Adverse effects of homeopathy, what do we know? A systematic review and meta-analysis of randomized controlled trials

Short Title: Systematic review of adverse effects in homeopathy

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Keywords: Adverse effects; adverse events; homeopathic aggravations; patient safety; systematic review; meta-analysis; risk assessment

Highlights:

- This review address the naive assumption that because of the generally diluted doses used homeopathy must be safe
- This review touches the neglected issue of the distinction between homeopathic aggravation, adverse reactions and adverse effects
- We found a similar risk for homeopathic treatment compared to controls such as placebo and conventional medicine.

Words: 5,187

Abstract

Objectives

Homeopathy is a popular treatment modality among patient, however there is sparse research about adverse effects of homeopathy. A concept unique for homeopathy, is homeopathic aggravation that is understood as a transient worsening of the patients' symptoms before an

expected improvement occurs. From a risk perspective it is vital that a distinction between homeopathic aggravations and adverse effects is established. There is a lack of systematic information on how frequent adverse effects and homeopathic aggravations are reported in studies. Therefore, a systematic review and meta-analysis were performed.

Design and setting
Sixteen electronic databases were searched for Randomized Controlled Trials (RCTs). The searches were limited from the year 1995 to January 2011. Forty-one RCTs, with a total of 6.055 participants were included. A subtotal of 39 studies was included in the additional meta-analysis.

Results
A total of 28 trials (68%) reported adverse effects and five trials (12%) reported homeopathic aggravations. The meta-analysis (including six subgroup comparisons) demonstrated that no significant difference was found between homeopathy and control with OR 0.99, 95% CI 0.86 to 1.14, I^2 = 54%. More than two third of the adverse effects were classified as grade 1 (68%) and two third were classified as grade 2 (25%) and grade 3 (6%) according to the Common Terminology Criteria for Adverse Effects. Homeopathic aggravation was classified as grade 1 (98%) and grade 3 (2%), suggesting that homeopathic aggravations were reported to be less severe than adverse effects. The methodological quality according to a method recommended in the Cochrane handbook for RCTs, was high.

Conclusion
Adverse effects including the concept of homeopathic aggravations are commonly reported in trials. The meta-analysis demonstrated that the proportion of patients experiencing adverse effects to be similar for patients randomized to homeopathic treatment compared to patients randomized to placebo and conventional medicine.

Introduction

Homeopathy was established and developed in Germany by Samuel Hahnemann in the late 18th century, and since then the theory and practice of homeopathy have developed outside the established health services. The action of homeopathic remedies is questioned as most remedies are diluted to such a high degree that there is only a theoretical probability that molecules of the original substance are present in the remedy (1-3). Accordingly, homeopathic remedies of high dilutions are pharmacologically inactive. On the other hand some

homeopathic remedies are less diluted (D6 or D12), meaning that these remedies could be pharmacologically active. However, research suggests (4) that it is low direct risk connected to homeopathic remedies. The possible risk is therefore classified as indirect, related to other aspects of clinical context and practice. In medical science, risk can be divided into direct and indirect risk. Direct risk is related directly to the intervention itself, such as the medication or the homeopathic remedy. Indirect risk is related to the treatment setting, such as the practitioner and the caring context (5-7).

In the United States 2.3% of the adult population used homeopathy in 2007, and 2.9 billion USD were spent on homeopathic remedies (8). The 12 month prevalence of those who have visited a homeopath in Europe has been found to vary between 2% in Great Britain (9) to 15% in Germany (10). A survey among older German adults revealed that 21% used homeopathy for their complaints (11). In Scandinavian countries the prevalence of persons who use homeopathy fluctuates between 7% and 14% (12).

Being female, having higher education, suffering from health complaints and using conventional health care have all been associated with the use of Complementary and Alternative Medicine (CAM), including homeopathy (13-15). Uncontrolled studies of homeopathy document consistent and sustained patient satisfaction (15). Patients used homeopathy for chronic, physical problems, as well as emotional complaints (14-16). The most frequent diagnoses for which they seek homeopathy are allergic rhinitis in adult males, headache in adult females and atopic dermatitis in children (17). Homeopathy is one of the most common CAM therapies in cancer care in Europe, ranging from 11% across cancer diagnoses (18) up to 19% in breast cancer patients (19). Among younger cancer patients in Germany, 45% reported that they have used homeopathic remedies during their illness (20). The majority of the patients used homeopathy with the aim to increase the body's ability to fight cancer or to improve physical or emotional well-being (19).

A concept specific to homeopathy is homeopathic aggravations, which is defined as "a temporary worsening of existing symptoms following the administration of a correctly chosen homeopathic remedy". This reaction is seen as a favourable response to the treatment and is expected to be followed by an improvement (2, 21-23). In 2003, Grabia and Ernst (24) published a systematic review to investigate how homeopathic aggravations was reported in RCTs. From a total of 25 trials, eight reported homeopathic aggravations and six reported adverse effects. The authors claimed that, for safety reasons, the concept should be reported in trials.

A systematic review of case reports published in 2012 (25) found that, among the included 38 primary reports, 30 reported direct adverse effects from homeopathic remedies and eight were related to adverse effects caused by the substitution of conventional medicine with homeopathy. This review initiated a broad and controversial discussion about the safety of homeopathic treatment which has already been raised with regard to the risk of homeopathy related to practice by Dantas in 1999 (26). In particular, Tournier et al (27) highlighted the importance of differentiation between homeopathic care and clinical negligence. Together with poor reporting quality of the primary sources (i.e. of applied potencies of the remedy) this may lead to a misinterpretation of causality. Nevertheless this scientific episode highlights the need for some criteria or guidelines that enables to document common standards of homeopathic treatment.

So far, homeopathic aggravations have mostly been reported in an anecdotal way. In one case (28), a nine-month old baby girl was given several homeopathic remedies to treat atopic dermatitis. The child developed Bullous Pemphigoid (BP) during the treatment period and when the baby was finally admitted to the hospital, the condition was life threatening. This situation occurred because the homeopath misinterpreted the worsening of the symptoms as homeopathic aggravations and continued the treatment. In this case only spars information regarding the prescription of the homeopathic remedies was documented and the author stated that "no conclusion about the role of the homeopathy in the triggering of BP can be made". However, Posadzki et al. in their review judged *Mercury intoxication* as a possible explanation of the adverse effect as judged by the author of the primary report (25).

This case illustrates the difficulty of judging the likelihood of homeopathic aggravations and adverse effects in homeopathy. Good data on a well-recognized, easily detectable adverse effects may be available from randomized clinical studies (RCTs) (29), and since limited knowledge of how adverse effects and homeopathic aggravations are reported in trials - A systematic review is needed.

Aims

The aims of this paper are to 1. Systematically investigate how homeopathic aggravations and adverse effects are reported in randomized controlled trials. 2. Classify adverse effects and homeopathic aggravations according to the Common Terminology Criteria for Adverse Effects (CTCAE) (30). 3. Perform a meta-analysis to evaluate the risk for patients using homeopathy (consultation and/or homeopathic remedies) compared to controls.

Terminology

Not only is the homeopathic intervention itself a very complex treatment situation, which includes much more components than the remedy, there is, moreover, an astounding variety of definitions of harmful events available. This situation makes a thorough discussion of the terminology, which forms the basis of the systematic review and meta-analysis presented here, necessary.

The homeopathic intervention is a very elaborate treatment situation that consists of in-depth consultations often reaching beyond the topic of bodily complaints and involving psychological problems as well. In addition, lifestyle advice is generally included and a part of the consultation.

