia
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Pain assessed with: McGill Pain Questionnaire Scale: 0 to 12 (affective); 0 to 33 (sensory) (higher is worse) follow-up: 3 months	The mean affective pain score was **3.5**	MD **0.20 lower** (1.71 lower to 1.31 higher)	-	53 (1 RCT) †	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on pain in people with fibromyalgia**
	The mean sensory pain score was **12.4**	MD **0.50 higher** (3.36 lower to 4.36 higher)				
Fatigue assessed with: POMS - fatigue domain Scale from: 0 to 28 (higher is worse) follow-up: 3 months	The mean fatigue score was **13.4**	MD **3.4 lower** (7.47 lower to 0.67 higher)	-	53 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,e,f	The evidence is very uncertain about the effect of homeopathy on fatigue in people with fibromyalgia**

Homeopathy compared to placebo for Fibromyalgia

Patient or population: Fibromyalgia
Setting: Community
Intervention: Homeopathy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with homeopathy				
Health-related quality of life assessed with: Global health rating Scale from: 3 to 15 (higher is better) follow-up: 3 months	The mean score was **7.7**	**MD 0.5 higher** (1.09 lower to 2.09 higher)	-	53 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,e,g	The evidence is very uncertain about the effect of homeopathy on health-related quality of life in people with fibromyalgia**
Emotional wellbeing assessed with: POMS - depression domain Scale from: 0 to 60 (higher is worse) follow-up: 3 months	The mean score was **8.1**	MD **0.8 lower** (6.16 lower to 4.56 higher)	-	53 (1 RCT)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of homeopathy on emotional wellbeing in people with fibromyalgia**
Pain disability - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on pain disability in people with fibromyalgia is unknown

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Missing data from one RCT (30 participants). Study authors report a significant difference favouring the homeopathy group for combined pain and sleep scores.

CI: confidence interval; **MD:** mean difference; **POMS:** Profile of mood states

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. One RCT contributing 100% of data was at high risk of bias. Certainty of evidence downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with fibromyalgia and is applicable to the Australian population with few caveats. Certainty of evidence not downgraded.

d. Very serious imprecision. One small study (sample size less than optimal) with wide confidence intervals (upper and lower bound overlap with both important benefit and harm). Certainty of evidence downgraded 2 levels.

e. Publication bias suspected. There is strong suspicion of selective reporting of results because the *p*-value, magnitude or direction of the results generated were considered unfavourable by the study investigators. Certainty of evidence downgraded.

f. Very serious imprecision. One small study (sample size less than optimal) with confidence intervals that include both benefit and no important difference. Certainty of evidence downgraded 2 levels.

g. Very serious imprecision. One small study (sample size less than optimal) with confidence intervals that include both no important difference and harm. Certainty of evidence downgraded 2 levels.

4.21.4.2 Secondary Comparison (vs inactive control)

Homeopathy compared to inactive control for Fibromyalgia

Patient or population: Fibromyalgia
Setting: Community
Intervention: Homeopathy
Comparison: Inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI) Risk with control (no intervention)	Risk with Homeopathy	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Pain intensity assessed with: McGill Pain Questionnaire Scale: 0 to 12 (affective); 0 to 33 (sensory) (higher is worse) follow-up: 22 weeks	The mean affective pain score was **6.5** The mean sensory pain score was **20.6** The mean pain intensity score was **78.1**	MD **2.00 lower** (4.34 lower to 0.34 higher MD **2.90 lower** (8.94 lower to 3.14 higher) MD **14.00 lower** (28.37 lower to 0.37 higher)	-	36 (1 RCT)	⨁⨁◯◯ Low [a,b,c,d,e]	Homeopathy may result in little to no difference in pain in people with fibromyalgia **
Fatigue assessed with: FIQ – fatigue Scale from: 0 to 10 (higher is worse) follow-up: 22 weeks	The mean fatigue score was **8.3**	MD **1.1 lower** (2.44 lower to 0.24 higher)	-	36 (1 RCT)	⨁⨁◯◯ LOW [a,b,c,d,e]	Homeopathy results in little to no difference in fatigue in people with fibromyalgia **
Health-related quality of life assessed with: FIQ - total score Scale from: 0 to 100 (higher is worse) follow-up: 22 weeks	The mean health-related quality of life score was **68.5**	MD **10.3 lower** (23.93 lower to 3.33 higher)	-	36 (1 RCT)	⨁⨁◯◯ LOW [a,b,c,d,e]	Homeopathy may result in little to no difference in health-related quality of life in people with fibromyalgia #
Emotional wellbeing assessed with: HADS Scale from: 0 to 42 (higher is worse) follow-up: 22 weeks	The mean emotional wellbeing score was **22.2**	MD **3.1 lower** (8.85 lower to 2.65 higher)	-	36 (1 RCT)	⨁⨁◯◯ LOW [a,b,c,e,f]	Homeopathy may result in little to no difference in emotional wellbeing in people with fibromyalgia**

Homeopathy compared to inactive control for Fibromyalgia

Patient or population: Fibromyalgia
Setting: Community
Intervention: Homeopathy
Comparison: Inactive control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI) Risk with control (no intervention)	Risk with Homeopathy	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
Pain disability - not reported	-	-	-	(0 studies)	-	The effect of homeopathy on pain disability in people with fibromyalgia is unknown

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** Effect estimates were considered on 3 levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

A 14-point change in the FIQ total score is considered clinically relevant (364)

CI: confidence interval; **FIQ:** Fibromyalgia impact questionnaire; **HADS:** Hospital anxiety and depression scale; **MD:** mean difference; **VAS,** Visual analogue scale

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.

b. Single study. Inconsistency not assessed. Certainty of evidence not downgraded.

c. No serious indirectness. The available evidence is in people with fibromyalgia and is applicable to the Australian population with few caveats. Certainty of evidence not downgraded.

d. Very serious imprecision. One small study (sample size less than optimal) with wide confidence intervals (upper and lower bound overlap with both benefit and harm). Certainty of evidence downgraded 2 levels.

e. Publication bias not suspected. Certainty of evidence not downgraded.

