

Homeopathic medicines for adverse effects of cancer treatments (Review)

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[Intervention Review]

Homeopathic medicines for adverse effects of cancer treatments

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ABSTRACT

Background

Homeopathic medicines are used by patients with cancer, often alongside conventional treatment. Cancer treatments can cause considerable morbidity and one of the reasons patients use homeopathic medicines is to help with adverse effects.

Objectives

Evaluate effectiveness and safety of homeopathic medicines used to prevent or treat adverse effects of cancer treatments.

Search strategy

The following were searched up to November 2008: Cochrane PaPaS Trials Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; CINAHL; BNI; CancerLIT; AMED; CISCOP; Hom-Inform; SIGLE; National Research Register; Zetoc; www.controlled-trials.com; <http://clinicaltrials.gov>; Liga Medicorum Homeopathica Internationalis (LMHI, Liga) conference proceedings; reference lists of relevant studies were checked; and homeopathic manufacturers, leading researchers and practitioners were contacted.

Selection criteria

Randomised controlled trials (RCTs) of homeopathic medicines in participants with a clinical or histological diagnosis of cancer where the intervention was aimed at preventing or treating symptoms associated with cancer treatments. All age groups, and all stages of disease were included.

Data collection and analysis

Two review authors independently assessed studies for inclusion and two review authors extracted data. Three review authors independently assessed trial quality using the Delphi List and the Cochrane Collaboration's tool for assessing risk of bias. Disagreements were resolved by consensus. Where available, data were extracted for analysis.

Main results

Eight controlled trials (seven placebo controlled and one trial against an active treatment) with a total of 664 participants met the inclusion criteria. Three studied adverse effects of radiotherapy, three studied adverse effects of chemotherapy and two studied menopausal symptoms associated with breast cancer treatment.

Two studies with low risk of bias demonstrated benefit: one with 254 participants demonstrated superiority of topical calendula over trolamine (a topical agent not containing corticosteroids) for prevention of radiotherapy-induced dermatitis, and another with 32 participants demonstrated superiority of Traumeel S (a proprietary complex homeopathic medicine) over placebo as a mouthwash for chemotherapy-induced stomatitis. Two other studies reported positive results, although the risk of bias was unclear, and four further studies reported negative results.

No serious adverse effects or interactions were reported attributable to the homeopathic medicines used.

Authors' conclusions

This review found preliminary data in support of the efficacy of topical calendula for prophylaxis of acute dermatitis during radiotherapy and Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis. These trials need replicating. There is no convincing evidence for the efficacy of homeopathic medicines for other adverse effects of cancer treatments. Further research is required.

PLAIN LANGUAGE SUMMARY

Homeopathic medicines for adverse effects of cancer treatments

Homeopathic medicines are used by many patients with cancer, usually alongside conventional treatment. Cancer treatments can cause adverse effects, and one of the reasons patients use homeopathic medicines is to help with these symptoms. This review looked at whether these medicines could help patients with problems caused by cancer treatments. Eight studies with a total of 664 participants were included in this review. Three studied adverse effects of radiotherapy, three studied adverse effects of chemotherapy and two studied menopausal symptoms associated with breast cancer treatment. Two studies with low risk of bias demonstrated benefit: one with 254 participants demonstrated benefits from calendula ointment in the prevention of radiotherapy-induced dermatitis, and another with 32 participants demonstrated benefits from Traumeel S (a complex homeopathic medicine) over placebo as a mouthwash for chemotherapy-induced stomatitis. These trials need replicating. Two other studies reported positive results, although the risk of bias was unclear, and four further studies reported negative results. The homeopathic medicines used in all eight studies did not seem to cause any serious adverse effects or interact with conventional treatment. No cancer treatments were modified or stopped because of the homeopathic interventions.

BACKGROUND

Complementary therapies, including homeopathic medicines, are used by many patients with cancer, usually alongside orthodox treatments. A systematic review of 26 surveys from 13 countries reported that up to 64% of patients with cancer (average 31.4%) used complementary therapies at some stage of their illness (Ernst 1998). Another study found that homeopathy was in the top five most commonly used complementary therapies in seven out of 14 European countries by patients with cancer (Molassiotis 2005). Homeopathic medicines are used by patients with cancer for symptomatic relief and general supportive care, as well as for adverse effects of cancer treatments. The clinical research to date has focused on homeopathic medicines for adverse effects of cancer treatments (Milazzo 2006), although it is important to note that this may not fully represent contemporary clinical practice.

Homeopathy is based on the broad concept of treating like with like, whereby a substance that can cause symptoms in a healthy individual can be used to treat patients presenting with similar symptoms. For instance, the homeopathic medicine, *Apis mellifica*

(made from bees) is used to treat conditions characterised by acute onset, marked swellings and pain relieved by cold applications, similar to the effect of a bee sting. The concept is not exclusive to homeopathy and can be found as early as in the writings of the Hippocratic Corpus (5th century BC) and in Paracelsus (late 15th century AD). It was the German physician, Samuel Hahnemann, (1755 to 1843) who developed this idea systematically and into a medical system, and coined the term homeopathy.

Homeopathic prescribing strategies vary and at least four types can be differentiated. In 'classical' or 'individualised' homeopathy, a single homeopathic medicine is prescribed according to the individual's presentation and history. In 'clinical' homeopathy, the same homeopathic medicine is used for a group of patients with the same clinical condition e.g. *Rhus tox* for arthritis. In 'complex' homeopathy more than one homeopathic medicine is used in a fixed combination or concurrently for a particular condition. In 'isopathy' the homeopathic medicine is based on the causal agent e.g. grass pollens for hay fever (Linde 1997). Related medical sys-

tems which use homeopathic medicines include Homotoxicology which was founded by HH Reckeweg (1905 to 1985) and is based on interpreting disease as an expression of the defensive effort of the organism against pathogenic toxins and detoxification with homeopathic medicines.

Homeopathic medicines are thought to be generally safe, both as regards adverse effects and interactions with other drugs. In a systematic review of adverse effects of homeopathy, the authors concluded that homeopathic medicines in high dilutions (i.e. very dilute), prescribed by trained professionals, are probably safe and unlikely to provoke severe adverse reactions. The main risks are indirect, pertaining to the practitioners, rather than the medicines. There is likely to be under-reporting of adverse effects. There is also confusion between homeopathic and herbal medicines in the reporting of adverse effects (Dantas 2000). This is particularly pertinent to cancer management as there is an increased awareness that some herbal medicines e.g. St John's Wort may interfere with some chemotherapy agents. The main risks of homeopathy are indirect; including patients rejecting or delaying conventional therapy with its substantial benefits including possible cure.

The most controversial aspect of homeopathy is the use of high dilutions. Homeopathic medicines can be prepared from botanical, zoological, mineral, chemical, microbiological or synthetic materials. The starting point for most homeopathic medicines is the Mother Tincture, an alcoholic extract of the original substance. Insoluble substances are initially triturated (ground up) with lactose before being suspended in the alcoholic diluent. This undergoes a process termed potentisation which consists of serial dilutions alternating with succussion (a form of vigorous shaking). A decimal (tenfold) dilution is denoted by the letter 'x' after, or 'D' before, the number of dilutions e.g. 3x/D3. A centesimal (hundredfold) dilution is denoted by the letters 'c' or 'cH' after the number of dilutions e.g. 30c/30cH. If a number is used without a letter prefix or suffix, centesimal dilution is generally implied. Homeopathic medicines can be diluted beyond Avogadro's number (also known as Loschmidt's Constant: the number of atoms or molecules in a mole of substance, which is of the order of 10^{23}), and at this stage the original substance has almost certainly been diluted out. Such dilutions are termed ultramolecular, and 12c or 23x/D23 are unlikely to contain molecules of the starting substance, but the molecular threshold is usually crossed before this dilution, depending factors include initial concentration and molecular weight. The leading current hypothesis to explain the effects of ultramolecular dilutions is the 'Information Theory Hypothesis' which states: "Water, and other polar solvents can, under specific conditions store specific information about substances with which they have previously been in contact and subsequently transmit this information to presensitised biosystems" (Fisher 1998), although this hypothesis has no convincing evidence to support it and does not seem plausible within a modern scientific framework. Despite the inherent implausibility of ultramolecular dilutions and the contro-

versy surrounding their use, this review includes all types of homeopathic medicines because in clinical practice both ultramolecular dilutions and material doses are used for patients with cancer.

The question this review seeks to address is: Are homeopathic medicines effective and safe in the prevention and treatment of adverse effects of cancer treatments? The scope of this review has been kept deliberately broad to include adverse effects of all standard cancer management strategies including radiotherapy, chemotherapy, surgery, biological and hormonal therapies.

OBJECTIVES

To evaluate the effectiveness and safety of homeopathic medicines used to prevent or treat adverse effects associated with cancer treatments.

METHODS

Criteria for considering studies for this review

Types of studies

All types of randomised controlled trials (RCTs) undertaken in any setting.