In terms of safety concerns, the homeopathic remedies themselves are mostly considered harmless (4). According to the current pharmacological model any potential harm related to remedies of high dilutions must be related to *indirect risk* (see table 1 for definitions of concepts), such as e.g. risk related to the setting effects, such as the practitioner (5, 31). According to current scientific knowledge, only remedies of low dilutions have a potential to induce *direct risk,* since they do contain substrate. Nonetheless, homeopathic treatment with ultra-molecular remedies has been proven to be clinically effective, but the mechanisms of effect remain unclear and under discussion. It has been speculated, that psychological mechanisms such as the placebo effect, potentially play a role (32)

As a consequence of this complex situation, a rather broad definition of risk, including both direct and indirect risk, maybe most appropriate in order to map the potential harm to patients related to the homeopathic treatment situation (33). This definition should encompass all potentially unwanted effects, without making assumptions about their mechanisms. In the light of the obvious shortcomings of the pharmacological model with regard to homeopathy, it is moreover, essential, that this definition is also able to cover incidents, that are most likely not related to a pharmacological effect.

In Norway, the National Norwegian Medicines Agency (34), uses the term *adverse effect.* In this definition, an adverse effect is understood as all diseases or unwanted and/or harmful reactions resulting from a medication or an intervention, regardless of their relation to the actual treatment. This definition is quite similar to how Edward and Aronson (35), define *adverse effects,* namely as a term that encompasses all unwanted effects. In this understanding

of adverse effect, no assumption about mechanism is made and as such, ambiguity is minimized.

According to Edward and Aronson (35), the term *adverse effect* in the above described understanding must be distinguish from the term *adverse events.* They understand adverse event as an adverse outcome that occurs *while* a patient is taking a drug, thus, there is a strong temporal association to the drug, but the harmful event must not necessarily be associated with it. Their definition is similar to the definition of adverse events used by the European Medicines Agency (36). There, *adverse events* are defined as "any untoward medical occurrence in a patient or clinical trial subject administered a medical product". But here as well, these events do not necessarily have a causal relationship with the treatment. At the same time, the European Medicines Agency defines *adverse effects* as a response to a medicinal product which is noxious and unintended (36). In conclusion, the European Medicines Agency as well as the National Norwegian Medicines Agency have a common understanding of the term adverse effect.

To complicate the situation even more, the term a*dverse reactions* is often used instead of *adverse effects* and both are often used interchangeable. However, an adverse effect is generally identified as being linked with the drug, whereas an adverse reaction is directly linked to the patient (35, 36).

Thus, even though it seems that there is a common intuitive understanding of what a harmful event related to a treatment is, it seems to be challenging to find a common terminology of terms to describe and define it. This confusing situation is most illustrative demonstrated by the fact, that even the current glossary of the CONSORT statement lacks a clear definition of *adverse event* and that a definition is still pending. http://www.consort-statement.org/resources/glossary. Several attempts have been made to facilitate the reporting of harm related issues and a checklist for such reports has been developed (37). As a conclusion, the authors are well aware that the decision of which definition to choose, is to a large extend a matter of choice and other choices are well possible and reasonable.

The National Research Center for Complementary and Alternative Medicine (NAFKAM) in Norway is a governmentally funded national agency, organized as part of the Department of Community Medicine at the Arctic University of Norway. One major goal related to the implementation of NAFKAM and thus a part of NAFKAMs assignment is to ensure and frame the safe use of complementary medicine for the Norwegian citizens. The systematic

review presented here is part of this assignment. It seem reasonable that NAFKAM utilizes a risk definition, which is in line the National Norwegian Medicines Agency(33), The Term "adverse effect" as it is understood in this definition includes more sources of risk than merely those related to the drugs and thus covers a sufficiently broad spectrum of potential risks. It is therefore also suitable for the complex treatments situation in complementary medicine in general and thus for homeopathy as a special case. Thus, we will use this term and understanding of harm for this review, being well aware, that this represents a conscious choice, rather than a generally accepted universal definition.

Moreover, we are aware, that the translation of the risk concept of homeopathic aggravation into a conventional medical terminology is challenging and may reflect a compromise, nonetheless a definition is needed in order to describe and document the potential risk related to homeopathy in all its facets. Homeopathic aggravation is a reaction to homeopathy which is a complex treatment regimen. Hence, a concept that includes both direct and indirect risk in order to categorize homeopathic aggravation into a conventional term is needed. We have therefore chosen to categorize homeopathic aggravation as *a special kind of adverse effects* in this review.

Hanemann stated in the Organon der Heilkunst § 161"….. the so-called homeopathic aggravation, or rather the primary action of the homeopathic medicine that seems to increase somewhat the symptoms of the original disease, to the first or few hours, this is certainly true with respect to diseases of a more acute character and of recent origin: but where medicines of long action have to combat a malady of considerable or very long lasting……Such increase of the original symptoms of a chronic disease can appear only at the end of treatment when the cure is almost quite finished." Consequently, temporary and short time aggravations may be observed and reported in RCTs. However, longer lasting homeopathic aggravations are rather unlikely to be observed in clinical trials.

As a final caveat, we would like to pay attention to the fact that the only available information on adverse effects and homeopathic aggravations for this review was based on the information provided by the authors of the included trials.

Therefore, the results presented here are based on the following definitions:

- Adverse effects
- homeopathic aggravations

Table 1: Definitions of harm concepts

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Terminology	**Definition**	**References**
Risk	A compound measure of the probability of an event, and the magnitude and impact of its potentially negative outcome of that event.	(38),(35)
Indirect risk	Risk related to the setting effects, such as the practitioner rather than to the medicine. For example, a practitioner with limited medical and homeopathic skills may overlook serious symptoms and thereby cause a delay in necessary conventional treatment.	(6), (33)
Direct risk	Risk related to the intervention, e.g., harm caused by pharmacological products, medical treatments and procedures	(5), (6)
Homeopathic aggravations (direct and indirect risk)	A temporary worsening of existing symptoms following the administration of a correctly chosen homeopathic prescription, which is expected to be followed by an improvement.	(23), (22)
Adverse effects (direct and indirect risk)	All diseases or unwanted and/or harmful reactions resulting from a medication or an intervention, regardless of their relation to the actual treatment.	(34),(35)
Adverse reactions (direct and indirect risk)	Present when the right drug was administered for the correct indication, in the proper dose, by the right route, yet still the patient develops an unwanted symptom, suffers unexpectedly, and is exposed to unpreventable harm. Adverse reactions may also result from some diagnostic tests, therapeutic interventions or devices.	(38),(39)
Adverse drug reactions (direct risk)	An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product. The reaction predicts hazards regarding future administration and warrant prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.	(35, 40)

Methods

Searches

The focus question was:

Is homeopathy associated with adverse effects and/or homeopathic aggravations?

The PICO format was used when searching for relevant articles, which included the following four parts:

Population: Patients using homeopathy, physicians and homeopaths who reported adverse effects and homeopathic aggravations in the included studies

Intervention: Homeopathy, including everything a homeopath does in the consultation, such as a diagnostic in-depth interview, prescription of remedies, and life-style advice

Comparison: Placebo, conventional medicine, usual care, waiting lists, other complementary and alternative treatments (including herbs)

Outcome: Adverse effects, adverse events, adverse reactions, tolerability, side effects (or other safety terminology) and homeopathic aggravations

The following electronic databases were searched: AMED, Cinahl, Cochrane Central Register for Controlled Trial (Central) in the Cochrane library, Embase, Medline, PsycINFO, PubMed, Datadiwan, GIRI, HomBRex, Hom-Inform, CAM Quest, CAMbase, Theme eJournals and Karger. A manual search was performed in complementary medicine journals, collections of publications from experts in homeopathy and homeopathic philosophy books. In order to find additional studies not found by electronic or manual searches, the reference lists of publications were also checked.

Search Methods: Depending on the database, various combinations of MESH terms and keywords were used. These MESH terms were used: *Homeopathy/Materia Medica/Risk Management/Drug tolerance.* These keywords were used: *Homeopathy/homoeopathy/homeopathic/homoeopathic side effect*, safety, adverse effect*, adverse events*, homeopathic aggravation**. The filters were clinical trials, RCTs, high specificity, any human conditions of humans, English and German. As the meta-analysis by Linde et al (41) included studies up to 1995, the searches were limited to the time period from January 1992 to January 2011.