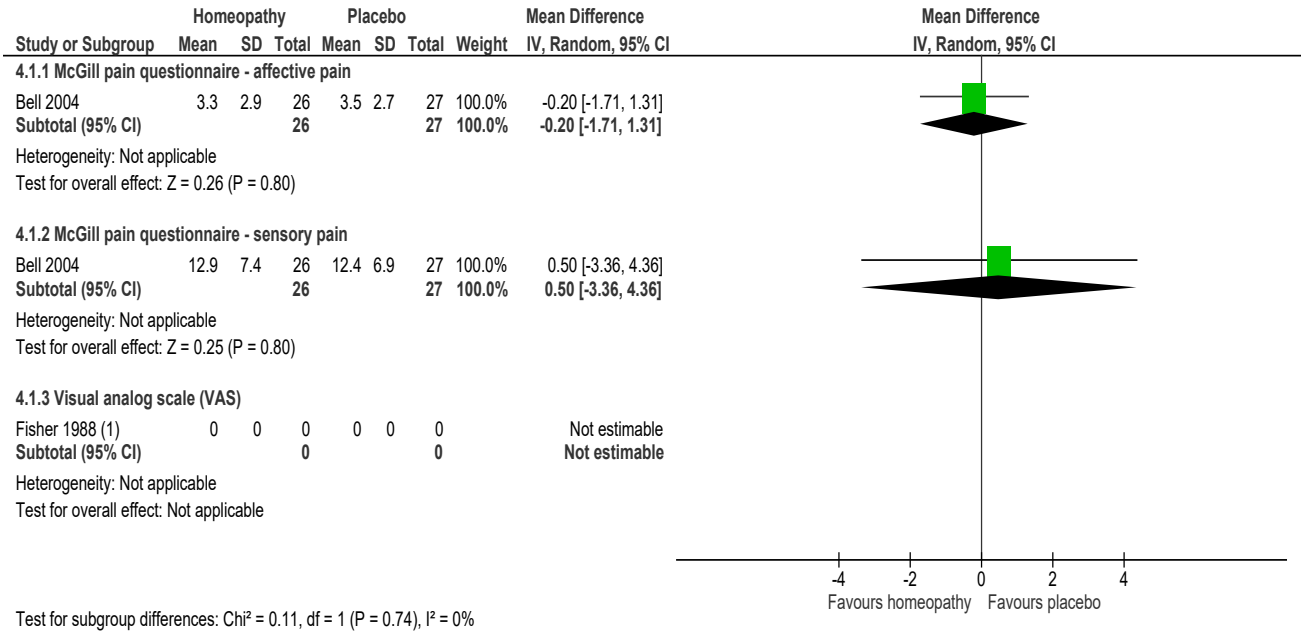
f. Very serious imprecision. One small study (sample size less than optimal) with wide confidence intervals (upper and lower bound overlap with both important and no important benefit). Certainty of evidence downgraded 2 levels.

4.21.5 Forest plots

Outcome results related to the primary comparison (homeopathy vs placebo) in people with fibromyalgia are presented in Figure 98 (pain intensity), Figure 99 (fatigue), Figure 100 (health-related quality of life) and Figure 101 (emotional wellbeing).

Outcome results related to the secondary comparison (homeopathy vs inactive control) in people with fibromyalgia are presented in Figure 102 (pain intensity), Figure 103 (fatigue), Figure 104 (health-related quality of life) and Figure 105 (emotional wellbeing).

Figure 98 Forest plot of primary comparison: Homeopathy vs placebo: Fibromyalgia – pain intensity



Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%

Footnotes

(1) Study does not report means, SD or n.Study authors report a significant difference favouring the homeopathy group for combined pain and sleep scores (p-value not reported).

Figure 99 Forest plot of primary comparison: Homeopathy vs placebo: Fibromyalgia – fatigue

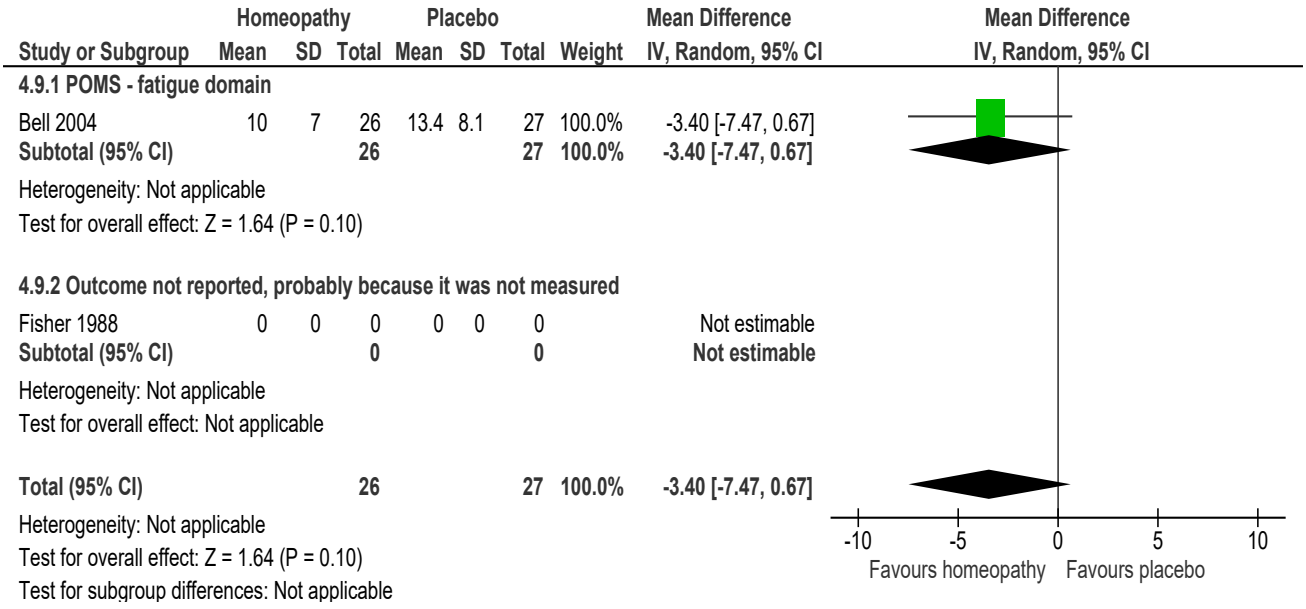


Figure 100 Forest plot of primary comparison: Homeopathy vs placebo: Fibromyalgia – health-related quality of life