Types of participants

- Participants with a clinical or histological diagnosis of any cancer who wanted to prevent or treat adverse effects associated with their cancer treatments.
- Participants of all ages, at any stage of disease, were included.

This review included studies where the intervention was aimed at preventing or treating symptoms related to cancer treatments. Some symptoms (e.g. fatigue), can be related to either the disease, its management, or both, making a clear distinction impossible. Any study where symptoms could at least be partially attributed to cancer treatments were included in this review.

Types of interventions

- Any use of homeopathic medicines versus placebo or active comparator or routine care or no treatment.

Homeopathy (also spelt homoeopathy) was defined, for the purpose of this review, as the use of homeopathic medicines prepared in accordance with officially recognised homeopathic pharmacopoeias. Where there was doubt about the classification of the medicine, we contacted authors or the product manufactures

for confirmation. Any homeopathic prescribing strategy was included.

Types of outcome measures

The following outcomes were considered:

- Any subjective or objective outcome measures aimed at assessing adverse effects of cancer treatments. These included quality of life and global scores if these were used to assess adverse effects. As not enough is known about the possible duration of effects, the review included short and long term outcome measures.
- Reports of adverse effects of homeopathy.
- Reports of adverse interactions of homeopathic medicines with cancer treatments.
- Modification or cessation of cancer treatments.

Search methods for identification of studies

We aimed to identify all potentially relevant studies, published and unpublished, irrespective of language.

Electronic searches

For the identification of studies included or considered for this review, detailed search strategies were developed for each database searched. These were based on the search strategy developed for MEDLINE by the review authors and the Trials Search Coordinator of the PaPaS Review Group using a combination of controlled vocabulary and free text terms and revised appropriately for each database (see Appendix 1).

Databases searched:

- Cochrane Pain, Palliative & Supportive Care Trials Register, searched on 19 November 2008.
- The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 4 2008, searched on 19 November 2008.
- MEDLINE 1966 to search date, searched on 19 November 2008.
- EMBASE 1980 to search date, searched on 19 November 2008.
- CINAHL 1982 to search date, searched on 24 November 2008.
- BNI 1985 to search date, searched on 1 December 2008.
- CancerLIT 1975 to search date, searched on 2 December 2008
- AMED 1985 to search date, searched on 26 November 2008

- CISCOM 1991 to search date. This database was unavailable when we came to do the search (Complementary and Alternative Medicine database produced by the Research Council for Complementary Medicine).
- Hom-Inform 1966 to search date, searched on 2 December 2008 (the homeopathy - specific database of the Glasgow Homeopathic Hospital).
- SIGLE 1976 to 2003, searched on 16 January 2009.
- National Research Register 1998 to search date, searched on 15 December 2007. This has been discontinued and archived.
- Zetoc 1993 to search date, searched on 1 December 2008.
- www.controlled-trials.com searched on 1 December 2008.
- <http://clinicaltrials.gov> searched on 1 December 2008.

Searching other resources

Unpublished studies

We attempted to contact homeopathic manufacturers and leading researchers and practitioners who were known to have expertise in using homeopathic medicines for patients with cancer.

Handsearching

The Liga Medicorum Homeopatheica Internationalis (LMHI, Liga) conference proceedings from 1970 to 2008 were hand searched by one review author (SK). We were unable to obtain proceedings of the years 1970, 1977, 1980, 1981, 1989, 1994, 1998, 2006 and 2007. The reference lists of all relevant studies were checked.

Foreign language studies

The search attempted to identify all relevant studies irrespective of language. The relevant sections of studies not in English were translated where necessary.

Data collection and analysis

Selection of studies

Abstracts of identified studies were read by two review authors (SB, SK) independently and full copies obtained if there was uncertainty as to whether the studies met the inclusion criteria. Foreign language studies were translated into English where necessary. Studies were assessed by two review authors (SB, SK) using a standard eligibility form. Further information was obtained from the manufacturer of one of the potential studies to establish whether the intervention met the inclusion criteria (Pommier 2004). Disagreement on the inclusion or exclusion of studies were discussed

by four review authors (SB, MC, PF, SK) until consensus was reached.

Data extraction and management

Data collection

Two review authors (MC, SK) independently extracted data on the following:

- participants: numbers randomised, age, sex, type of cancer, type of cancer treatment;
- intervention: homeopathic medicines - name, potency, frequency, duration, type of homeopathic prescribing strategy;
- outcome measures: outcome measures assessing adverse effects as reported;
- results: relevant trial outcome data from each study;
- dropouts;
- study withdrawals;
- reports of adverse effects of homeopathy;
- reports of adverse interactions of homeopathic medicines with cancer treatments;
- modification of cessation of cancer treatments.

For studies using individualised homeopathy, the following additional aspects were considered:

- experience of treating homeopath(s);
- level of individualisation of homeopathic medicine choice (unrestricted/partial);
- ability to change homeopathic medicine choice (unrestricted/partial/not possible); and
- appropriateness of outcome assessment from a homeopathic perspective (i.e. sufficient duration of follow-up and outcome measures used) (Bell 2003).

Information is reported in the 'Characteristics of included studies' table.

Data analysis

Where available, data were extracted for presentation by one review author (MC), and independently checked by a second review author (SK), however, no pooling of data was possible. The principal analysis was by narrative review.

Assessment of risk of bias in included studies

The quality of the studies was assessed by three review authors independently (SB, MC, SK) using the Delphi List (Verhagen 1998) and the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008). Disagreements were resolved by discussion. The Delphi List has nine criteria for looking at the quality of RCTs:

- Treatment allocation (two criteria):
 - Was a method of randomisation performed?
 - Was the treatment allocation concealed?
- Were the groups similar at baseline regarding the most important prognostic indicators?
- Were the eligibility criteria specified?
- Was the outcome assessor blinded?
- Was the care provider blinded?
- Was the patient blinded?
- Were point estimates and measures of variability presented for the primary outcome measures?
- Did the analysis include an intention to treat analysis?

Each of the questions were answered 'Yes/No/Don't know', and explanatory notes added where necessary (see Table 1).

Table 1. Quality assessment using the Dephi List

Study ID	Was a method of randomisation performed?	Was the treatment allocation concealed?	Were the groups similar at baseline?	Were eligibility criteria specified?	Was the outcome assessor blinded?	Was the care provider blinded?	Was the patient blinded?	Were the point estimates and measures of variability presented for the primary outcome measure?	Did the analysis include an intention to treat (ITT) analysis?
Balzarini 2000	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	No
	Method not described	“On opening the envelopes containing the randomisation code we discovered that 29 patients had been administered the verum and 32 the placebo”	Introduction specifies dose of radiotherapy used, although there is no reporting of baseline characteristics. All women had a quadrantectomy and axillary surgery		Reporting could be more specific, see quote from paper under treatment allocation	Reporting could be more specific, see quote from paper under treatment allocation	Reporting could be more specific, see quote from paper under treatment allocation	Means reported, but standard deviations only reported for some outcomes	Five dropouts described, but not included in analysis
Bourgois 1984	Yes	Don't know	Yes	Yes	Don't know	Don't know	Yes	Yes	No

	Method not described	Allocation concealment implied. Quote from the statistical section of the paper "Before opening the code the examiner has given his opinion on the number of Arnica and placebo"	Subjects were randomly recruited from an open study of 60 white, middle aged women suffering from breast cancer, and the paper states: "The populations are homogeneous"		Described as "double blind", but details are limited; one outcome was assessed by the patient; also see quote under allocation concealment	Described as "double blind", but details are limited	Described as "double blind", but details are limited. "The vials were similar and all labelled 'Arnica' implying patient blinding"		There is evidence of selection and attrition bias in the report
Daub 2005	Yes	Yes	Yes	Yes	Don't know	Don't know	Don't know	Yes	No
	Randomised list completed centrally by the statistician	Randomised list completed centrally by the statistician			No placebo suppositories were available	No placebo suppositories were available	No placebo suppositories were available		Ten dropouts described, but not included in the analysis. Data from all relevant patients were reported
Jacobs 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Computer-generated random numbers, known only to the homeopathic pharmacist	Code not broken until after initial data analysis was completed							

Table 1. Quality assessment using the Dephi List (Continued)

Kulkarni 1988	Yes	Don't know	Don't know	No	Don't know	Don't know	Don't know	No	Yes
	Method not described	Insufficient detail in the report	Insufficient detail in the report		Trial described as "randomised double study" but no details on blinding	Trial described as "randomised double study" but no details on blinding	Trial described as "randomised double study" but no details on blinding		There were no withdrawals, so ITT happened by default
Oberbaum 2001	Yes	Yes	Don't know	Yes	Yes	Yes	Yes	Yes	No
	Software program RAN-CODE version 3.0 in blocks of 2 (from lead author), controlled by the manufacturer of Traumeel S	The randomisation code was revealed on completion of the study	No details of chemotherapy administered	No exclusion criteria specified				Variability for primary outcomes can be calculated from data presented	Although stated as ITT, two withdrawals are described but not included in the analysis
Pommier 2004	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
	Computer-generated random allocation lists with block size of six each, stratified for skin type	The allocated agents were delivered directly to the patients by the pharmacist in similar packaging			Patients were instructed not to use the agent two hours or less before an irradiation session or before the treatment evaluation	Patients were instructed not to use the agent two hours or less before an irradiation session or before the treatment evaluation	Patient blinding was not considered possible because of the differences in texture, colour and smell of the two agents		Stated as ITT, and there was no comment on withdrawals or dropouts; all participants appear to have been included in the analysis

Table 1. Quality assessment using the Dephi List (Continued)

	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Thompson 2005									
	A random numbers table was kept by the pharmacy	Quote from the paper: "At no point could investigators foresee assignments and continued to be blinded throughout the trial"							

Studies were described as having a low risk of bias if all the six criteria in the risk of bias table were met.