The first author, T.S, performed the searches, read the articles, and extracted the data, while T.A. was consulted in cases of doubt. [The Cochrane Library (searches from 2002-2011) and the PubMed (searches from 2002-1992) search strings are attached in the appendix].

The inclusion comprised randomized, therapeutic trials that were double blinded. The trials excluded had no registration of homeopathic aggravations or adverse effects. Moreover, all drug proving trials, homeopathic pathogenic trials and duplicated publications were excluded.

Methodological assessment of the included RCTs

In this present study, the methodological quality of the RCTs was assessed using the criteria in the Cochrane Reviewers' Handbook (42). The following criteria were included in the

assessment: Participants, dropouts, power calculation, intention-to-treat analysis, method (allocation concealment and blinding), intervention, duration of treatment, main finding, and funding (table 2). The trials were rated as follows:

A was used to indicate an RCT with a high level of quality in which all the criteria were met. Adequate measures to conceal allocation were made. The central randomization was either serial numbered, opaque, sealed envelopes or other descriptions that contained convincing elements of concealment. Hence, low risk of bias.

B was used when the authors did not report allocation concealment at all, or reported an approach that did not fit one of the categories in A. Hence, moderate risk of bias.

C was used when the method of allocation was not concealed, such as alternation methods or the use of case record numbers. Such trials were excluded because of high risk of bias.

Total number and classification of adverse effects and homeopathic aggravations

Studies were extracted for data on adverse effects and homeopathic aggravations according to the following criteria: The total number of adverse effects, number of patients experiencing adverse effects, the total number of homeopathic aggravations and the total number of patients experiencing aggravations, and the CTCAE grading of the symptoms. When summarizing the data, the total number of adverse effects and homeopathic aggravations were counted, regardless of the number of participants who experienced them. This means that one patient may experience more than one adverse effect. Adverse effects and homeopathic aggravations were recorded as reported and stated in the included trials. This means that the CTCAE grading was entirely dependent on the information provided in the articles.

In order to evaluate the harmful events according to severity, the CTCAE grading system was chosen (30).The CTCAE system grades adverse effects from 1 to 5, where 1 is mild, 2 is moderate, 3 is severe or medically significant, 4 is life threatening, and 5 is lethal. When reporting the grading of adverse effects, we reported the harmful events without the number of patients experiencing the events.

The CTCAE grading system was also applied for homeopathic aggravations. The reason was that the grading system relates to new or worsening symptoms, which means that the cause of the new or worsening symptoms is irrelevant for the grading. Three researchers (TA, AK, TS) categorized and graded the data. When disagreements occurred, the events were discussed until

consensus was reached. TS is a certified homeopath and acupuncturist, and the TA is a certified acupuncturist in Norway.

Meta- analyses

For the calculation of the meta-analysis, the study populations were divided in patients experiencing adverse effects vs. patients not experiencing adverse effects in both homeopathy and control groups. If the studies were homogenous regarding the study design, participants, interventions, control and outcome measures, they were combined in a meta-analysis. Heterogeneity was defined as being significant, if $P < 0.10$.

Based on the total number of participants randomized to the treatment or control group, odds ratios and 95% confidence intervals were calculated from the number of patients who experienced adverse effects in each group. In 15 studies with no adverse effects in one or both groups, a continuity correction of 0.5 was added to arrive at a valid approximation of an odds ratio according to the current recommendations on analysing adverse effect data (43). To perform a meta-analysis, data were entered directly from the data sheets into Review Manager 5 computer program (44).

Results

Outcome of the literature searches

A total of 1,129 articles with RCTs were identified. They were initially examined on the basis of titles and abstracts, and 1,079 were excluded from further examination for the following reasons: Seventy-five articles did not record adverse effects or homeopathic aggravations, 44 described homeopathic proving trials, 324 were irrelevant (according to the criteria), 439 were multiple article registrations in databases, 62 were written in other languages than English and German and 135 were CAM studies other than homeopathy. Seven articles were included after searching German databases. After a closer examination of the 57 identified studies (45-47) (48-51) (52-102), 16 were excluded (table 1) (46-48, 89-102). A total of 41 RCTs (48-88) with 6,055 subjects were included in this review.

Figure1. Flow chart of the randomized controlled trials

The control intervention was a placebo in most of the RCTs (n=31) (48-51, 53, 55-57, 60-71, 73, 74, 76, 78-83, 87, 88, 103). Further, placebo and conventional medicine in one trial (n=1) (86), herbal medicine (Gingo biloba) in one trial (n=1) (59), usual care in one trial (n=1) (72) and conventional medicine in five trials (n=5) (75, 82, 84, 85, 87). Any human condition of humans and any homeopathic remedy were considered.

Table 2: Excluded studies

Methodological quality of the RCTs

A total of 32 trials (78%) were rated as **A**, demonstrating that the methodological quality in these trials was of high quality with low risk of bias. Nine trials (22%) were rated as **B** (48, 50, 53, 59, 64, 67, 69, 73, 75), demonstrating average quality and medium risk of bias. A total of 22 trials (54%) reported both sample size calculations and intention to treat analyses. Eight trials (20%) did not report sample size calculations or intention to treat analyses (53, 57, 60, 61, 64, 67, 68, 73). Four of these studies also had a methodological quality of **B** (medium quality) (53, 64, 67, 73). Based on this evaluation we concluded that the methodological quality of the majority of these trials was high. Key data of these studies are summarized in table 3. The column *Participants* refers to the number of participants randomized to either the treatment or control group. *Dropout* refers to participants in the treatment and control group who left the study. Therefore, participants who completed the study can be calculated as follows, e.g., Aabel 2000: (n=37) – (n=3) = (n=34) in the treatment group and (n=33) – (n=1) = (n=32) in the control group.

Table 3: Assessment of the methodological quality of the randomized controlled trials

Adverse effects

From a total of 41 RCTs, 28 trials (68%) reported adverse effects. A total of 491 participants experienced 690 adverse effects, 426 in the treatment groups and 264 in the control groups. Twelve trials (29%) reported no cases of adverse effects. The adverse effects were mostly categorized as gastro-intestinal disorders, headache/dizziness or dermatitis. Sixty-eight percent (n=466) were characterized as CTCAE grades 1, 25% as grade 2 (n=174), 6 % as grade 3 (n=39), 0,4 % as grade 4 (n=3) and 0,2 % as grade 5 (n=2).The adverse effects categorized as grade 4 and 5 were not related to study medication. Key data of adverse effects are summarized in table 4.

The adverse effects were patients or physician reported and the harmful events were causality assessed in three trials (55, 56, 70). There was an inconsistent use of referring measures of adverse effects. Twenty-seven trials (54-56, 59, 61, 62, 64, 65, 70-73, 75-78, 80-86, 88, 91) used the terminology adverse effects or adverse events. These trials assessed the symptoms as mild/moderate or severe, or serious or non-serious. A three or four point tolerability scale was used in six trials (49, 50, 59, 84, 85, 88). Adverse effects were descriptively reported in five trials

(49, 51, 60, 78, 79). Four trials used the term adverse drug reactions (66-68, 75), two trials applied side effects (63, 69), and one trial used unexpected effects (58).

Homeopathic aggravations

Five RCTs (12%) (54, 65, 79, 80, 86) reported homeopathic aggravations four of these also reported adverse effects. One hundred and seven participants experienced a total of 158 homeopathic aggravations, 91 in the treatment groups and 67 in the control groups. The remaining 36 RCTs (88%) reported no cases of homeopathic aggravations. Homeopathic aggravations were patient and physician reported, and the studies did not report whether the patients had been informed about the possibility of experience such events. Homeopathic aggravations were reported as worsening of the patients' symptoms, such as exacerbation of allergy, asthma, eczema, headache and hot flushes. Ninety-eight present was classified as CTCAE grade1 (n=171) and 2% was classified as grade 3 (n=4) (severe asthma attacks). Non-events were classified as grade 2, 4, and 5.