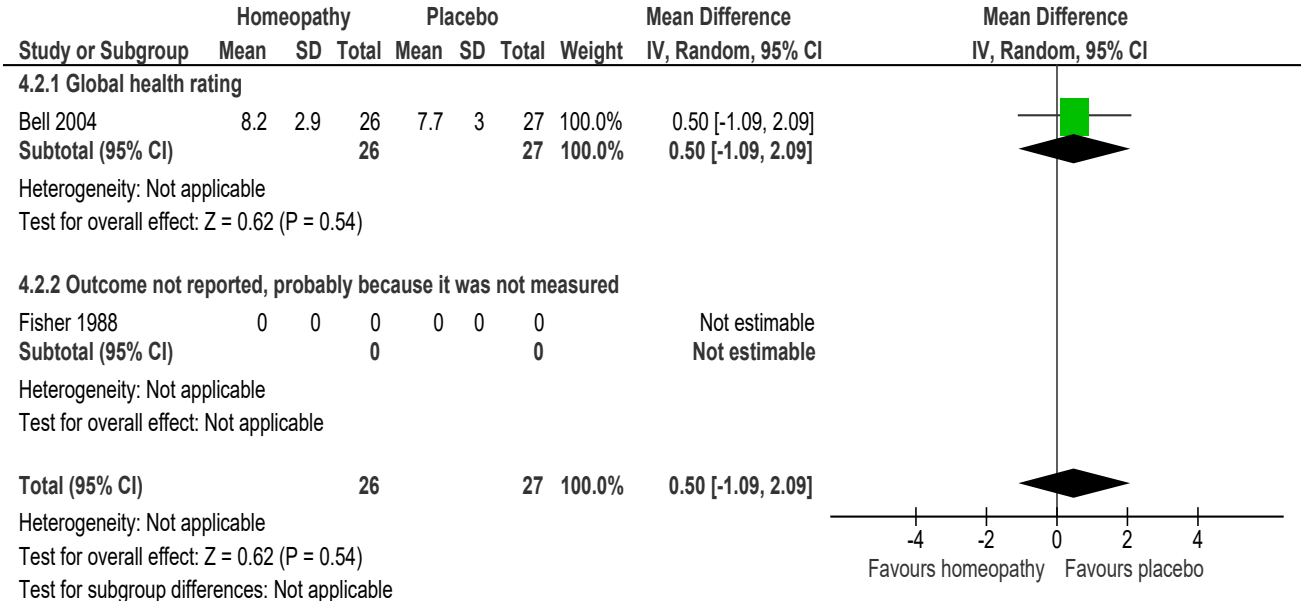


Figure 101 Forest plot of primary comparison: Homeopathy vs placebo: Fibromyalgia – emotional wellbeing

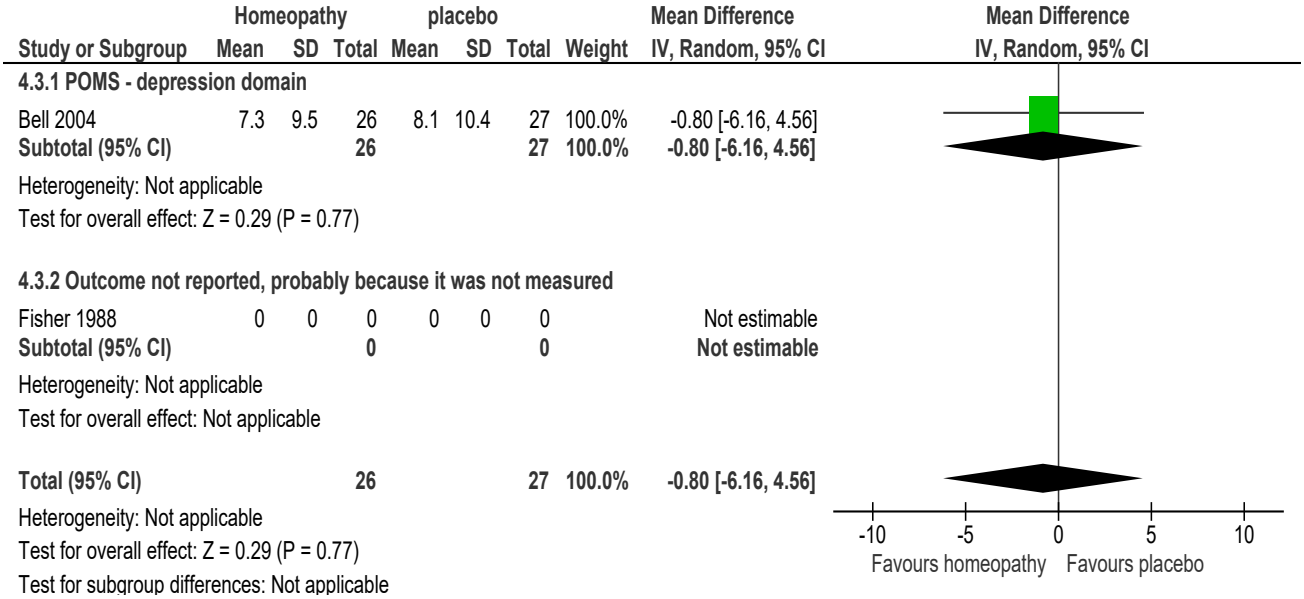


Figure 102 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Fibromyalgia – pain intensity

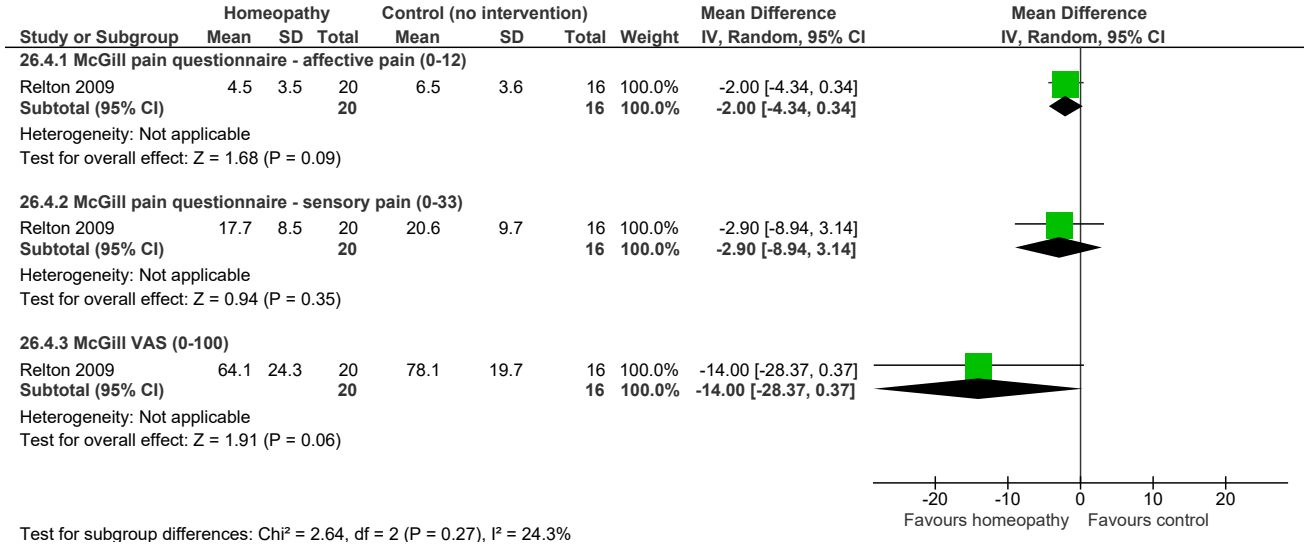


Figure 103 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Fibromyalgia – fatigue