Studies were described as high quality if all of the nine Delphi criteria were met, and there was a low risk of bias.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

The searches identified a total of 11 studies of which eight met the inclusion criteria for this review.

Results of the search

Electronic searches identified a total of seven potential studies ([Balzarini 2000](#); [Bourgeois 1984](#); [Felisi 1994](#); [Jacobs 2005](#); [Kulkarni 1988](#); [Oberbaum 2001](#); [Thompson 2005](#)). Hand searching identified one additional potential study ([Srihari 1995](#)). Two additional potential studies were identified via the internet ([Daub 2005](#); [Genre 2003](#)). One potential study was identified by an expert in the field ([Pommier 2004](#)).

Included studies

Eight controlled trials (seven placebo controlled and one trial against an active treatment) with a total of 664 participants met the inclusion criteria. Full English papers were available for six studies ([Balzarini 2000](#); [Jacobs 2005](#); [Kulkarni 1988](#); [Oberbaum 2001](#); [Pommier 2004](#); [Thompson 2005](#)). One full paper was available

in French and translated ([Bourgeois 1984](#)) and one in German ([Daub 2005](#)).

Three studies with a total of 402 participants tested homeopathic medicines for adverse effects of radiotherapy ([Balzarini 2000](#); [Kulkarni 1988](#); [Pommier 2004](#)). Two studies with 97 participants tested homeopathic medicines for adverse effects of chemotherapy ([Daub 2005](#); [Oberbaum 2001](#)). One study with 29 participants tested a homeopathic medicine for adverse effects of venous cannulation (insertion of a cannula into a blood vessel) in patients receiving chemotherapy ([Bourgeois 1984](#)). Two studies with a total of 136 participants tested homeopathic medicines for menopausal symptoms due either to oestrogen withdrawal or hormonal therapies as part of the management of breast cancer ([Jacobs 2005](#); [Thompson 2005](#)).

Excluded studies

Of the identified studies, three were excluded for the following reasons: one was not described as randomised ([Srihari 1995](#)); one was excluded because it was only available in abstract form and the results were not included in the abstract ([Genre 2003](#)): the lead author was contacted but not willing to provide us with the results as the data was not published; and one appeared to be an earlier report of the [Balzarini 2000](#) study ([Felisi 1994](#)). We were unable to contact either lead author to confirm this.

Risk of bias in included studies

The methodological quality of included studies was assessed using the Delphi List ([Verhagen 1998](#)) (details in [Table 1](#)); also see the

Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008) (details in risk of bias tables and in Figure 1 and Figure 2).

Figure 1. Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.

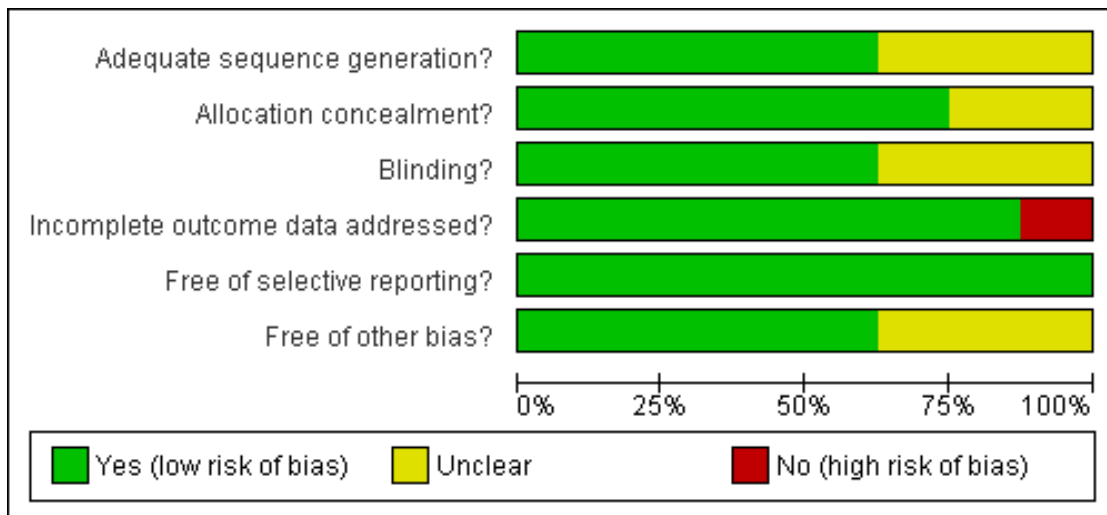


Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Balzarini 2000	?	+	+	+	+	?
Bourgois 1984	?	?	?	-	+	?
Daub 2005	+	+	?	+	+	+
Jacobs 2005	+	+	+	+	+	+
Kulkarni 1988	?	?	?	+	+	?
Oberbaum 2001	+	+	+	+	+	+
Pommier 2004	+	+	+	+	+	+
Thompson 2005	+	+	+	+	+	+

Four studies had a low risk of bias (Jacobs 2005; Oberbaum 2001; Pommier 2004; Thompson 2005), three studies had an unclear risk of bias (Balzarini 2000; Daub 2005; Kulkarni 1988) and one study had a high risk of bias (Bourgois 1984).

Allocation

All eight included studies were reported as randomised, although the method of randomisation was explicitly described in only three (Jacobs 2005; Pommier 2004; Thompson 2005). Allocation concealment was clearly described in four studies (Jacobs 2005; Oberbaum 2001; Pommier 2004; Thompson 2005), and there were statements suggesting allocation concealment in two other studies (Balzarini 2000; Daub 2005).

Blinding

Blinding of patients, care providers and observers was described in three studies (Jacobs 2005; Oberbaum 2001; Thompson 2005). Two studies included statements that implied blinding of patients and care providers, but this was not explicit (Balzarini 2000; Bourgois 1984). No explicit information on blinding was reported in two studies (Daub 2005; Kulkarni 1988). Two studies were single blind (outcome assessor blinded). In one study it was not possible to blind the participants because of the differences in texture, colour and odour of the two interventions (Pommier 2004), and in the other there was no placebo suppository available (Daub 2005).

Effects of interventions

Eight studies with a total of 664 participants met the inclusion criteria.

Studies on adverse effects of radiotherapy

Three studies with a total of 402 participants tested homeopathic medicines for adverse effects of radiotherapy (Balzarini 2000; Kulkarni 1988; Pommier 2004).

Kulkarni 1988 was a study of homeopathic medicines to prevent adverse reactions of radiotherapy. The study was set in a radiotherapy department in India. Eighty two participants with a range of cancers, including head and neck, thoracic and pelvic, were randomised into either homeopathic Cobaltum 30, homeopathic Causticum 30 or placebo. Outcomes were measured weekly during radiotherapy using an 18 point radiation reaction profile that assessed a wide range of adverse effects. The average grading was calculated in each group at the end of the study. The authors reported "about 30%" reduction in the degree of reactions in both groups taking homeopathic medicines compared with placebo. Data were not available in a suitable form for analysis in this review.

Balzarini 2000 was set in a hospital in Italy. It was a study of homeopathic medicines for skin reactions associated with radiotherapy. Sixty six women with breast cancer who had undergone a quadrantectomy and axillary dissection were randomised to receive either a combination of two homeopathic medicines, Belladonna 7c twice daily and X ray 15c once daily, or placebo. Both groups

used a topical medication containing fluocortolone, generally prescribed at the start of radiotherapy. Skin reactions to radiotherapy were assessed by physicians using ordinal scales rating skin colour and heat to touch, and nominal scales rating hyperpigmentation and oedema. Assessments were made weekly during the six week radiotherapy course and at 15 and 30 days after radiotherapy was completed. Total severity during radiotherapy and during recovery were calculated as the sum of all four parameters. The authors reported that there was no significant difference in the total severity of skin reactions during radiotherapy, but a statistically significant reduction in total severity during recovery for the group treated with homeopathy ($P = 0.05$). A statistical correction for multiple comparisons is reported, but may not have been applied. Extracted data is displayed in 'Data and analyses'.