Two trials classified homeopathic aggravations as adverse effects (80, 86). One study (52) reported these data descriptively, another study (11) classified them as adverse reactions, and one trial(104) classified worsening of symptoms as homeopathic aggravations. Both complex and single remedies of low and high dilutions were associated with reported adverse effects or homeopathic aggravations. Key data of homeopathic aggravations are summarized in table 4.

Table 4: and

Meta-Analyses

Adverse effects data from 39 RCTs were included in the meta-analysis with a total of 5.902 subjects (figure 2).

1. *Homeopathy versus overall control*

An overall comparison was made between homeopathy and control. Thirty-nine trials (5.902 participants) made this comparison and no significant difference was found between homeopathy and control (426/2947 versus 264/2955), with OR 0.99, 95% CI 0.86 to 1.14, I^2 = 54%.

Different subgroup meta-analyses according to the categories of controls were performed and presented below.

2. *Homeopathy versus placebo*

A comparison was made between homeopathy and placebo. Thirty-one trials (4.836 participants) made this comparison and no significant difference was found between homeopathy and placebo (n= 220/2436 versus n=157/2400), with OR 1. 03, 95% CI 0.89 to 1.20, I^2 = 49%.

3. *Homeopathy versus conventional medicine*

There was no significant difference between homeopathy and conventional medicine in a meta-analysis of five trials (43/355 versus 71/401), with OR 0.82, 95% CI 0.56 to 0.1.21, I^2 = 67%.

4. *Homeopathy versus herbs*

A comparison was made between homeopathy and herbal medicine. One trial (170 participants) made this comparison, and no significant difference was found between the groups (OR 0.72, 95% CI 0.25 to 2.07, *P* = 0.54).

5. *Homeopathy versus usual care*

A comparison was made between homeopathy and usual care. One trial (47 participants) made this comparison and reported the same number of adverse effects in the homeopathy as in the usual care group (1//23 versus 1/24), with OR 1.02, 95% CI 0.30 to 3.51, *P* = 0.97.

6. *Homeopathy versus conventional medicine and placebo*

There was no significant difference between homeopathy and conventional medicine and placebo in a meta-analysis of one trial (7/46 versus 5/47), with OR 1.20, 95% CI 0.71 to 2.03, *P* = 0.50.

One study, in which the numbers of adverse effects without stating the respective number of patients affected by the adverse effects, was excluded from the analyses (105). Another study (52), that reported only homeopathic aggravation was also excluded from the meta-analysis.

Figure 2: Forest plot for the randomized controlled trials, including sub-group analysis according to the category of controls.

In order to investigate whether there was a difference between studies of low and high potency homeopathy, we performed a One Way Anova test. We found that the mean number

of adverse effects in studies (n=20) with low potency (D4 toD30) was 8.5%, compared to 15.5% in studies (n=6) with high potency (D200 and higher) (p=0.181).

Discussion

In this present review we found that adverse effects were reported in 68% of the RCTs, More than two third of these events was classified as CTCAE grade 1 (minor) and one third as grade 2 and 3 (moderate and severe/significant). The meta-analysis demonstrated the proportion of patients experiencing adverse effects to be similar for patients randomized to homeopathic treatment compared to patients randomized to control such as placebo and conventional medicine.

The CTCAE grading of adverse effects and homeopathic aggravations was solely based on the information provided in the articles. This grading must, therefore, be interpreted with caution. As such, the grading applied here should be understood as merely an approximation to a CTCAE grading.

Studies of effect require as a general rule randomized controlled trials. Adverse effects, however, may also be effectively investigated in non-randomized studies (106). Papanikolaou (107) compared the risks of 13 major harms due to medical interventions using data from both randomized controlled trials and observational studies. The results suggested that, if a nonrandomized study finds harm, changes are that a randomized study would find even greater harm in terms of the magnitude of absolute risk. The authors concluded that contrary to current belief, non-randomized studies were often more conservative in their estimates of risk compared to randomized trials. Moreover, rare adverse effects or long-term adverse effects are rather unlikely to be observed in clinical trials, and a thorough investigation may require the inclusion of cohort studies (42). Our study team have therefore in addition to the study presented here, also conducted a systematic review and meta-analysis of observational studies that will be published later.

A limiting factor in all meta-analyses is heterogeneity of included studies. Being aware that heterogeneity might be underestimated in a fixed effect model, and the current discussion on applying fixed or random effect models in meta-analyses of binary adverse data (108), we decided to perform a simple random effect model. This model is also recommended in meta-analysis of rare binary adverse effect data (43). According to the argumentation of Friedrich et al. (109) we decided to include studies with zero-cell counts because the exclusion of such trials enhances the "risk of inflating the magnitude of the pooled treatment effect". By using a

continuity correction of 0.5 for studies with zero-cell counts, odds ratio can still be estimated and summed up with standard meta-analysis methods. The inclusion of zero event studies is particularly important in cases of adverse effects as applying the standard continuity correction leads to a conservative, but error free, approximation of the risk of adverse effects (108). Moreover, the sample sizes of such trials contribute to the total effect size and make this more valid. On the other hand, this present review investigating adverse effects, so whether the pattern of adverse effects are homogeneous across studies should be of no concern, given they were for different conditions and involving different treatments, one would expect heterogeneity.

The studies using high potency homeopathy had twice as many adverse effects reported than studies using low potency, however not at a significant level. We believe that this result is due to low number of studies included in the analysis. The reason was that the name and potency of the homeopathic remedies administrated to study participants were not reported in several trials (e.g. individualized homeopathy).

To address the question about publication bias we did a funnel plot. This demonstrated the absence of publication bias in this systematic review, hence not shown in this present paper. However, the topic in this review was not treatment effect, but the frequency of adverse effects in the included trials.

Strong efforts have been made to retrieve all RCTs on the subject, but one cannot be absolutely certain that they have all been found. On the other hand, the additional searches in German databases, a country with a strong homeopathic research tradition, strengthen the possibility that the majority of the available studies have been included. This methodological approach may have minimized the possibility for selection bias in this systematic review.

A total of 62 (n=62) studies were excluded because they were in other languages, mainly Russian and French. Many researchers find that data from more than 40 studies in a systematic review may be difficult to handle and therefore not recommended (110). We believe that the studies excluded from this review should be included in a separate review.

An inconsistent use of safety terminology was found in the included trials. Harm data was reported by different concepts, such as adverse effects, adverse events, side effects and adverse drug reactions. The grading was measured on different scales (mild, moderate and severe or serious vs. non-serious). Moreover, homeopathic aggravations were classified as

adverse effects and adverse reactions. This inconsistent use of terminology made it difficult to categorize and evaluate the data systematically. Hence, a consistent taxonomy is preferable and in line with WHO recommendations (111).

The adverse effects in this present review were found to be minor to moderate and transient events, which is in line with Dantas and Rampes (4). Grabia and Ernst (24) found in a systematic review of homeopathic aggravations in 25 placebo-controlled RCTs, 33 adverse effects in the placebo groups and 97 in the homeopathy groups. No grading of the adverse effects was given in the article.

It is possible that adverse effects have been under-reported. Many patients and homeopaths find it difficult to accept that homeopathy can cause adverse effects, since the treatment is "natural "and thereby considered to be safe. Moreover, many homeopaths believe that high diluted remedies does not cause adverse effects (112).