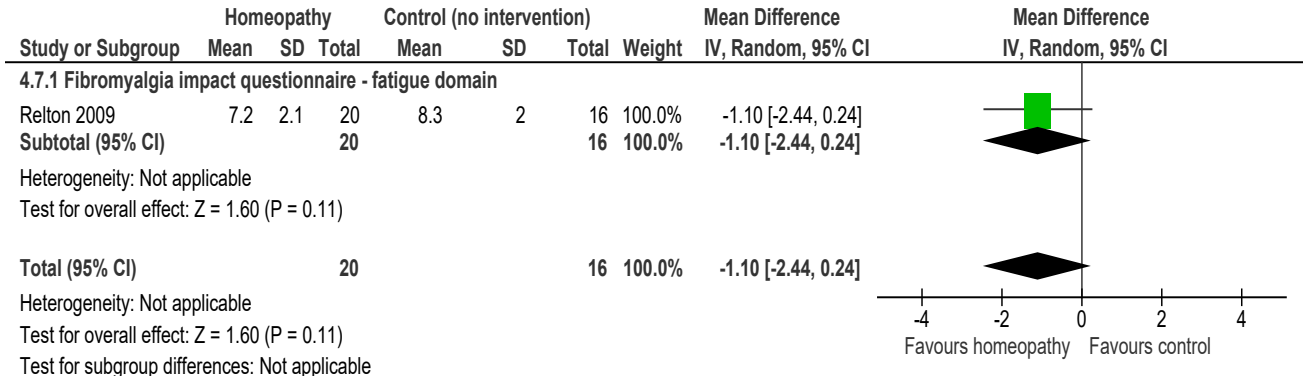


Figure 104 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Fibromyalgia – health-related quality of life

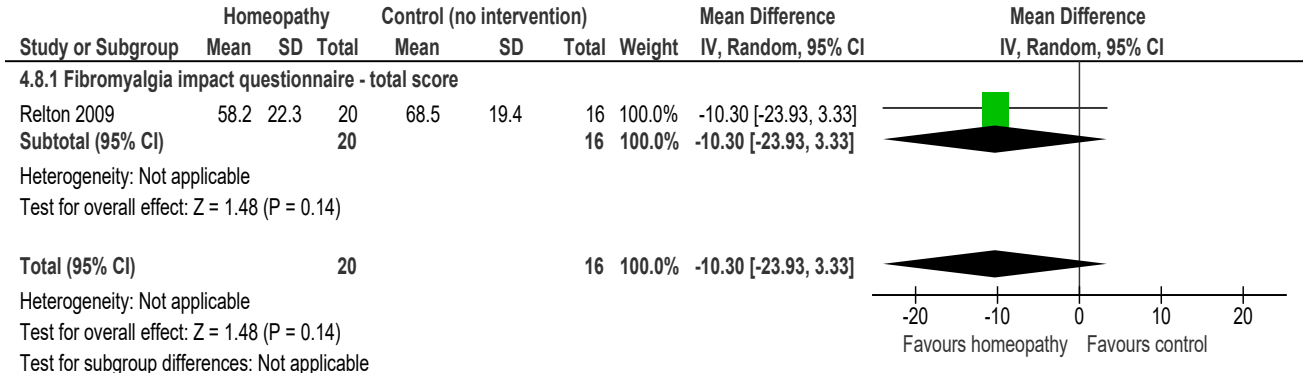
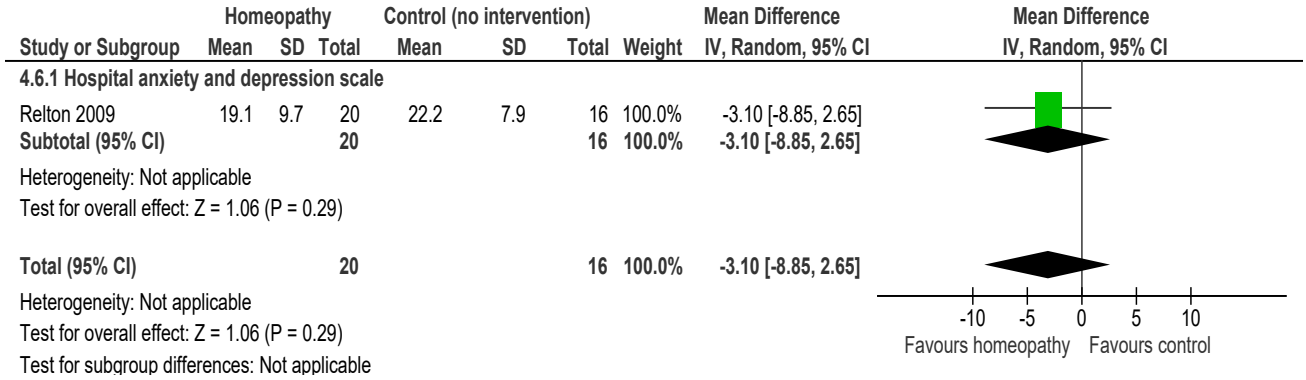


Figure 105 Forest plot of secondary comparison: Homeopathy vs inactive control (no intervention): Fibromyalgia – emotional wellbeing



5 Discussion

5.1 Summary of main results

We conducted a systematic review of RCTs to evaluate the effectiveness of homeopathy for 20 clinical or preclinical conditions prioritised (by NTWC) as most relevant to the use of homeopathy in Australia. We identified 93 RCTs that were included in the results. Of these studies, 66 RCTs compared homeopathy with 'placebo' and 12 RCTs compared homeopathy with 'inactive control' – the main two comparators of interest. All 20 conditions prioritised by NTWC that included either critical or important outcomes were included in the final analysis and are presented in the summary of findings tables.

Results for studies of prioritised conditions with active comparators (including usual care, where considered active) are presented in Appendix F2 and described in the results section. These are not included in the synthesis or summary of findings tables, as the wide range of comparators and outcomes did not allow for synthesis as planned in the protocol.

Our confidence in the result from the body of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. GRADE combines information to assess overall how certain systematic review authors can be that the estimates of the effect (reported across a study/s for each critical or important outcome) are correct[12].

Certainty of evidence is interpreted as follows:

Certainty	**Definition**
High certainty	The authors have a lot of confidence that the true effect is similar to the estimated effect.
Moderate certainty	The true effect is probably close to the estimated effect.
Low certainty	The true effect might be markedly different from the estimated effect.
Very low certainty	The true effect is probably markedly different from the estimated effect

For 20 prioritised conditions there was moderate or low certainty of evidence about the effect of homeopathy compared with placebo or inactive control on at least one outcome considered critical or important by NTWC.