Pommier 2004 was a study of a homeopathic ointment for the prevention of acute dermatitis during radiotherapy for breast cancer. It was set in a regional cancer centre in France. Two hundred and fifty four women with a diagnosis of non metastatic breast cancer who had been treated with either a lumpectomy or mastectomy, were randomised to receive either calendula ointment or trolamine (a topical agent which does not contain corticosteroids that had been used routinely for many years in their institution). Topical agents were applied twice daily or more until completion of radiotherapy depending on occurrence of dermatitis or pain. It was a single blind trial as the agents were different in texture, colour and smell. The primary outcome measure was the occurrence of acute dermatitis of grade two or higher, assessed weekly by physicians at radiotherapy consultations, according to the Radiation Therapy Oncology Group (RTOG). The authors reported the occurrence of acute dermatitis grade two or higher was significantly lower (41% versus 63% $P < 0.001$) with the use of calendula than with trolamine. Extracted data is displayed in 'Data and analyses'.

Studies on adverse effects of chemotherapy

Two studies with 97 participants tested homeopathic medicines for adverse effects of chemotherapy (Daub 2005; Oberbaum 2001). One study with 29 participants tested a homeopathic medicine for adverse effects of venous cannulation in patients receiving chemotherapy (Bourgois 1984).

Oberbaum 2001 was a study of homeopathic medicines for the treatment of chemotherapy-induced stomatitis in participants undergoing stem cell transplantation. The study was set in a children's medical centre in Israel. Thirty two participants (mean age 10 years) were randomised to receive Traumeel S (a proprietary complex homeopathic medicine; see details of this in the 'Characteristics of included studies' table) as a mouthwash or placebo on Day 2, alongside a twice daily mouth wash and gentle tooth brushing. Severity of stomatitis was assessed using the WHO five point grading scale for mucositis. Primary comparisons were area under the curve (AUC) and time to first worsening of stomatitis symptoms. The authors reported statistically significant benefits in both comparisons for the group receiving homeopathy. Extracted data is displayed in 'Data and analyses'.

[Daub 2005](#) was a study of homeopathic antiemesis for chemotherapy. It was set in a university hospital women's clinic in Germany. Sixty five women with primary or recurrent breast cancer undergoing chemotherapy were randomised to receive either Vomitusheel S suppository and Gastricumeel oral tablets (each intervention, a combination of six homeopathic medicines, details can be seen in the '[Characteristics of included studies](#)' table, or Sambucus Nigra D3 oral tablets (a homeopathic medicine used as the placebo). For the first day, all participants received standard antiemetics. If nausea or vomiting occurred on subsequent days, participants received either the homeopathic medicines or placebo. If no resolution of symptoms was achieved within two hours, participants were treated with conventional antiemetics. Outcomes were assessed as the percentage of patients requiring additional conventional medication after the first day. The authors reported that 68.2% of patients in the homeopathy group required additional conventional treatment compared with 59.1% in the control group. There was no significant difference between the two groups. Extracted data is displayed in '[Data and analyses](#)'.

[Bourgeois 1984](#) was a study of homeopathic medicines to protect venous function in women undergoing intravenous chemotherapy for breast cancer. The study was set in France and women who had reacted positively to homeopathic Arnica in an open study were randomly recruited. Twenty nine women were randomised to receive either Arnica 5c or placebo for three days before and three days after intravenous chemotherapy for two cycles. Outcomes assessed were pain produced by the injection or haematoma(s) (a collection of blood outside the blood vessels), venous tone assessed by the number of haematomas, and venous accessibility assessed by the number of attempts at cannulation (insertion in to the blood vessel). The authors reported significant improvements from baseline in the treatment group, but there were no statistically significant differences between active and placebo groups. Extracted data is displayed in '[Data and analyses](#)'.

Studies on menopausal symptoms

Two studies with a total of 136 participants tested homeopathic medicines for the treatment of menopausal symptoms associated with breast cancer treatments ([Jacobs 2005](#); [Thompson 2005](#)).

[Jacobs 2005](#) was a study of homeopathic medicines for menopausal symptoms in women with breast cancer. The study was set in the USA in a population recruited through oncologists in medical centres. Eighty three women who had been treated for breast cancer were randomised to one of three arms to receive either an individualised single homeopathic medicine, Hyland's Menopause (a proprietary complex homeopathic medicine; see details in the '[Characteristics of included studies](#)' table), or placebo in a double dummy method. The primary outcome measure was the hot flush severity score (frequency times severity) as measured by a one week hot flush diary at entry to the trial and at 1, 2, 3, 6, 9 and 12 months after randomisation. The authors reported that there were no significant differences in the hot flush severity score between the groups. Data was not available in a suitable form for analysis

in this review.

[Thompson 2005](#) was a study of homeopathic medicines for symptoms of oestrogen withdrawal in women who had been treated for breast cancer. The study was set in a homeopathic hospital outpatient department in Scotland. Fifty three women experiencing more than three hot flushes per day were randomised to receive either individualised homeopathic medicines or placebo. The primary outcomes were the activity score and profile score using MY-MOP (Measure Your Medical Outcomes Profile) a four item patient generated instrument. The authors reported that there were no statistically significant differences between groups, but clinically relevant improvements in symptoms and mood disturbance were seen for both groups in the 16 week study period. Extracted data is displayed in '[Data and analyses](#)'.

DISCUSSION

This review analysed eight studies of homeopathic medicines for the prevention or treatment of adverse effects of chemotherapy, radiotherapy, and menopausal symptoms caused by hormonal therapies or oestrogen withdrawal. Homeopathic medicines were evaluated because despite many available conventional therapies, troublesome symptoms are still commonly experienced and homeopathy is perceived by some patients as a safe, acceptable adjunct to conventional management.

Summary of main results

Included studies

Eight studies with a total of 664 participants met the inclusion criteria: three studies tested homeopathic medicines for adverse effects of radiotherapy; three studies tested homeopathic medicine for adverse effects of chemotherapy; and two studies tested homeopathic medicines for menopausal symptoms due either to oestrogen withdrawal or hormonal therapies as part of the treatment of breast cancer.

One of the three studies on adverse effects of radiotherapy was of high quality and low risk of bias. It demonstrated superiority of a topical calendula preparation over trolamine (a topical agent which does not contain corticosteroids) in preventing acute dermatitis during radiotherapy in 254 women with breast cancer ([Pommier 2004](#)). The other two studies reported positive results for skin reactions and other adverse effects of radiotherapy, however, these studies had an unclear risk of bias ([Balzarini 2000](#); [Kulkarni 1988](#)). There were three studies on adverse effects of chemotherapy. One study with 32 participants had a low risk of bias and demonstrated benefit from Traumeel S (a proprietary complex homeopathic medicine) used as a mouth wash in the treatment of chemotherapy-induced stomatitis ([Oberbaum 2001](#)). The remaining two studies were negative, one had an unclear risk of bias ([Daub 2005](#)) and the other had a high risk of bias ([Bourgeois 1984](#)).

The two studies of homeopathic medicines on menopausal symptoms were of high quality and low risk of bias. The primary outcomes in these trials did not provide evidence for the efficacy of homeopathic medicines over placebo (Jacobs 2005; Thompson 2005).

No serious adverse effects that could be attributed to homeopathic medicines or interactions with conventional treatment were reported in the included studies.

No cancer treatments were stopped due to homeopathic interventions and one study showed less frequent interruptions of radiotherapy in the group receiving the homeopathic intervention (Pommier 2004).

The positive studies with low risk of bias in this review used homeopathic medicines with material doses. Calendula has anti-inflammatory actions when applied topically which may explain any effects seen in this trial. Many of the constituents in Traumeel S also have anti-inflammatory effects, but whether this mechanism of action operates at these doses is uncertain.

Unpublished and ongoing studies

There are two studies underway on Traumeel S, one a replication of the Oberbaum 2001 study (Sadhev 2004), and one looking at the safety of Traumeel S for mucositis in head and neck cancer patients undergoing radiation therapy (Krempl 2005).

The Genre 2003 study using Cocculine (a proprietary complex homeopathic medicine) in the prevention of nausea and vomiting among patients receiving adjuvant chemotherapy for breast cancer is as yet unpublished. There is another study underway using the same homeopathic intervention; a placebo-controlled evaluation of Cocculine efficacy in the management of nausea after chemotherapy in breast cancer (Ray-Coquard 2005). See details of these studies in the 'Characteristics of ongoing studies' table.

Overall completeness and applicability of evidence

This review was based on a wide ranging and comprehensive literature search.

It is difficult to draw firm conclusions because of the paucity of evidence, clinical heterogeneity and lack of repetition of the included trials. We found eight eligible studies which examined a total of 10 interventions. Most studies were small (only one had over 100 participants, Pommier 2004), and only two examined the same treatment for the same condition (individualised homeopathy for menopausal or oestrogen withdrawal symptoms) (Thompson 2005; Jacobs 2005). But even here there is considerable heterogeneity, as both allowed unrestricted individualised homeopathic prescribing resulting in substantial differences in treatments used. In one study (Jacobs 2005), a total of 35 different homeopathic medicines were prescribed, in the other (Thompson 2005), 71. Of the five most frequently prescribed medicines, only two were common to both studies. Furthermore the studies used qualitatively different outcomes: Jacobs 2005 focused on menopausal symptoms, Thompson 2005 used MYMOP as the primary out-

come, this is based on change in symptoms nominated by the patient. Further data regarding individualised homeopathy is listed in the 'Characteristics of included studies' table.