Grabia and Ernst (24) reported also that 40 cases of aggravation in the placebo groups and 63 cases in the homeopathy groups. The authors concluded that although the included RCTs mentioned the phenomenon of homeopathic aggravations, the evidence was not strong enough to provide support for the existence of aggravations. The frequency of homeopathic aggravations reported in the review from Grabia and Ernst, is in accordance with the findings from this present review. However, the frequency of reported homeopathic aggravations may be too low, since there is a lack of an adequate reporting system that include homeopathic aggravations.

Conclusion

Adverse effects including the concept of homeopathic aggravations are commonly reported in trials. The meta-analysis demonstrated that the proportion of patients experiencing adverse effects to be similar for patients randomized to homeopathic treatment compared to patients randomized to placebo and conventional medicine. The different harm terminology applied in the included studies and lack of standard reporting procedures made this work challenging and may bias this findings.

Competing Interests

The authors declare that they have no competing interests and that no financial interest exists.

Authors' contributions

TS conceived the study, performed the searches and selected studies for inclusion and collected study data, assessed the studies for risk of bias (methodological assessment), developed the risk of bias table, prepared the data for the statistical analysis and drafted the manuscript. FM and AK developed the risk of bias table, prepared the data for the statistical analysis and reviewed the subsequent version of the manuscript. TA selected studies for inclusion and collected study data and reviewed the subsequent version of the manuscript. JL performed the statistical analysis (the forest plots) and prepared the data for the statistical analysis. All authors read and approved the final manuscript.

Acknowledgements

We want to thank Claudia Witt and Rainer Lüdtke for sharing and preparing data on homeopathic aggravations for us and Jane Ekelund, Åsa Sohlén and Kari Riddervold for technical support. We also want to thank The Norwegian Homeopathic Association for financial support.

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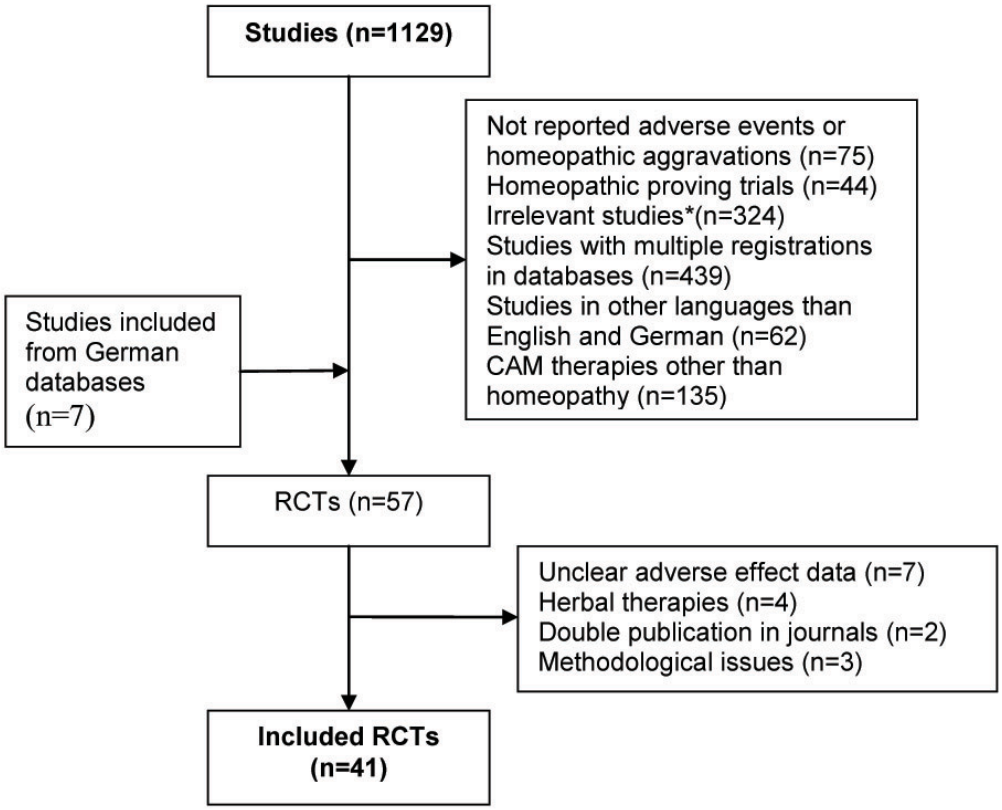

Figure 1. Flow chart for the randomized controlled trials

***Irrelevant studies:** Systematic reviews, guidelines, research reviews, cost-benefit evaluations, case-reports, letters, comments, debates, self-management and other abstracts

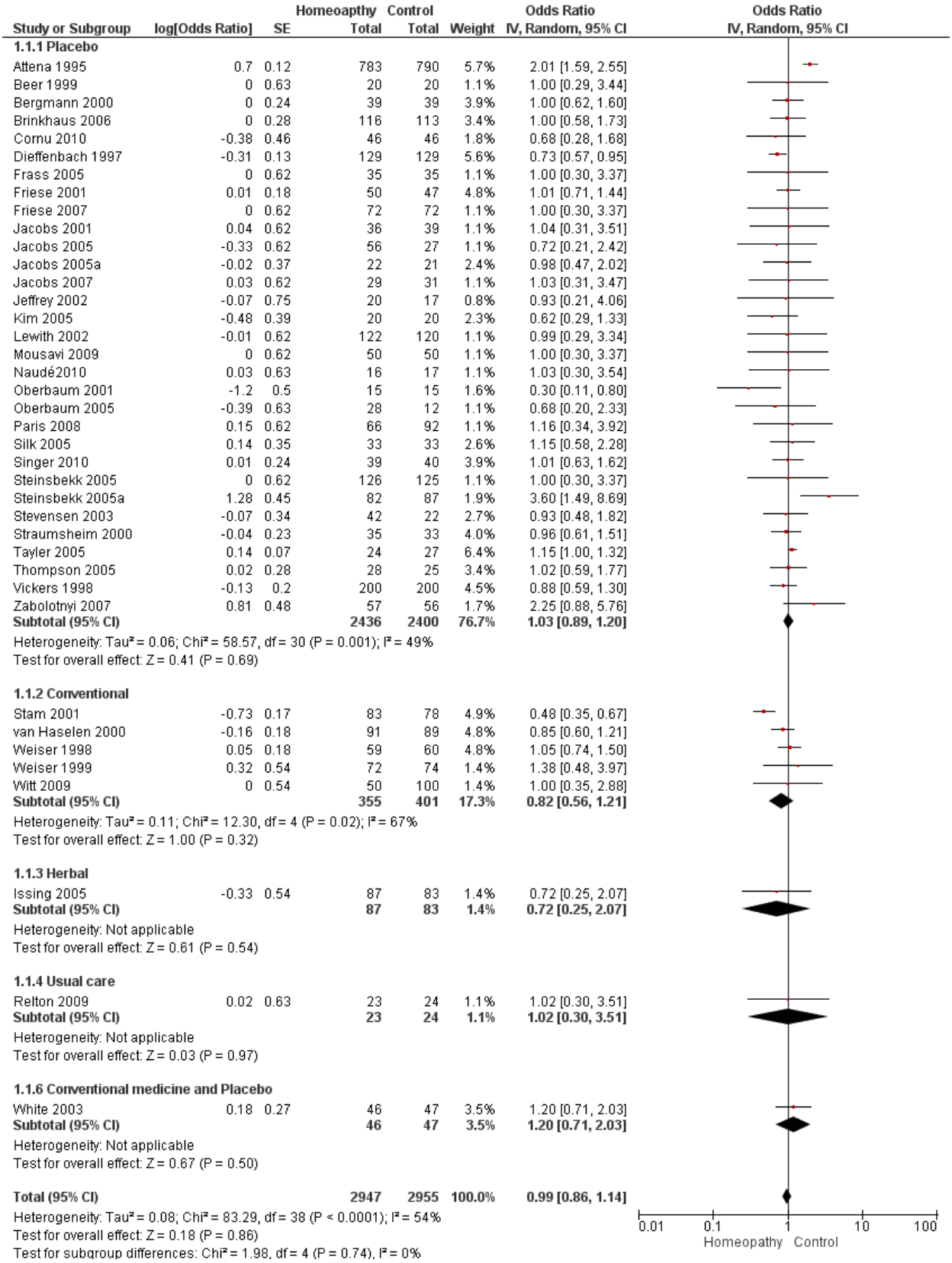

Figure 2: Forest plot for the randomized controlled trials, including sub-group analysis according to the category of controls