For the primary comparison (homeopathy vs placebo) the review found:

- low certainty that homeopathy may result in:
    - a moderate reduction in medication use (1 RCT, 108 participants) in people with allergic rhinitis
    - a small reduction in disease severity (3 RCTs, 172 participants) in people with atopic dermatitis

- low certainty that homeopathy may result in little (to no) benefit in:
    - improving quality of life (2 RCTs, 106 participants) in people with atopic dermatitis,
    - reducing infection frequency (1 RCT, 96 participants) in people with recurrent otitis media

[12] The estimated effect could suggest either that the therapy in question has an effect (e.g. works better than placebo) or that it has little to no effect. The result for each outcome for a condition is described both in terms of the certainty and the direction of effect. For example, "the evidence provides low certainty that homeopathy may have little (to no) effect compared to placebo on [outcome x] in [condition y]" means that the evidence suggests the effect does not differ from the placebo, but the certainty is low so the true result may be different.

- improving quality of life (1 RCT, 170 participants) or reducing medication use (2 RCTs, 377 participants) or in people with recurrent upper respiratory tract infections
- reducing anxiety (3 RCTs, 150 participants), depression (1 RCT, 44 participants), or emotional functioning (1 RCT, 44 participants) in people with anxiety
- reducing insomnia severity, sleep quality or sleep onset latency (1 RCT, 60 participants) in people with insomnia
- improving quality of life (2 RCTs, 291 participants) or reducing medication use (1 RCT, 89 participants) in people with asthma
- reducing symptom severity (1 RCT, 292 participants) or symptom duration (3 RCTs, 448 participants) in people with diarrhoea
- reducing disease severity (1 RCT, 200 participants) in people with psoriasis
- reducing pain intensity (1 RCT, 134 participants), stiffness (1 RCT, 134 participants) or improving quality of life (1 RCT, 134 participants) in people with back or neck pain
- improving quality of life (1 RCT, 108 participants) in people with menopausal symptoms or complaints
- reducing fatigue (1 RCT, 86 participants) or improving quality of life (1 RCT, 86 participants) in people with chronic fatigue conditions.

The evidence is very uncertain of the effect of homeopathy compared with placebo for 39 out of the 94 critical or important outcomes prioritised for analysis in this review. For these 39 outcomes, confidence in the size of the effect estimate is very uncertain and a clinically important difference was not observed (this may relate to study design, size, or duration of the study). Of the 94 outcomes prioritised as critical or important, there were no studies found comparing homeopathy with placebo for 32 of those outcomes, and therefore the effect of homeopathy on those outcomes is unknown.

Overall, it is not possible to say anything about the effects of homeopathy compared with placebo for 8 populations, including: depression, neurodevelopmental disorders, digestive complaints, irritable bowel syndrome, headache disorders, arthropathies, menstrual disorders and fibromyalgia as there was not enough evidence.

For the secondary comparison (homeopathy vs inactive control), the review found:

- moderate certainty that compared with inactive control, homeopathy probably results in:
    - a moderate reduction in infection frequency (1 RCT, 256 participants) in people with recurrent upper respiratory tract infections.[13]

- low certainty that compared with inactive control homeopathy may result in:
    - a slight reduction in antibiotic use (2 RCTs, 306 participants) in people with recurrent upper respiratory tract infections.[14]
    - a moderate reduction in symptom severity (1 RCT, 60 participants) in people with menstrual disorders.[15]

- moderate certainty that compared with inactive control, homeopathy probably has little (to no) effect in:

[13] In the primary comparison, the evidence provided very low certainty (1 RCT, 40 participants) about the effect of homeopathy on infection frequency in people with recurrent upper respiratory tract infections.

[14] In the primary comparison, the evidence provided low certainty that homeopathy may have little to no effect on antibiotic use (2 RCTs, 377 participants) in people with recurrent upper respiratory tract infections.

[15] In the primary comparison, the evidence was very uncertain about the effect of homeopathy on symptom severity for menstrual disorders (2 RCTs, 115 participants)

    - reducing depression severity (1 RCT, 566 participants) in people with depression.

- low certainty that compared with inactive control homeopathy may have little (to no) effect in:
    - reducing symptom severity (1 RCT, 210 participants) in children with recurrent otitis media
    - reducing symptom severity (2 RCTs, 86 participants), health-related quality of life (2 RCTs, 86 participants), hospitalisation (1 RCT, 35 participants) or medication use (1 RCT, 35 participants) in people with asthma
    - reducing symptom severity (1 RCT, 76 participants) or health-related quality of life (1 RCT, 76 participants) in people with irritable bowel syndrome
    - reducing pain (1 RCT, 36 participants), fatigue (1 RCT, 36 participants), health-related quality of life (1 RCT, 36 participants), or emotional wellbeing (1 RCT, 36 participants) in people with fibromyalgia.

(These results suggesting low certainty of little or no difference are generally consistent with those from the primary comparison with placebo, although sometimes the level of certainty differs.)

The evidence is very uncertain of the effect of homeopathy compared with inactive control (inclusive of no intervention, waitlist or usual care if considered inactive) for 12 out of the 94 critical or important outcomes prioritised for analysis in this review. For these outcomes, confidence in the effect estimate is very uncertain. Of the 94 outcomes prioritised as critical or important, there were no studies found for 67 of those outcomes, and therefore the effect of homeopathy compared to inactive control on those outcomes (out of 94) is unknown.

An assessment of benefits and harms of homeopathy was not conducted for this review, as it was out of scope of this review to assess adverse effects of homeopathy.

5.2 Overall completeness and applicability of evidence

This review aimed to identify the available RCT evidence on the effectiveness of homeopathy. Only studies that assessed homeopathy versus placebo or homeopathy versus inactive control (no intervention, waitlist, usual care [inactive]) were included in the synthesis. Studies of prioritised conditions with active comparators (including usual care where considered active) were not able to be included in the synthesis or summary of findings tables, as the wide range of comparators and outcomes did not allow for synthesis as planned in the protocol.

There were 161 studies that met the eligibility criteria for the review but were not included in the evidence evaluation. This is because they examined the effects of homeopathy in populations (or conditions) not prioritised by NTWC for analysis or synthesis. These studies are listed in an inventory titled *Citation details of studies from non-priority populations* (Appendix C3, Table C.3).

Databases in languages other than English were not searched. Studies published in a language other than English (identified through English databases) were not translated and were not included in the synthesis but listed in an inventory for completeness (Appendix C4.2). There were 89 studies identified in a language other than English.

The available evidence was from a range of countries including Brazil, Egypt, Germany, France, India, Russia, Spain, Ukraine, the United Kingdom and the United States. Most studies examined homeopathy delivered in a manner that would be considered applicable to the Australian context; inclusive of individualised and non-individualised prescriptions, accompanied by consultations with a homeopath. Most studies evaluated homeopathic products that were administered orally (either as tablet or pellet), but some were topically applied or administered via a nasal spray. A variety of potencies or dilutions were examined. Studies examining the effect of individualised homeopathy tended to shortlist a group of interventions from which the homeopath chose. The planned comparison between individualised and non-individualised homeopathy could not be completed because of the small number of studies per comparison.