Quality of the evidence

The methodological quality of included studies was assessed using the Delphi List (Verhagen 1998) (see Table 1), and the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008). Three of the eight included studies were of high quality and low risk of bias (Jacobs 2005; Pommier 2004; Thompson 2005) but only one of these studies was positive (Pommier 2004). One further study with 32 participants had a low risk of bias and reported a positive result for a homeopathic mouthwash (Oberbaum 2001). Three studies had an unclear risk of bias; two reported a positive result (Balzarini 2000; Kulkarni 1988) and one reported a negative result (Daub 2005). There was one further negative trial, which had a high risk of bias (Bourgois 1984).

Potential biases in the review process

This review found few studies, and most were small. The populations studied and the interventions tested were heterogeneous. Reporting was poor in a number of the papers.

Agreements and disagreements with other studies or reviews

A previous systematic review looked at RCT's and controlled clinical trials for the efficacy of homeopathic medicines used as a sole or additional therapy in cancer care (Milazzo 2006). It did not include three of the eight RCT's included in this review (Bourgois 1984; Daub 2005; Pommier 2004). The authors of the systematic review reported that there was insufficient evidence to support clinical efficacy of homeopathic therapy in cancer care (Milazzo 2006).

AUTHORS' CONCLUSIONS

Implications for practice

Prophylactic use of calendula ointment may be considered as an option for patients undergoing radiotherapy for breast cancer, although this intervention requires further evaluation. Compared with trolamine, it reduced the incidence of acute dermatitis of grade two or above in women undergoing radiotherapy for breast cancer in one clinical trial involving 254 participants. The calendula ointment used in this study was prepared according to the German Homeopathic Pharmacopoeia and so the results may not apply to topical preparations of calendula extracts prepared by different methods.

There is no convincing evidence for the efficacy of other homeopathic medicines for adverse symptoms and skin reactions related

to radiotherapy. Two small studies were positive but both had an unclear risk of bias.

Based on a single trial involving 32 participants, one particular homeopathic combination (Traumeel S - a proprietary complex homeopathic medicine) appears to show promise in the treatment of chemotherapy-induced stomatitis.

High quality trials to date provide no evidence for the efficacy of homeopathic medicines over placebo in women with breast cancer suffering from menopausal symptoms.

No serious adverse effects that could be attributed to homeopathic medicines or interactions with conventional treatment were reported in the included studies. No cancer treatments were modified or stopped because of the homeopathic interventions.

Implications for research

Further studies are warranted using calendula ointment for acute dermatitis in patients undergoing radiotherapy. It may be worthwhile considering different formulations since 30% of participants reported that the ointment was difficult to apply.

Further independent trials of Traumeel S for cancer treatment associated mucositis are warranted, and one is underway (Sadhev 2004).

Further RCTs of homeopathic medicines for adverse symptoms and skin reactions related to radiotherapy are needed to confirm the results described in this review. Since patients frequently use

homeopathic medicines for general supportive care, rather than control of specific symptoms, outcome measures should be broader than those used in some of the included studies, and should differentiate between symptoms as well as using global and quality of life scores. Radiotherapy-associated fatigue might be considered as a separate outcome, and observation beyond the end of radiotherapy should be included.

In the design of future studies of individualised homeopathy, consideration should be given to the possibility of an interaction between effects attributable to the homeopathic consultation and those of the homeopathic medicine itself.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Balzarini 2000

Methods	Country: Italy Recruitment: sequential recruitment of participants undergoing radiotherapy Design: prospective randomised double blind (subject and observer blind) placebo controlled trial with two parallel arms Duration of trial: 10 weeks (30 days following a six week course of radiotherapy)
Participants	66 women who had undergone conservative surgery for breast cancer and were being treated with radiotherapy Age: mean 52.7 years, range 28.3 to 70 (7.0 in text, presumed error) years
Interventions	Prescribing strategy: clinical homeopathy a) homeopathic medicines - Belladonna 7c three granules twice daily and X-ray 15c three granules once daily b) placebo
Outcomes	Primary outcome measures Skin reactions to radiotherapy assessed by physician observers using ordinal and nominal scales as follows: Skin colour: normal 0; pink 1; red / violet 2 Heat to touch: normal 0; faint 1; intense 2 Oedema: absent 0; present 1 Hyperpigmentation: absent 0; present 1 The efficacy of the treatment was assessed by the comparison of these parameters taken individually and by calculating an Index of Total Severity (sum of the scores of the four parameters) weekly during radiotherapy, and during recovery, 15 and 30 days after the end of the radiotherapy
Notes	Reported results Primary outcome measures Total severity during radiotherapy and during recovery were calculated as the sum of all four parameters. The authors reported that there was no significant difference in the total severity of skin reactions during radiotherapy, but a statistically significant reduction in total severity during recovery for the group treated with homeopathy ($P = 0.05$). A statistical correction for multiple comparisons is reported, but may not have been applied. Adverse reactions One participant dropped out of the study due to what was described as an aggravation of her menopausal symptoms.
<i>Risk of bias</i>	

Balzarini 2000 (Continued)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised, but the actual method is not described; there is reference to "opening envelopes containing the randomisation code" in the results section of the paper
Allocation concealment?	Yes	See above
Blinding? All outcomes	Yes	Described as double blind and see comment under sequence generation above
Incomplete outcome data addressed? All outcomes	Yes	Five participants were not included in the analysis; reasons for their withdrawal were given, but group allocation was not described
Free of selective reporting?	Yes	All of the outcomes described in the methods were reported.
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Bourgeois 1984

Methods	Country: France Recruitment: randomly recruited from patients responding positively to Arnica in a previous open trial Design: randomised, patient and outcome assessor blind, placebo controlled trial Duration of trial: two months
Participants	29 women with breast cancer undergoing intravenous chemotherapy Age: 54.41 years with a range of 7.61 years
Interventions	Prescribing strategy: clinical homeopathy a) homeopathic Arnica 5c b) placebo Both administered as three granules four times a day for three days before and three days after treatment for two chemotherapy cycles
Outcomes	Primary outcome measures 1. Pain produced by injection or haematoma graded by patient on a vertical line between 0 (no pain) and 160 (intense pain) 2. Venous tone assessed by the number of haematomas 3. Venous accessibility graded from one (first attempt easy) to ten (five and more than five attempts)

Bourgois 1984 (Continued)

Notes	<p>Reported results Primary outcome measures The authors reported significant improvements from baseline in the treatment group, but there were no statistically significant differences between active and placebo groups. Adverse reactions None reported Thesis published in French</p>	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote (from translation): "In a random manner, 17 patients received Arnica and 12 patients placebo according to the envisaged protocol". No further details reported
Allocation concealment?	Unclear	Allocation concealment implied. Quote from the statistical section of the paper "Before opening the code the examiner has given his opinion on the number of Arnica and placebo"
Blinding? All outcomes	Unclear	Described as "double blind". Quote from the translation "The vials were similar and all labelled 'Arnica". However insufficient information on outcome assessor blinding from the report to be sure
Incomplete outcome data addressed? All outcomes	No	Selective inclusion and exclusion of data from dropouts
Free of selective reporting?	Yes	All of the outcomes described in the methods were reported.
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Daub 2005

Methods	<p>Country: Germany Recruitment: University hospital women's clinic Design: prospective randomised placebo controlled trial with two parallel arms Duration of trial: at least three cycles of chemotherapy planned at three weekly intervals</p>
Participants	<p>65 women undergoing chemotherapy for breast cancer Age: 28-67 years</p>

Interventions	<p>Prescribing strategy: homotoxicology</p> <p>On day 2, if symptomatic (conventional antiemetics were used for the first day)</p> <p>a) Vomitusheel S - a proprietary complex homeopathic medicine containing Ipecacuanha D2 (1.1 mg), Aesthusea D2 (1.1 mg), Nux vomica D2 (1.1 mg), Apomorphium hydrochloricum D4 (1.65 mg), Colchicum D4 (2.75 mg), Ignatia D4 (3.3 mg) given as a suppository and Gastricumeel - a proprietary complex homeopathic medicine containing Argentum nitricum D6 (30 mg), Acidum arsenicosum D6 (30 mg), Pulsatilla D4 (60 mg), Nux vomica D4 (60 mg), Carbo vegetabilis D6 (60 mg), Antimonium crudum D6 (60 mg) given as oral tablets</p> <p>b) Sambucus nigra D3 oral tablets used as the placebo</p> <p>If symptoms did not resolve within two hours conventional antiemetics were given</p> <p>The placebo was another homeopathic medicine that the authors chose because "no antiemetic properties had been described"</p>	
Outcomes	<p>Primary outcome measure</p> <p>Percentage of patients who did not require additional conventional medication for nausea and vomiting related to chemotherapy, the results reported as the percentage of patients who did require additional conventional medication</p> <p>Secondary outcomes measure</p> <p>Intensity of nausea questionnaire</p> <p>Vomiting</p> <p>Quality of Life</p> <p>Side effects</p>	
Notes	<p>Reported results</p> <p>Primary outcome measures</p> <p>68.2% of patients in the homeopathy group required additional conventional treatment compared with 59.1% in the control group. There was no significant difference between the two groups (p=0.6)</p> <p>Secondary outcome measures</p> <p>There was nothing of significance to report</p> <p>Adverse reactions</p> <p>No mention of adverse effects of homeopathy were reported</p>	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised list completed centrally by the statistician
Allocation concealment?	Yes	Randomised list completed centrally by the statistician
Blinding? All outcomes	Unclear	No placebo suppositories were available