Table 1: Definitions of concepts

Table 1: Definitions of harm concepts		
Terminology	**Definition**	**References**
Risk	A compound measure of the probability of an event, and the magnitude and impact of its potentially negative outcome of that event.	(36),(32)
Indirect risk	Risk related to the setting effects, such as the practitioner rather than to the medicine. For example, a practitioner with limited medical and homeopathic skills may overlook serious symptoms and thereby cause a delay in necessary conventional treatment.	(6), (37)
Direct risk	Risk related to the intervention, e.g., harm caused by pharmacological products, medical treatments and procedures	(5), (6)
Homeopathic aggravations (direct and indirect risk)	A temporary worsening of existing symptoms following the administration of a correctly chosen homeopathic prescription, which is expected to be followed by an improvement.	(38), (22)
Adverse effects (direct and indirect risk)	All diseases or unwanted and/or harmful reactions resulting from a medication or an intervention, regardless of their relation to the actual treatment.	(39),(32)
Adverse reactions (direct and indirect risk)	Present when the right drug was administered for the correct indication, in the proper dose, by the right route, yet still the patient develops an unwanted symptom, suffers unexpectedly, and is exposed to unpreventable harm. Adverse reactions may also result from some diagnostic tests, therapeutic interventions or devices.	(36),(40)
Adverse drug reactions (direct risk)	An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product. The reaction predicts hazards regarding future administration and warrant prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.	(32, 41)

Table 2: Excluded studies

Table 2: Excluded studies		
Study id	Method	Reason for exclusion
Aabel, 2010	RCT	On a general level, discussed whether a prophylactic treatment schedule could minimize the problems of HA in homeopathy. No AE/HA data
Bell, 2004	RCT	No AE/HA data
Bell, 2004	RCT	No AE/HA data
Bernstein, 2006	RCT	Active medication was a herbal ointment
Ferrera , 2008	RCT	Active medication was not homeopathic medication
Frass, 2011	RCT	Double publication
Friese 1997	RCT	Double publication (Friese 2001)
Garrett, 1997	RCT	Unclear randomization process
Hill, 1996	RCT	Active medication was a herbal product (mother tincture)
Jeaner, 2000	RCT	Data on “secondary effects”, which was not defined
Katz, 2005	RCT	No results available, due to low compliance
Mousavi, 2009	RCT	Suggested that the verum (Ignatia) was a potentially low risk option in treating lichten planus, without reporting AE/ HA
Schirmer, 2000	RCT	Not a homeopathic intervention. Reinjection of patient´s own blood ("Eigenblut")
Seeley, 2006	RCT	The study reported no complications after face lifts, no AE/HA data from homeopathic treatment
Strösser, 2000	RCT	No AE/HA data
Tveiten, 2003	RCT	Pooled data from two studies
AE: Adverse effects HA: Homeopathic aggravations		

Table 4. Adverse effects and homeopathic aggravations reported in the randomized controlled trials

Study ID	Number of participants		Total number of adverse effects (AE) (Number of participants experienced AE)		Grade 1-5 (CTCAE)										Number of homeopathic aggravation (HA) (Number of participants experienced HA)		Grade 1-5 (CTCAE)									
					Treatment					Control							Treatment					Control				
	Treatment	Control	Treatment	Control	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5	Treatment	Control	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
Aabel S, 2000	37	33	NR	NR											13(13)	4(4)	9		4			4				
Attena F, 1995	783	790	98 (77)	NR (17)	0		98								NR	NR										
Beer AM, 1999	20	20	0 (0)	0 (0)	0										NR	NR										
Bergmann J, 2000	39	39	8 (8)	8 (8)	8	8					6	2			NR	NR										
Brien S, 2010	49	34	125 (?)	60 (?)	60	122		3			59		1			57(?)	37(?)	57					37				
Brinkhaus B, 2006	116	113	NR (11)*	NR (19)*	0										NR	NR										
Comu C, 2010	46	46	6*(6)*	12*(12)*	12			3*	1*	2*			7	3	2	NR	NR										
Dieffenbach, 1997	129	129	2 (2)	4 (4)	4	2					3	1				NR	NR										
Frass M, 2005	35	35	0 (0)	0 (0)	0											NR	NR										
Friese KH, 2001	50	47	29 (22)	23 (17)	23	11	18				5	18				NR	NR										
Friese KH, 2007	72	72	1 (1)	1 (1)	1	1					1					NR	NR										
Issing W, 2005	87	83	1 (1)	2 (2)	2	1					2					NR	NR										
Jacobs J, 2001	36	39	0 (0)	0 (0)	0											NR	NR										
Jacobs J, 2005	56	27	0 (0)	NR(1)	0											Increased severity and number of hot flashes/headache	NR										
Jacobs J, 2005a	22	21	0 (0)	0 (0)	0											NR	NR										
Jacobs J, 2007	29	31	1 (1)	1(1)	1			1					1			A higher pain score temporary after taking the remedy	NR										
Jeffrey SLA, 2002	20	17	0 (0)	0 (0)	0											NR	NR										
Kim LS, 2005	20	20	2 (2)	5 (5)	5	2					5					1(1)	0(0)	1									
Lewith GT, 2002	122	120	0 (0)	0 (0)	0											NR	NR										
Mousavi F, 2009	50	50	0 (0)	0 (0)	0											NR	NR										
Naudé DF, 2010	16	17	0 (0)	0 (0)	0											NR	NR										
Oberbaum M, 2001	15	15	14 (7)*	19(14)*	5			8	6*				5	14*		NR	NR										
Oberbaum M, 2005	28	12	0 (0)	0 (0)	0											NR	NR										
Paris A, 2008	66	92	0 (0)	0 (0)	0											NR	NR										
Relton C, 2009	23	24	0 (0)	0 (0)	0											NR	NR										
Silk R, 2005	33	33	8 (4)	3 (3)	3	8					3					NR	NR										
Singer SR, 2010	39	40	8 (8)	8 (8)	8	6	1	1			4	4				NR	NR										
Stam C, 2001	83	78	12 (12)	38 (37)	38	12					34		4			NR	NR										
Steinsbekk A, 2005	126	125	0 (0)	0 (0)	0											NR	NR										
Steinsbekk A, 2005a	82	87	15 (15)	0 (0)	0	15										NR	NR										
Stevinson C, 2003	42	22	5 (5)	5 (3)	5	5					5					NR	NR										
Straumsheim P, 2000	35	33	11 (11)	11 (11)	11		11					11				17(33)	20(30)	17					20				
Taylor MA, 2000	24	27	11 (11)	7 (7)	7	11					7					10(10)	5(5)	10					5				
Thompson EA, 2005	28	25	7 (7)	6 (6)	6	7					6																

Study ID	Number of participants		Total number of adverse effects (AE) (Number of participants experienced AE)		Grade 1-5 (CTCAE)										Number of homeopathic aggravation (HA) (Number of participants experienced HA)		Grade 1-5 (CTCAE)									
					Treatment					Control							Treatment					Control				
	Treatment	Control	Treatment	Control		G1	G2	G3	G4	G5	G1	G2	G3	G4	G5	Treatment	Control	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
van Hasselen RA, 2000	91	89	12 (12)	16 (16)	16	7	3	2			7	4	5			NR	NR										
Vickers A, 1998	200	200	9 (9)	12 (12)	12	9					11		1			NR	NR										
Weiser M, 1998	59	60	29 (16)	28 (15)	28	29					28																
Weiser M, 1999	72	74	3 (2)	1 (1)	1	3					1					NR	NR										
White A, 2003	46	47	7 (7)	5 (5)	5	7					5					6(6)	5(5)	6					5				
Witt A, 2009	50	100	0 (0)	2 (2)	2						2					NR	NR										
Zabolotnyi DI, 2007	57	56	8 (6)	1 (1)	1	5	3				1					NR	NR										
SUM	3033	3022	426 (263)	264 (228)	264	271	134	15	0	0	195	40	24	3	2	91(63)	67(44)	100	0	4	0	0	71	0	0	0	0

NR: Not reported in publication, * Not related to study medication, ?: Te number of participants was unclear reported in the study.