Among the 20 prioritised conditions, 24 (~26%) out of the 94 outcomes prioritised as critical or important were not measured or reported in studies comparing homeopathy with either placebo or inactive control (no intervention, waitlist or usual care [inactive]). There were few studies with missing outcome information or information that was not translatable (such as that included in graphs). As per the protocol, we made no requests to authors for this information and did not attempt to translate information contained in graphs. It is considered unlikely this information would have impacted the overall conclusions of this review.

Studies included in this review are those published up until July 2022. There was a large amount of evidence for homeopathy not published at the time of the search (192 studies listed as ongoing) or not yet evaluated (150 studies awaiting classification). Among the priority populations included in this review, an estimated 48 RCTs (3748+ participants) comparing homeopathy with placebo or an inactive control are awaiting classification and a further 69 RCTs (5858 target participants) were listed as ongoing. It is likely that many of these studies would meet the eligibility criteria for this review, the results of which may (or may not) have an impact on the overall results.

5.3 Certainty of the evidence

The certainty of evidence across outcomes was generally downgraded for issues with imprecision (related to sample size and wide confidence intervals) or concerns that the effect estimate was over (or under) estimated. The suspicion of publication bias (relating to the likelihood that studies with outcome results not favourable to the intervention were not reported) was applied less often. With regards to risk of bias, the certainty of evidence was downgraded only when a sensitivity analysis showed clear interaction between the effect estimates and the studies judged to be at high risk of bias (or when all studies contributing data were at high risk of bias). Downgrades for studies with some concerns of bias was generally not applied.

In rare instances, the certainty of evidence was downgraded for inconsistency, when the effect estimates differed importantly across studies, as indicated by minimal or no overlap in the confidence intervals, and no clear explanation for statistical heterogeneity. Downgrades for indirectness were also rare, although in some cases noted that the studies may not be directly applicable to the Australian healthcare context, meaning the delivery of the intervention or the participants included within the trial may have unknown factors that do not directly match homeopathy as delivered in Australia or a broader population group.

5.4 Potential biases in the review process

To ensure transparency in the review process, we published the final NTWC endorsed research protocol on PROSPERO prior to commencing the literature search. The protocol is consistent with others in the Natural Therapies Review. In order to capture the majority of studies assessing the effectiveness of homeopathy, we comprehensively searched multiple databases and did not apply date, language, population or outcome restrictions in our search. In addition, we provided detailed documentation of the inclusion criteria to avoid inconsistent application of study selection criteria and used standardised procedures for data collection and critical appraisal. Where possible, we have applied a methodological approach consistent with the *Cochrane Handbook for Systematic Reviews of Interventions* and other best practice methods.

While we have attempted to control for potential biases, some deviations from the protocol were necessary for pragmatic reasons. To ensure these deviations from protocol are clear, deviations and post-hoc decisions have been documented and explained in **Appendix G**.

Data collection was performed by two researchers, the first collected data using data extraction forms and the second checked for completeness and accuracy in data extraction. Decisions regarding prioritisation of conditions and critical or important outcomes were made by the NTWC, with input from NTREAP, who were blinded to the number and details of the studies found.

We did not specifically search for or include studies published in languages other than English in the analysis, so it is possible that we may have missed studies that may (or may not) impact the overall conclusions of this review, although this is considered unlikely given agreements observed with other reviews (see below).

5.5 Agreements and disagreements with other studies or reviews

A search for published systematic reviews (via PubMed and the Cochrane Library) relating to each priority population was conducted at the time of the evidence synthesis.

5.5.1 Atopic conditions

Two systematic reviews assessing the effect of homeopathy for allergic rhinitis (12) and eczema (365) were identified. Similar to our findings, these systematic reviews were not able to conclude that homeopathy is effective for atopic conditions. The review authors for both systematic reviews noted the poor methodological quality of the identified studies which limited interpretation of the results.

5.5.2 Recurrent infections (otitis media)

No systematic reviews assessing the effectiveness of homeopathy in the treatment of children with recurrent otitis media were found in the literature. There was one systematic review that assessed the effectiveness of homeopathy specifically for the treatment of otitis media *with effusion* (366). The review identified 3 RCTs that were also identified and assessed in this review (Harrison 1999, Jacobs 2001, Sinha 2012). One RCT compared homeopathy with a placebo (total 75 participants), one compared homeopathy with an inactive control (no intervention) (33 participants), and one compared homeopathy with an active control (33 participants). The identified review (366) concluded that further research was required to draw conclusions on the effectiveness of homeopathy for the treatment of otitis media with effusion in children. No conclusions were drawn as to the certainty of the evidence presented in the 3 RCTs identified.

5.5.3 Recurrent infections (upper respiratory tract)

No systematic reviews assessing the effectiveness of homeopathy for recurrent URTIs were found in the literature. A Cochrane review that assessed the effectiveness of homeopathy for preventing and treating acute respiratory tract infections (aRTI) in children was found (109). The review identified 11 RCTs (total 1813 participants) that compared homeopathy with a control treatment (either placebo or conventional treatment) for aRTIs. Outcomes reported in these RCTs included disease severity, antibiotic use, recurrence of aRTI and adverse events. Of the RCTs identified in the Cochrane review, 4 were not included in this review, as they did not fit the criteria or definition for prevention of recurrent URTIs. Although the population assessed in the Cochrane review was specific to prevention and treatment of acute infection in children, the conclusions were found to align with this current review; with the certainty of evidence judged to be low or very low for most outcomes. Similar to this review, the Cochrane review found the studies "did not show any consistent benefit of homeopathic medicinal products compared to placebo on aRTI recurrence or cure rates in children" (109).

5.5.4 Recurrent infections (genitourinary)

No systematic reviews assessing the effectiveness of homeopathy in the treatment of recurrent genitourinary tract infections were found in the literature.

5.5.5 Anxiety

One systematic review assessing the effectiveness of homeopathy for anxiety was found in the literature (367). The review included 8 RCTs, 4 uncontrolled trials/case series, one pragmatic outcome study, several surveys and audit/patient outcome studies, and single-case reports/studies. The authors found that evidence on the benefit of homeopathy in anxiety and anxiety disorders is limited; noting that the RCTs were of poor methodological quality and report contradictory results. The other studies (e.g. uncontrolled trials) report positive results, however without a control group, interpretation of results was limited.

Compared with this review, 3 RCTs are listed as awaiting classification (one RCT was not able to be retrieved and 2 RCTs were published in languages other than English), and 3 other RCTs were published in journals not indexed in any of the databases searched as part of this systematic review. As the identified systematic review was published in 2006, 3 of the studies identified as part of this review were not included in that analysis.