Daub 2005 (Continued)

Incomplete outcome data addressed? All outcomes	Yes	Dropouts were described but were not included in the analysis
Free of selective reporting?	Yes	All of the outcomes described in the methods have been reported
Free of other bias?	Yes	The study appears to be free of other sources of bias

Jacobs 2005

Methods	Country: USA Recruitment: letters from oncologists in medical centres and posters in the same locations Design: prospective randomised subject, care provider, statistician blind placebo controlled trial with three parallel arms Duration of trial: one year
Participants	83 women with a history of carcinoma in situ or Stage I to III breast cancer who had completed all surgery, chemotherapy and radiotherapy (women taking Tamoxifen were also included) who had hot flushes for at least one month, with an average of at least three hot flushes per day in the week prior to beginning treatment Age: mean 55.5 years
Interventions	Prescribing strategy: individualised or complex homeopathy a) individualised homeopathy - single medicine given once monthly or bimonthly b) Hyland's Menopause, a proprietary combination homeopathic medicine (Amyl Nitrate 3x, Sanguinaria canadensis 3x and Lachesis 12x) given three times a day c) placebo Double dummy method was used so that all groups took two medicines or placebos daily and monthly. For the individualised homeopathy, there was unrestricted remedy choice and unrestricted ability to change remedy. Outcome assessments were appropriate from a homeopathic perspective. All homeopathic practitioners had at least 10 years experience in classical homeopathy.
Outcomes	Primary outcome measure Hot flush severity score (frequency times severity of hot flushes from symptom diary) at entry to the study and at 1, 2, 3, 6, 9 and 12 months after randomisation Secondary outcome measures Total number of hot flushes Kupperman Menopausal Index (KMI) SF-36 (Short Form 36) quality of life score FSH (Follicle Stimulating Hormone) level before and after treatment

Notes	<p>Reported results</p> <p>Primary outcome measure</p> <p>There was no significant difference found in the primary outcome measure, the hot flush severity score, although there was a positive trend in the single remedy group during the first 3 months of the study ($p = 0.1$). A statistically significant improvement in general health score in both homeopathy groups ($P < 0.05$) on the SF-36 after 1 year was found. There was an attrition rate of 33.7%.</p> <p>The authors performed a subgroup analysis (post hoc) defined by use of tamoxifen. One of these comparisons was reported as statistically highly significant. In the group not receiving Tamoxifen, there was a statistically significant increase in the hot flush severity score in the homeopathic combination group.</p> <p>Secondary outcome measures</p> <p>There were no statistically significant differences between the three groups in the KMI score or in individual symptoms of the KMI score except for an increase in headaches in the group taking the homeopathic combination at 6 and 12 months.</p> <p>The general health score of the SF36 was significantly increased in both homeopathy groups compared with placebo.</p> <p>There were no other significant findings from the secondary outcome measures.</p> <p>Adverse reactions</p> <p>There was an increase in the number and severity of hot flushes in the subgroup not taking Tamoxifen and receiving the proprietary combination (post hoc).</p>
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers, known only to the homeopathic pharmacist
Allocation concealment?	Yes	Code not broken until after initial data analysis was completed
Blinding? All outcomes	Yes	Subject, care provider, statistician blind
Incomplete outcome data addressed? All outcomes	Yes	Regression analysis performed, and (according to the study flow chart) all patients were analysed.
Free of selective reporting?	Yes	All of the outcomes described in the methods have been reported.
Free of other bias?	Yes	The study appears to be free of other sources of bias.

Kulkarni 1988

Methods	Country: India Recruitment: participants undergoing a course of radiotherapy treatment at Bombay Hospital radiotherapy department Design: prospective randomised placebo controlled trial with three parallel arms Duration of trial: 43 days (as indicated on sample proforma for collecting outcome data)
Participants	82 participants with head and neck, pelvic or thoracic cancers undergoing a course of radiotherapy treatment Age: not reported
Interventions	Prescribing strategy: clinical homeopathy a) homeopathic Cobaltum 30 b) homeopathic Causticum 30 c) placebo Each treatment taken as 3 pills each morning throughout the entire course of radiotherapy. The dilution method of the homeopathic medicines was not stated and we were unable to contact the lead author.
Outcomes	Primary outcome measure Radiation reaction profile - a symptom list with 18 items (one blank) each graded 0-3 On this measure, a total of 0-5 indicates very minimal reaction, 6-10 moderate but tolerable reactions, 11 and above severe degree of reaction usually resulting in interruption of the therapy. Scores recorded once weekly during the course of radiotherapy
Notes	Reported results Primary outcome measure Average grading of radiation reactions: placebo 8.5, Cobaltum 4.7, Causticum 5.4 The authors reported "about 30%" overall reduction in the degree of reactions in both groups taking homeopathic medicines compared with placebo Adverse reactions No adverse effects of homeopathic medicines were reported. Modification or cessation of cancer treatments In the conclusion it was stated that "It certainly improves patient's compliance to continue radiation treatments as per the treatment plans". However, there was no data to confirm this statement.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote from paper: "patients were randomly divided into 3 arms". No further details reported
Allocation concealment?	Unclear	The method of concealment was not described

Kulkarni 1988 (Continued)

Blinding? All outcomes	Unclear	Trial described as "randomised double study" and placebo is indistinguishable from homeopathy in outward appearance but insufficient information to be sure
Incomplete outcome data addressed? All outcomes	Yes	No withdrawals or missing outcome data, so intention to treat analysis by default; all participants appear to have been included in the analysis
Free of selective reporting?	Yes	All the primary outcome measures have been reported in the pre-specified way
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Oberbaum 2001

Methods	Country: Israel Recruitment: consecutive participants who were admitted to Schneider Children's Medical Center Design: prospective randomised placebo controlled trial with two parallel arms Duration of trial: 20 day treatment protocol; 44 week follow up
Participants	32 participants suffering from malignant diseases who had undergone allogeneic or autologous stem cell transplantation Age: 3 to 25 years Mean age in years (SD) Traumeel S 10.1 (7.0) placebo 9.7 (5.7) Distribution 3-4 years Traumeel S 3 placebo 5 5-9 years Traumeel S 6 placebo 3 10-14 years Traumeel S 2 placebo 3 15-19 years Traumeel S 3 placebo 3 20-25 years Traumeel S 1 placebo 1
Interventions	Prescribing strategy: homotoxicology a) Traumeel S - a proprietary complex homeopathic medicine. Each 2.2 ml ampoule contains: Arnica montana D2 (2.2 mg), calendula officinalis D2 (2.2 mg), Achillea millefolium D3 (2.2 mg), Matricaria chamomilla D2 (2.2 mg), Symphytum officinale D6 (2.2 mg), Atropa belladonna D2 (2.2 mg), Aconitum napelus D2 (1.32 mg), Bellis perenis D2 (1.1 mg), Hypericum perforatum D2 (0.66 mg), Echinacea angustifolia

Oberbaum 2001 (Continued)

	<p>D2 (2.2 mg), Echinacea purpurea D2 (2.2 mg), Hammamelis virginica D1 (0.22 mg), Mercurius solubilis D1 (1.1 mg) and Hepar sulphuris D6 (2.2 mg) b) placebo (saline) Both supplied as 2.2 ml ampoules used as a mouthwash for a minimum of 30 seconds, five times per day, alongside standard mouthcare</p>
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Outcomes	<p>Primary outcome measure WHO grading for mucositis - a five point scale (0-4) used to grade stomatitis. The two main treatment comparisons, as specified in the protocol, were of the area under the curve (AUC) for stomatitis symptoms, and the time to first worsening of stomatitis symptoms. Secondary outcome measures A subjective scoring system as judged by the participant or parent assessing the degree of pain, dryness and dysphagia.</p>
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Notes	<p>Reported results Primary outcome measure The mean AUC scores were 10.4 in the Traumeel S group and 24.3 in the placebo group (Wilcoxon rank-sum score, 167.5; expected score, 232.5; $P < 0.01$). The log-rank test indicated that a statistically significant difference (chi-square test, 13.4 with 1 degree of freedom; $P < 0.001$) between the two groups in the time to worsening of symptoms. In those patients whose symptoms worsened, the median time to worsening was 4.7 days in the Traumeel S group and 4.0 days in the placebo group. Secondary outcome measures The subjective symptom score showed a reduction of all three symptoms in the Traumeel S group compared to placebo. Adverse reactions Two patients (one in the Traumeel S treatment group and one in the placebo group) received a single dose of study drug but then refused further treatment, complaining of nausea.</p>
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Software program RANCODE version 3.0 in blocks of 2 (from lead author), controlled by the manufacturer of Traumeel S
Allocation concealment?	Yes	The randomisation code was revealed on completion of the study.
Blinding? All outcomes	Yes	The code was kept by the manufacturer, the study coordinator and the statistician, none of whom were involved with any aspect of the treatment of participating patients.