Table 3. Assessment of the methodological quality of the randomized controlled trials

The column "Participants" refers to the number of participants randomized to either treatment or control group. "Dropout" refers to participants who left the study in either the treatment or the control group respectively.

Study ID	Indication	Participants		Dropout		PC / ITT analyses	Methodological assessment	Intervention	Duration of treatment	Main findings	Funding
		Treatment	Control	Treatment	Control		Cochrane Handbook	Treatment vs Control	Days (d)		
Aabel S, 2000	Pollen allergy	57	55	5	1	Yes/No	A-clear	Betula C30 vs placebo	28	ND	The Research Council of Norway
Attena F, 1995	Influenza-like syndromes	765	790	NR	NR	No/No	B-unclear	Oscillococcinum C200 vs placebo	49	ND	NR
Bear AM, 1999	Premature rupture of the membranes (PROM) at term	20	20	0	0	Yes/No	B-unclear	Caulophyllum D4 vs placebo	1 (seven hours with hourly drug application)	ND	NR
Bergmann J, 2000	Fertility disorders (Amenorrhoe and Oligomenorrhoe)	59	59	6	5	Yes/No	B(S)	Complex homeopathic remedy (Phyto-Hypophyson L) vs placebo	112 (4 cycles)	No significant differences with respect to "baby take home rate". Significant increase of progesterone during the luteal phase in the oligomenorrhoe verum group.	NR
Brien S, 2010	Rheumatoid arthritis	49	54	14	15	Yes/Yes	A-clear	Individual and complex homeopathy vs placebo	168	Homeopathic consultation associated with relevant benefits, not the remedies	The National Institute of Health Research, Samueli Institute USA, Southampton Complementary Medicine Research Trust
Brinkhaus B, 2006	Knee surgery	116	115	0	2	Yes/Yes	A-clear	Arnica D30 vs placebo	11	Arnica more effective than placebo in post operative swelling	NR
Camu C, 2010	Aortic valve surgery	46	46	0	0	Yes/Yes	A-clear	Arnica and Bryonia 5CH vs placebo	5	No evidence of effect for Arnica/Bryonia compared to placebo	The Laboratories Boiron, Sante-Foy-lès-Lyon, France
Oleffenbach, 1997	Acute respiratory tract infection	129	129	0	0	Yes/Yes	A-clear	Complex homeopathic remedy (Bronchoselect) vs placebo	21	Significant differences in disease duration and in duration until improvement	NR
Frass M, 2005	Severe sepsis	35	35	2	1	No/No	A-clear	Homeopathic remedies in C200 vs placebo	30-180	Homeopathy may be beneficial for the survival of critically ill patients	NR
Friese K-H, 2001	Adenoid vegetations	50	47	12	11	Yes/Yes	A-clear	Four different homeopathic remedies vs placebo	90	ND	Karl and Veronica Carstens Stiftung, Essen, Germany
Friese KH, 2007	Acute rhinosinusitis	72	72	1	65	Yes/Yes	B-unclear	Complex homeopathic remedy (Cinnabsan Pentarkan H) vs placebo	7	Significant improvements in the treatment group and not in the placebo group.	NR
Issing W, 2008	Vertigo	67	65	6	6	No/Yes	B-unclear	Vertigoheel vs Ginkgo biloba	56	Both treatments improved vertigo status. Vertigoheel was non-inferior to Ginkgo biloba	Biologische Heilmittel Heel GmbH, Germany
Jacobs J, 2001	Acute otitis media in children	56	59	2	1	Yes/Yes	A-clear	Individualised homeopathic remedies vs placebo	5	ND	The Standard Homeopathic Company
Jacobs J, 2005	Menopausal symptoms in breast cancer survivors	56: 30 complex remedy and 26 individualised remedy	27	5	1	No/No	A-clear	Complex vs individualised homeopathy vs placebo	365	ND	IDEA award. Army Breast Cancer Research Project

Study ID	Indication	Participants		Dropout		PC / ITT analyses	Methodological assessment	Intervention	Duration of treatment	Main findings	Funding
		Treatment	Control	Treatment	Control		Cochrane Handbook	Treatment vs Control	Days (d)		
Jacobs J, 2005	Hyperactivity disorder (ADHD)	22	21	2	3	No/Yes	A-clear	Individualized homeopathic remedies vs placebo	126	ND	The Centers for Disease Control and Prevention
Jacobs J, 2007	Dengue fever	29	31	0(0)	0	No/No	A-clear	A fixed combination of six homeopathic remedies vs placebo	7	ND	Boiron Research Institute, Newtown Square, USA
Jeffrey SLA, 2002	Pain after carpal-tunnel release surgery	20	17	0	0	No/No	B-unclear	Arnica D6 and Arnica ointment vs placebo	14	Significant reduction in pain after two weeks in the treatment group. No differences in grip strength and wrist circumference	NR
Kim LS, 2005	Seasonal allergic rhinitis	20	20	2	4	Yes/Yes	A-clear	Homeopathic allergen preparation D6 (isopathy) vs placebo	28	Statistical reduction of the allergy rhinitis symptoms in the homeopathic group	NR
Lewith GT, 2002	House dust mite allergy in asthmatic people	122	120	21	19	Yes/Yes	A-clear	Homeopathic immunotherapy C30 vs placebo	112	ND	Smith's Charity, NHS Executive South and West Research and Development Directorate, Boiron and Maurice Laing Foundation
Mousavi F, 2009	Minor aphthous ulcer	50	50	0	0	No/No	B-unclear	Individualized homeopathic remedies vs placebo	6	A significant difference was found in favour of homeopathy regarding pain and ulcer size	NR
Naudé DF, 2010	Chronic primary insomnia	16	17	2	1	No/No	A-clear	Individualized homeopathic remedies vs placebo	28	A significant difference was found, in favour of the homeopathic treatment	NR
Oberbaum M, 2001	Chemotherapy-induced stomatitis in children	15	15	1	1	No/Yes	A-clear	Traumeel S (homeopathic complex remedy) vs placebo	14	A statistical difference was found, in favour of the homeopathic treatment	The International Society of Homotoxicology, Baden-Baden, Germany
Oberbaum M, 2005	Mild postpartum bleeding	25	12	0	0	Yes/Yes	B-unclear	Arnica D6/D30 and Bellisperennis D6/D30 vs placebo	3	A statistical difference was found, in favour of the homeopathic treatment	Mirski Foundation, Shaare Zedek Medical Center, Jerusalem
Paris A, 2008	Effect on analgesic intake following knee ligament reconstruction	66	94: 67 of the 27 waiting list control	0	0	Yes/Yes	A-clear	Complex homeopathy vs placebo vs waiting list control	3	ND	Laboratoires Boiron, France
Relton C, 2009	Fibromyalgia syndrome	25	24	5	5	Yes/Yes	A-clear	Usual care +individualized homeopathy vs usual care	154	A statistical difference was found in favour of the homeopathic treatment regarding primary outcome measure	Barnsley Hospital NHS Foundation Trust and the charity Homeopathy Action Trust
Silk R, 2005	Common cold in a geriatric population	33	33	0	0	No/No	B-unclear	Homeopathic zincgluconate glycine vs placebo	6	The homeopathic remedy was therapeutic in the treatment of common cold in a geriatric population	NR
Singer SR, 2010	Pain relief following hallux valgus surgery	39	40	0	1	Yes/Yes	A-clear	Homeopathic medication (Traumeel S) vs placebo	14	ND	HEEL Company Baden-Baden, Germany. Researchers had full control over the flow, data
Stam C, 2001	Acute low or back pain	83	78	2	4	No/Yes	B-unclear	Homeopathic gel (Spiroflor) vs topical medication (cremor capsici compositus)	7	Both treatments are equally effective in the treatment of low or back pain	NR