A second systematic review assessing the effectiveness of homeopathy in psychiatry also found that there is no support for the efficacy of homeopathy in anxiety or stress-related conditions (368).

5.5.6 Depression

One systematic review assessing the effectiveness of homeopathy for the treatment of depression and depressive disorders was identified (369). The systematic review included 2 RCTs comparing homeopathy to active control (anti-depressant). One of the studies also included placebo matched controls and this study has been included in this analysis (Katz 2005). As so few controlled studies were found, other studies such as uncontrolled and observational studies were also included.

The conclusion of the identified review aligns with this review. There is no evidence to support a benefit for homeopathy in the treatment of depression due to lack of clinical trials of high quality. The existing evidence is of poor methodological quality, which limits the interpretation of evidence.

5.5.7 Neurodevelopmental disorders (ADHD)

One systematic review (370) evaluating the effectiveness of homeopathy for the treatment of ADHD was identified in the literature. The review included 4 RCTs (total 168 participants) that compared homeopathy with a placebo or control group (inclusive of waitlist, no treatment, medication, educational or behavioural interventions). These 4 RCTs were identified and considered relevant for inclusion in this review, along with 3 additional RCTs that were published after the identified systematic review.

The results of the published review are in agreeance with this review, suggesting there is little evidence of benefit for homeopathy on global symptoms, core symptoms of inattention, hyperactivity or impulsivity, or related outcomes such as anxiety in people with ADHD (370).

5.5.8 Insomnia and sleep problems

One systematic review (371) assessing the effectiveness of homeopathy for insomnia was found in the literature. The systematic review included 4 RCTs comparing homeopathy with placebo (total 145 participants analysed). Of these, 3 RCTs were identified in this review, but were published in a language other than English and were not included in the data synthesis. The other RCT was published in a journal not indexed in any of the databases searched as part of this systematic review. As the identified systematic review was published in 2010, none of the studies identified as part of this review were included in that analysis.

The conclusions of the identified review align with this review, suggesting there is no evidence to support a benefit for homeopathy in the treatment of insomnia. The existing evidence is in small studies of overall poor methodological quality, which limits interpretation of the evidence.

5.5.9 Headache disorders

One systematic review assessing the effectiveness of homeopathy for headache disorders was found in the literature (372). The review was published in 2004 and included 4 RCTs comparing homeopathy with placebo (total 291 participants). All 4 RCTs were identified in this review, with one RCT (Brigo 1991) awaiting classification as it was published in a language other than English.

The conclusions of the identified review align with this review, suggesting there is no clear evidence to support for the use of homeopathy in the management of headache or migraine. The existing evidence is in small studies of overall poor methodological quality, which limits interpretation of the evidence.

5.5.10 Asthma

Two systematic reviews (9, 373) assessing the effectiveness of homeopathy in people with chronic asthma was identified in the literature.

One Cochrane review was published in 2004 (373) and included 6 RCTs (556 participants) that compared homeopathy with placebo. Three out of 6 RCTs were not included in the data synthesis for this review as they were published in a language other than English. The Cochrane review (373) assessed the outcome measures of lung function, symptoms, medication use, exacerbations, quality of life, global assessment of change and adverse events. Results from these outcomes showed no significant difference in asthma symptoms, and conflicting results for lung function between the studies. The authors concluded there was not enough evidence to reliably assess the role of homeopathy in people with asthma.

The more recent review (9) included evidence from 16 controlled trials, the majority of which were also published in a language other than English. The authors concluded the trials were positive, but inconsistent, due to methodological flaws relating to incomplete study reporting, inadequacy of independent replications, and small sample size.

Results from this review are in agreement with the results reported in the published reviews.

5.5.11 Diarrhoea

No systematic reviews assessing the effectiveness of homeopathy in people with diarrhoea were identified in the literature.

5.5.12 Infant colic or other digestive disorders.

No systematic reviews assessing the effectiveness of homeopathy in infantile colic or other digestive disorders were found in the literature.

5.5.13 Irritable Bowel Syndrome

One Cochrane systematic review (374) assessing the effect of homeopathic treatment for IBS was found in the literature that suggested there were no conclusions to be made about the usefulness of individualised homeopathic treatment for the treatment of IBS.

The review included 2 RCTs comparing homeopathy with placebo and 2 RCTs that compared homeopathy to inactive control (no intervention or usual care). The 2 RCTs comparing homeopathy to placebo were identified through the Department's public call for evidence (375, 376). The studies were conducted in Germany and published in 1976 and 1979 and, in the absence of English translations, are listed as awaiting classification. One other study with 2 citations (377, 378) was reported in Congress proceedings (Congress of the Faculty of Homoeopathy), but study details were not able to be retrieved for this review. The Cochrane review considered the results from the study to be uncertain. As such, the non-inclusion of this study is not likely to seriously influence the results reported in this review.

For the comparison of homeopathy vs control (delivered as adjunct to usual care), the Cochrane review included one study (Peckham 2012) that provided data for two outcomes (quality of life and symptom severity) (similar to this review). The available data was judged to be of low certainty, which is in agreeance with the results reported in this review.

5.5.14 Psoriasis

No systematic reviews assessing the effectiveness of homeopathy in the treatment of psoriasis were found in the literature.

5.5.15 Arthropathies

No systematic reviews assessing the effectiveness of homeopathy in people with arthritis were found in the literature.

5.5.16 Back and neck pain

No systematic reviews assessing the effectiveness of homeopathy in people with back and/or neck pain were identified in the literature.

5.5.17 Menopausal symptoms or complaints

No systematic reviews assessing the effectiveness of homeopathy for the treatment of menopausal symptoms were identified in the literature.

5.5.18 Menstrual disorders

No systematic reviews assessing the effectiveness of homeopathy in menstrual disorders were found in the literature.

5.5.19 Fatigue conditions

No systematic reviews assessing the effectiveness of homeopathy in the treatment of chronic postviral fatigue conditions were found in the literature.

5.5.20 Fibromyalgia

Two reviews (379, 380) assessing the effect of homeopathy as a treatment for fibromyalgia were found in the literature. These reviews assessed the same 3 RCTs that were also included in this review, both of which found that the results from these studies were subject to bias. The conclusions of these identified reviews align with this review whereby the evidence is of low or very low certainty about the effectiveness of homeopathy in people with fibromyalgia.

5.6 Limitations

5.6.1 At study and outcome level

The main limitation at the study and outcome level, is the low number of RCTs and small sample size per comparison, which reduces the statistical precision of the effect estimate and can also reduce our overall confidence in the certainty of evidence. There were also many evidence gaps, with no data for many outcomes listed as critical or important for this review. Of a total of 94 prioritised outcomes, 62 outcomes had available evidence compared with placebo; of these 54 included evidence from 1 or 2 RCTs (sample size range 24 to 377 participants) and 8 included evidence from 3 RCTs (sample size range 124 to 448 participants). Compared with inactive control, 27 outcomes had available evidence; of these all 27 included evidence from 1 or 2 RCTs (sample size range 36 to 566 participants).