Oberbaum 2001 (Continued)

Incomplete outcome data addressed? All outcomes	Yes	Two participants (one from the Traumeel S group and one from the placebo group) received one dose of the study drug and refused further treatment complaining of nausea; they were not included in the analysis.
Free of selective reporting?	Yes	All the primary outcome measures have been reported in the pre-specified way.
Free of other bias?	Yes	Traumeel S is a proprietary medicine and there are no statements regarding any commercial interests of the authors in the paper. The lead author was contacted regarding any conflict of interest, and stated that neither he nor any of the other authors had any commercial interest in the company producing Traumeel S.

Pommier 2004

Methods	Country: France Recruitment: participants undergoing radiotherapy at the regional cancer centre, Centre Leon Berard Design: prospective randomised single blind (outcome assessor blind) randomised controlled trial Duration of trial: until the completion of radiotherapy
Participants	254 women between 18 to 75 years with non metastatic breast cancer treated with either lumpectomy or mastectomy with or without adjuvant post operative chemotherapy or hormonal treatment. Women having concomitant chemotherapy or with bilateral or breast in situ cancer, who were pregnant or allergic to either preparation were excluded Age: mean 55.4 years (range 26.5 to 74.5 years)
Interventions	Prescribing strategy: clinical homeopathy a) Calendula extract ointment. An ointment prepared according to the German homeopathic pharmacopoeia, consisting of a soft paraffin extract of fresh <i>Calendula officinalis</i> flowering tops (20% w/w). b) Trolamine topical agent. (Biafine; Genmedix Ltd, France) consisting of purified water, liquid paraffin, ethylene glycol monostearate, stearic acid, propylene glycol, paraffin wax, squalane, avocado oil, trolamine/sodium alginate, triethanolamine, cetyl palmitate, methylparaben (sodium salt), sorbic acid (potassium salt), propylparaben (sodium salt), and fragrance. Topical agents were used at the onset of radiotherapy, twice daily or more depending on occurrence of dermatitis or pain until completion of radiotherapy. No other creams, lotions or gels were allowed

Outcomes	<p>Primary outcome measure The occurrence of acute dermatitis of grade 2 or higher according to the Radiation Therapy Oncology Group (RTOG). This was assessed once a week during radiotherapy consultations by physicians.</p> <p>Secondary outcome measures Pain assessed on a 10 cm visual analogue scale (VAS) A self assessed satisfaction questionnaire at the end of the study The occurrence, duration and reasons for interruption of radiotherapy or of allocated cream applications were registered Allergic reactions and quantity of the agents used</p>
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Notes	<p>Reported results</p> <p>Primary outcome measure The occurrence of acute dermatitis of grade 2 or higher was 41% (95% CI, 37 to 46) in the calendula group and 63% (95% CI, 59 to 68) in the trolamine group (P < 0.001)</p> <p>Secondary outcomes measures Pain: the mean maximal pain evaluated on the VAS was 1.54 (95%CI, 1.2 to 1.89) in the calendula group and 2.10 (95%CI, 1.72 to 2.48) in the trolamine group (P = 0.03) Adherence to application of creams as evaluated by the physicians: considered good for 84% of patients receiving calendula and 92% of those receiving trolamine (P = 0.047) Allergic-type reactions: none in the calendula group, four in the trolamine group (pruritis and urticaria). Satisfaction: calendula was considered difficult to apply by 30% of participants (two stopped because of this difficulty) compared to 5% applying trolamine. Satisfaction with regard to prevention of erythema was 69% with calendula and 39% with trolamine, and for pain was 65% with calendula and 46% with trolamine. Body mass index and adjuvant chemotherapy before radiotherapy after lumpectomy were significant prognostic factors for acute dermatitis.</p> <p>Adverse reactions No adverse reactions to calendula were reported</p> <p>Modification or cessation of cancer treatments Treatment interruptions: one in the calendula group for a reason unrelated to radiotherapy and 15 interruptions in the trolamine group, 12 because of skin toxicity, one due to a lymphocoele abscess and two unrelated to radiotherapy. The mean length of treatment interruption in the trolamine group was 10 days (range 2-22 days).</p>
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random allocation lists with block size of six each, stratified for skin type
Allocation concealment?	Yes	The allocated agents were delivered directly to the patients by the pharmacist in similar packaging

Pommier 2004 (Continued)

Blinding? All outcomes	Yes	Subject blinding was not considered possible because of the differences in texture, colour and smell of the two interventions. The outcome assessors were blinded, and patients were instructed not to use the agent two hours or less before an irradiation session or before the treatment evaluation. The review authors judged that the outcome was unlikely to be influenced by the lack of subject blinding.
Incomplete outcome data addressed? All outcomes	Yes	Stated as intention to treat analysis, and there was no comment on withdrawals or dropouts; all participants appear to have been included in the analysis
Free of selective reporting?	Yes	All the primary outcome measures have been reported in the pre-specified way
Free of other bias?	Yes	The study appears to be free of other sources of bias

Thompson 2005

Methods	Country: UK Recruitment: women were recruited from the local oncology centre, surgical breast units, and the community through poster advertising Design: prospective randomised placebo controlled trial with two parallel arms Duration of trial: 16 weeks
Participants	53 women who had been treated for breast cancer, who had more than three hot flushes per day, did not have metastatic disease, were not on any other treatment for hot flushes, did not have any severe concurrent illnesses, and who were not undergoing, or about to receive, any adjuvant chemotherapy Age: mean 52.7 years
Interventions	Prescribing strategy: individualised homeopathy a) individualised homeopathy - five consultations and prescriptions in various forms b) placebo For the individualised homeopathy, there was unrestricted remedy choice and unrestricted ability to change remedy. Outcome assessments were appropriate from a homeopathic perspective. All homeopathic practitioners had at least 10 years experience in classical homeopathy.
Outcomes	Primary outcome measure MYMOP - a change of 0.8 was considered to be a clinically relevant change Secondary outcome measures Menopausal Symptom Questionnaire Patient diaries of frequency and severity of hot flushes

Thompson 2005 (Continued)

	<p>EORTC QLQ C30 (European Organisation for Research and treatment of Cancer Quality of Life Questionnaire C30) HADS (Hospital Anxiety and Depression Scale) FAQ (Final assessment Questionnaire) GHHOS (Glasgow Homeopathic Hospital Outcome Scale)</p>	
Notes	<p>Reported results Primary outcome Eighty-five percent (85%) (45/53) of women completed the study. There was no evidence of a difference seen between groups for either MYMOP activity (adjusted difference = -0.4, 95% confidence interval CI -1.0 to 0.2, p = 0.17) or profile scores (adjusted difference = -0.4, 95% CI -0.9 to 0.1, P = 0.13). Clinically relevant improvements in symptoms and mood disturbance were seen for both groups over the study period. Secondary outcomes There was little to report in the results of the secondary outcome measures. Adverse reactions Adverse effects were reported by approximately one quarter of women in both groups.</p>	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A random numbers table was kept by the pharmacy
Allocation concealment?	Yes	Quote from the paper: "At no point could investigators foresee assignments and continued to be blinded throughout the trial"
Blinding? All outcomes	Yes	Subject (outcome assessor) and care provider blind
Incomplete outcome data addressed? All outcomes	Yes	Regression analysis performed, and described as intention to treat.
Free of selective reporting?	Yes	All of the outcomes described in the methods have been reported.
Free of other bias?	Yes	The study appears to be free of other sources of bias.