Study ID	Indication	Participants		Dropout		PC / ITT analyses	Methodological assessment	Intervention	Duration of treatment	Main findings	Funding
		Treatment	Control	Treatment	Control		Cochrane Handbook	Treatment vs Control	Days (d)		
Steinsbekk A, 2005	Prevention of upper respiratory tract infections in children	126	125	0 (0)	25	Yes/Yes	A-clear	Homeopathic remedies either Calc-Carb, Puls or Sulphur vs placebo	84	ND	Norwegian Research Council
Steinsbekk A, 2005	Prevention of upper respiratory tract infections in children	82	87	14	15	Yes/Yes	A-clear	Individualised homeopathic treatment vs waiting list with self-selected conventional health care	84	Individualised homeopathic care had clinically relevant benefits compared to a waiting list	Norwegian Research Council
Stevinson C, 2003	Prevention of pain and bruising after hand surgery	42:21(D30) + 21(D6)	22	2	0	Yes/Yes	A-clear	Homeopathic Arnica D30 or Arnica D6 vs placebo	21	ND	Dr Susi Kumar and Jamila Mitra Charitable Trust (UK)
Straumsheim P, 2000	Preventing migraine attack	35	35	5 (not reported which group)	5 (not reported which group)	Yes/No	A- clear	Individualised homeopathy vs placebo	112	ND	Norwegian Research Council
Taylor MA, 2000	Perennial allergic rhinitis	24	27	1	0	Yes/No	A-clear	Homeopathic immunotherapy C30 vs placebo	28	Homeopathic dilutions differed from placebo	Fonds voor het Wetenschappelijk Onderzoek Homeopathie, Blackie Foundation Trust
Thompson EA, 2005	Symptoms of estrogen withdrawal in breast-cancer survivors	25	25	5	5	Yes/Yes	A-clear	Individualised homeopathy vs placebo	112	ND	Homeopathic Research Committee
van Haselen RA, 2000	Osteoarthritis of the knee	91	89	5	9	Impossible due to lack of data/Yes	A-clear	Homeopathic gel vs NSAID gel	28	The homeopathic gel was as effective and well tolerated as the NSAID gel	The medical Scientific department of VSM gancosmiddelen, NL
Vickers A, 1998	Muscle soreness following long-distant running	200	200	59	60	Yes/Yes	A-clear	Arnica D30 vs placebo	5	ND	Blackie Foundation Trust
Weiser M, 1996	Vertigo	59	60	6	6	Yes/the last observation carried forward principle	A-clear	Homeopathic remedy vs betahistine hydrochloride	42	Both a clinically relevant reduction of vertigo in both groups	NR
Weiser M, 1999	Seasonal allergic rhinitis	72	74	4	7	Yes/per protocol analysis	A-clear	Homeopathic nasal spray vs intranasal cromolyn sodium therapy	42	The nasal spray was as effective as conventional therapy	Hexal GmbH, Baden-Baden Germany
White A, 2003	Childhood asthma	46	49	9	9	Yes/yes	A-clear	Individualised homeopathy vs placebo (both groups received conventional treatment)	365	ND	The Prince of Wale's Foundation for Integrated Health, London, UK
Witt A, 2009	Vulvovaginal candidiasis	50	100:50 and 50 additional lactobacilli	2	4	Yes/No	A-clear	Individualised homeopathy vs itraconazole vs itraconazole +lactobacilli	365 (homeopathy), 182 (itraconazole and lactobacilli)	Itraconazole was statistically more effective than homeopathic treatment.	Non funding
Zabolotnyi DI, 2007	Acute maxillary sinusitis	57	56	1	6	Yes/Yes	A-clear	Complex homeopathic remedy (sinfrontal) vs placebo	22	Complex homeopathy was significantly better than placebo	NR

[1] Authors interpretation, Classical homeopathy: Prescribing of a single remedy according to to the similia law, Complex homeopathy: A combination of a number of homeopathic agents or remedies, Homeopathic immunotherapy: Homeopathic (Ultramolecular) doses of an allergen, Isopathy: A homeopathic subform, where the preparations are made from the causal illness or its byproducts, PC: Power calculation, ITT: Intention to treat analysis, QOL: Quality of life, NS: No statistical difference between the groups NR: Not reported in publication: A = low risk of bias, B = moderate risk of bias.

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ID	Search	Hits	Edit	Delete
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#2	MeSH descriptor **Homeopathy** explode tree **1**	202	edit	delete
#3	(#1 OR #2)	545	edit	delete
#4	(#1 OR #2), from 1995 to 2001	199	edit	delete
#5	(aggravation*):ti,ab,kw or (homeopathic aggravation*):ti,ab,kw	293	edit	delete
#6	(adverse effect*):ti,ab,kw or (safety):ti,ab,kw or (adverse event*):ti,ab,kw or (side effect*):ti,ab,kw	164129	edit	delete
#7	MeSH descriptor **Drug Toxicity** explode all trees	1259	edit	delete
#8	MeSH descriptor **Safety** explode all trees	2950	edit	delete
#9	(#5 OR #6 OR #7 OR #8), from 1995 to 2001	40429	edit	delete
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#1	(homeopathic):ti,ab,kw or (homoeopathic):ti,ab,kw or (homeopathy):ti,ab,kw or (homoeopathy):ti,ab,kw	523	edit	delete
#2	MeSH descriptor **Homeopathy** explode tree 1	194	edit	delete
#3	(#1 OR #2)	523	edit	delete
#4	(#1 OR #2), from 2002 to 2010	129	edit	delete
#5	(aggravation*):ti,ab,kw or (homeopathic aggravation*):ti	276	edit	delete
#6	(adverse effect*):ti,ab,kw or (safety):ti,ab,kw or (adverse event*):ti,ab,kw or (side effect*):ab	150487	edit	delete
#7	MeSH descriptor **Drug Toxicity** explode all trees	1120	edit	delete
#8	(#5 OR #6 OR #7), from 2002 to 2010	54135	edit	delete
#9	(#3 AND #8), from 2002 to 2010	35	edit	delete

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#16	Search **((#12) OR #13) OR #15** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English, published in the last 10 years**	09:51:45	35380
#15	Search **("Risk Management"[Mesh] OR "Drug Tolerance"[Mesh])** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English, published in the last 10 years**	09:50:44	8197
#13	Search **(((adverse effect[Title/Abstract]) OR adverse event[Title/Abstract]) OR side effect[Title/Abstract]) OR safety [Title/Abstract]** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English, published in the last 10 years**	09:49:36	28129
#12	Search **(aggravation[Title/Abstract]) OR homeopathic aggravation[Title/Abstract]** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English, published in the last 10 years**	09:48:39	108
#11	Search **(#7) OR #9** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English, published in the last 10 years**	09:43:54	146
#9	Search **("Homeopathy"[Mesh] OR "Materia Medica"[Mesh])** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English, published in the last 10 years**	09:39:18	118
#7	Search **(homeopathy[Title/Abstract]) OR homeopathic[Title/Abstract]** Limits: **Humans, Clinical Trial, Randomized Controlled Trial, English, published in the last 10 years**	09:37:22	127

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