5.6.2 At review level

This review was limited to the assessment of the evidence for certain conditions and groups of people to inform the Australian Government about health policy decisions for private health insurance rebates. This review was not designed to assess all the reasons that people use homeopathy, or the reasons practitioners prescribe homeopathy and was not intended to inform individual choices about homeopathic medicines. Conditions were prioritised by NTWC, who were guided by relevant patient and/or practitioner reported Australian survey data (where available) and expert advice from NTREAP during the prioritisation process.

The primary comparator of interest was homeopathy compared to placebo, with the secondary comparator being homeopathy versus inactive control (no intervention, wait list or usual care). The outcomes assessed were limited to those deemed critical or important by NTWC for each priority condition. Most conditions had evidence available for 3 or 4 critical or important outcomes. However, it is challenging to conclude the effectiveness of homeopathy compared with placebo for the prioritised conditions as the evidence was of very low certainty in 32 out of 94 (35%) outcomes and the effectiveness of 32 of 94 outcomes (35%) remain unknown. In addition, over 100 RCTs were found in the priority conditions that were awaiting classification or remain ongoing at the time of the search. Results of these studies may (or may not) support the use of homeopathy.

The effectiveness of homeopathy compared with other interventions was not assessed in this review. Data from these studies are listed in Appendix F2. It is unlikely the results of these studies would impact the overall conclusions of this review.

It was out of scope of the review to assess safety. Consistent with the previous review (1) , it was noted that evidence regarding safety was rarely reported in the primary studies. The sustainability of the effect is also unknown, as the review did not assess any longer-term data.

The breadth and diversity of conditions identified for inclusion in this review means that it is possible that some conditions, outcome domains and outcome measures have been misclassified or missed during the outcome prioritisation process.

A final limitation is that the literature search for primary studies was last conducted in July 2022, it is possible that given the identification of a number of studies awaiting classification and ongoing, there may be additional evidence available for inclusion in the review. However, it is considered unlikely that new evidence would substantially impact the overall conclusions of this review.

6 Authors' conclusions

6.1 Implications for health policy

This report was commissioned by the Australian Government as part of the Natural Therapies Review, with findings intended to inform decisions relating to whether private health insurance cover should be reinstated to homeopathy. As such, specific recommendations are not provided. For the populations (or conditions) assessed, homeopathy appears to provide little to no benefit for most of the included outcomes where evidence was available, when compared with placebo (the gold-standard methodology to establish the efficacy of a treatment). Similar results were seen in the few studies that compared homeopathy to inactive control (no intervention, waitlist, or usual care, if considered inactive). The evidence assessed in this review was rated as moderate to very low certainty. The prioritised conditions and outcomes were prioritised to align with the reasons why consumers commonly use homeopathy in Australia.

For the primary comparison of homeopathy versus placebo, there are 2 conditions for which the evidence provides low certainty of benefit compared to placebo for one outcome (allergic rhinitis and atopic dermatitis). In contrast there were 11 conditions where the evidence provides low certainty that homeopathy provides little (to no) benefit compared to placebo for one (atopic dermatitis, otitis media, psoriasis, menopausal symptoms), 2 (recurrent upper respiratory tract infections, asthma, diarrhoea, chronic fatigue conditions) or 3 (anxiety, insomnia, back or neck pain) outcomes.

The effect of homeopathy versus placebo was uncertain for 39 outcomes across 16 conditions (allergic rhinitis, atopic dermatitis, otitis media, recurrent upper respiratory tract infections, depression, neurodevelopmental disorders, headache disorders, asthma, diarrhoea, digestive complaints, psoriasis, arthropathies, back or neck pain, menopausal symptoms or complaints, menstrual disorders, and fibromyalgia). In addition, there are 8 conditions for which the effect of homeopathy versus placebo is unknown or the evidence is of very low certainty across all prioritised outcomes (depression, neurodevelopmental disorders, headache disorders, digestive complaints, irritable bowel syndrome, arthropathies, menstrual disorders and fibromyalgia).

For the secondary comparison of homeopathy versus inactive control there is one condition for which the evidence provides moderate certainty of benefit for one outcome (recurrent upper respiratory tract infections), however the certainty versus placebo for this outcome was very low. There were also 2 conditions for which the evidence suggests homeopathy may provide benefit versus inactive control for one outcome (recurrent upper respiratory tract infections and menstrual disorders), however the evidence versus placebo was that there may be no effect or was uncertain. For one condition, there was evidence that homeopathy probably provides little (to no) benefit for one outcome (depression) when compared with inactive control, however the certainty versus placebo for this outcome was very low. There was also evidence for 5 conditions that homeopathy versus inactive control may have little (to no) effect, generally consistent with the results for placebo (otitis media, depression, asthma, irritable bowel syndrome, fibromyalgia).

Compared with an inactive control, the effect of homeopathy was uncertain for 12 outcomes across 6 conditions (recurrent upper respiratory tract infections, recurrent lower urinary tract infections, neurodevelopmental disorders, asthma, digestive complaints, and menopausal symptoms or complaints). There are 10 conditions for which the effect of homeopathy compared with inactive control is unknown (allergic rhinitis, atopic dermatitis, anxiety, insomnia, headache disorders, diarrhoea, psoriasis, arthritis, back and neck pain and fatigue conditions).

Many of the studies where evidence was available were compared to placebo. For completeness, homeopathy versus inactive control was included as a secondary comparator. In some of the studies compared to inactive control, the inactive control was “usual care”. This means participants were encouraged to continue any usual medication or practices, but it is not always known or reported what those are and they can vary from person to person. Therefore, where usual care is included, it is often not possible to tell the effects of homeopathy alone, and instead the results show the effect of homeopathy as an adjunct to usual care.

6.2 Implications for research

There was a large amount of evidence for homeopathy not published at the time of the search. Among the priority populations included in this review, an estimated 51 RCTs (3788+ participants) comparing homeopathy with placebo or an inactive control are awaiting classification and a further 71 RCTs (6182 target participants) were listed as ongoing. Evidence reported in these studies are expected to contribute to future updates where studies are completed, and results published.

There are many trials on the effectiveness of homeopathy compared with placebo or an inactive control. To ensure that future research is able to answer questions about the effectiveness of homeopathy it is important that trials are well conducted (e.g. including outcomes and measures defined in core outcome sets, focus on greater retention or follow-up of participants in trials) and that reporting is comprehensive (e.g. including standard deviations or confidence intervals, providing end of treatment score, reporting both total scores and sub scores of outcome measures). A focus on priority populations relevant to Australia for which there is an absence of evidence would also be of benefit.

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