Characteristics of excluded studies *[ordered by study ID]*

Felisi 1994	This is a conference report that appears to describe the same study as Balzarini 2000
Srihari 1995	Not described as randomised

Characteristics of ongoing studies *[ordered by study ID]*

Genre 2003

Trial name or title	Randomized, double-blind study comparing homeopathy (Cocculine) to placebo in prevention of nausea/vomiting among patients receiving adjuvant chemotherapy for breast cancer
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Genre 2003 (Continued)

Methods	Randomised controlled trial
Participants	80 participants who were planned to receive adjuvant chemotherapy (six cycles maximum) for breast cancer
Interventions	a) Cocculine (a proprietary complex homeopathic medicine) b) placebo Both added to standard antiemetic treatment, and administered the day before and the day of chemotherapy (two tablets x 3/day)
Outcomes	Nausea/vomiting were evaluated directly by patients for each cycle of chemotherapy (autoevaluation booklet)
Starting date	January 2002
Contact information	Genre D Medical Oncology Department, Université de la Méditerranée, Marseilles, France oncomed@marseille.fnclcc.fr
Notes	

Krempl 2005

Trial name or title	A trial of homeopathic medication Traumeel S for the treatment of radiation-induced mucositis
Methods	Randomised controlled trial
Participants	Inclusion criteria: Head and neck cancer patients post resection of primary tumour with negative or microscopically positive surgical margins Patients undergoing planned radiation therapy Age 18 to 99 years Nonsmokers Exclusion criteria: Head and neck cancer patients post resection of primary tumour with grossly positive surgical margins Patients receiving adjuvant chemotherapy Pediatric patients (age <18) Pregnant women
Interventions	a) Placebo: Saline b) Traumeel S 1 mL (a proprietary complex homeopathic medicine) c) Traumeel S 2 mL (a proprietary complex homeopathic medicine) d) Traumeel S 3 mL (a proprietary complex homeopathic medicine)
Outcomes	The specific aim will be to determine the safety of Traumeel S for mucositis in head and neck cancer patients undergoing radiation therapy [Time Frame: 4 years]

Krempl 2005 (Continued)

Starting date	October 2005
Contact information	Dini Chissoe, BS 405-271-5504 geraldine-chissoe@ouhsc.edu Ingrid Block, RN, MS 405-271-8777 ingrid-block@ouhsc.edu
Notes	

Ray-Coquard 2005

Trial name or title	Placebo-controlled evaluation of Cocculine efficacy in the management of nausea after chemotherapy in breast cancer
Methods	Randomised controlled trial
Participants	Inclusion criteria: Women with histologically proven non metastatic breast cancer No previous chemotherapy Treatment planning including 6 adjuvant CT courses with the first 3 being necessarily of the FAC50, FEC100 or TAC type Age > = 18 years ECOG performance status (PS) <= 2 (WHO scale) Patient able to read and understand French Written, voluntary, informed consent Exclusion criteria: Previous treatment with chemotherapy (including neo-adjuvant chemotherapy for breast cancer) Previous malignancies (except basal cell skin cancer or cervical cancer in situ or any other curatively treated malignancy in complete remission for more than 5 years) Contraindication to corticosteroids or 5-HT3 receptor antagonists Treatment with Cocculine or any other anti-emetic drug in the 15 days before inclusion Pregnant or lactating women Follow-up impossible for social, geographical, familial or psychological reasons Patients who cannot be contacted by phone
Interventions	a) Cocculine (a proprietary complex homeopathic medicine) b) placebo
Outcomes	Primary outcome measures: Score of "nausea" calculated using the FLIE questionnaire (Functional Living index for Emesis with 5-day recall) at the time of the first adjuvant CT course [Time Frame: The nausea items of FLIE questionnaire are completed by patients on the 6th day of the 1st course.]

Ray-Coquard 2005 (Continued)

	<p>Secondary outcome measures:</p> <p>Score of "vomiting" and global score of "nausea + vomiting" calculated using the FLIE questionnaire at the time of the 1st, 2nd and 3rd adjuvant CT courses [Time Frame: Nausea and vomiting items of FLIE questionnaire are completed by patients on the 6th day of the 1st, 2nd and 3rd adjuvant CT courses]</p> <p>Score of "nausea" calculated using the FLIE questionnaire at the time of the 2nd and 3rd adjuvant CT courses [Time Frame: Nausea items of FLIE questionnaire are completed by patients on the 6th day of the 2nd and 3rd adjuvant CT courses]</p> <p>Patient autoevaluation (D1-D5) of nausea severity using a visual analogue scale and of the frequency of vomiting during the 1st, 2nd and 3rd adjuvant CT courses [Time Frame: Visual analogue scale are completed by patients the 1st five days of the 1st, 2nd and 3rd adjuvant CT courses]</p> <p>Rate of toxic effects (nausea and vomiting) recorded by investigators at the end of each of the 6 CT courses [Time Frame: Recorded by investigators at the end of each of the 6 CT courses]</p> <p>Evaluation of compliance: patient autoevaluation and counting of remaining tablets [Time Frame: Patients register date and hour of tablets taking on a diary. Box remaining tablets will be count at the end of the 6 CT courses.]</p>
Starting date	September 2005
Contact information	<p>PEROL David, MD +33 478 78 28 79 perold@lyon.fnclcc.fr</p> <p>GIRERD Nathalie + 33 478 78 59 27 girerdch@lyon.fnclcc.fr</p>
Notes	

Sadhev 2004

Trial name or title	Traumeel S in Preventing and Treating Mucositis in Young Patients Undergoing Stem Cell Transplantation
Methods	Randomised clinical trial
Participants	<p>Inclusion criteria:</p> <p>Age 3 to 25 years</p> <p>Planned treatment with allogeneic or autologous hematopoietic stem cell transplantation. Conditioning chemotherapy regimen for transplantation must be myeloablative. Source of stem cells from any of the following: bone marrow; placental cord; cytokine-mobilized peripheral blood.</p> <p>Availability of 1 of the following donor types: HLA-matched sibling or parent; related donor mismatched for a single HLA locus (class I or II); unrelated marrow or peripheral blood stem cell donor; unrelated umbilical cord blood HLA-matched or mismatched (class I) donor.</p> <p>No known allergy to Echinacea.</p> <p>Not pregnant or nursing.</p> <p>Fertile patients must use effective contraception.</p>

Sadhev 2004 (Continued)

	No concurrent oral vancomycin paste. No concurrent oral glutamine supplementation. No other mouth care or oral medications within 30 minutes after administration of study drugs. No other concurrent treatment to prevent mouth sores.
Interventions	a) Patients receive oral Traumeel S (a proprietary complex homeopathic medicine) mouth rinse 5 times daily beginning on day -1 before transplantation b) Patients receive oral placebo mouth rinse 5 times daily beginning on day -1 before transplantation
Outcomes	Severity and duration of chemotherapy induced (with or without total body irradiation) mucositis
Starting date	April 2004
Contact information	ClinicalTrials.gov identifier: NCT00080873
Notes	

DATA AND ANALYSES

Comparison 1. Homeopathic treatment of skin reactions to radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total severity of skin reaction during radiotherapy	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Total severity of skin reaction during recovery following radiotherapy	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Prevention of acute dermatitis during radiotherapy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Comparison 2. Homeopathic treatment of chemotherapy induced stomatitis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Area under curve of stomatitis symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Time to first worsening of stomatitis symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 3. Homeopathic antiemesis for chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Numbers requiring conventional medication	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Comparison 4. Homeopathy for oestrogen withdrawal in breast cancer patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MYMOP ADL score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 MYMOP overall profile score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 5. Homeopathy for adverse effects of venous cannulation in patients receiving chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Haematomas	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Accessibility	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 2, 2009

CONTRIBUTIONS OF AUTHORS

Robbert van Haselen (RvH) conceived the idea and with Sosie Kassab (SK) developed the protocol. All authors contributed to the concept and design of the study. The search strategy was developed by SK and the Trials Search Coordinator of the PaPaS Review Group. SK did the handsearching and with Peter Fisher (PF) contacted practitioners and researchers in the field. SK and Saul Berkovitz (SB) reviewed results of the searches and included studies into the review. SB facilitated translations of papers. Disagreement on the inclusion or exclusion of studies were discussed by SB, Mike Cummings (MC), PF and SK. Data was extracted by MC and SK and quality assessed by SB, MC and SK. Authors and manufacturers were contacted by MC, PF and SK for additional information. MC entered data into RevMan. SB, MC, PF and SK interpreted the analysis. MC and SK drafted the final review. SB and PF commented on it critically for intellectual content. All authors finally approved the document for publication.

SK will be responsible for conducting any updates.

DECLARATIONS OF INTEREST

Peter Fisher has received fees from homeopathic manufactures for lectures and seminars.

Sosie Kassab is Director of Complementary Cancer Services at the Royal London Homoeopathic Hospital and uses homeopathic medicines for patients with cancer alongside their conventional care.

Robbert van Haselen was Deputy Director of Research at the Royal London Homoeopathic Hospital when an application for funding for this Cochrane Review was made from ViFAB. He had a major input into the development of the protocol which was published in 2004. He left the hospital in 2005 and took up his post as Director of Research for Heel in Germany in 2006 (the company that makes Traumeel S, one of the interventions included in this review). Prior to his leaving, we had run some of the searches and identified some potential studies but had not gone through the process of formally selecting studies for inclusion into the review. He had no input into the selection of included studies, data extraction, quality assessment or interpretation of the analysis. On finally approving the

publication, he did not make any recommendations for change to the implications for clinical practice, research or to the conclusions, but commented on it critically for intellectual content.

SOURCES OF SUPPORT

Internal sources

- Royal London Homoeopathic Hospital, UK.

External sources

- Knowledge and Research Center for Alternative Medicine (Danish Acronym: ViFAB), Denmark.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Cochrane assessment of risk of bias.

Where there was doubt about the classification of the medicine, we contacted authors or the product manufactures for confirmation. We did not routinely check the specific pharmacopoeas in the reports where the interventions were clearly homeopathic medicines.