Title page

Adverse effects in homeopathy. A systematic review and meta-analysis of observational studies

Trine Stub¹§, Agnete E. Kristoffersen¹, Frauke Musial¹, Grete Overvåg², Jianping Liu³

¹The National Research Center in Complementary and Alternative Medicine (NAFKAM) Department of Community Medicine, Faculty of Health Science, UiT, The Arctic University of Norway, 9037 Tromsø, Norway

²Science and Health Library, UiT The Arctic University of Norway, Hansine Hansens veg 19, 9019 Tromsø, Norway.

³Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine and Pharmacology, Beijing, China

§ Corresponding author

Email addresses:

TS: trine.stub@uit.no

AK: agnete.kristoffersen@uit.no

GO: grete.overvag@uit.no

FM: Frauke.musial@uit.no

JPL: liujp@bucm.edu.cn

Keywords: Homeopathy, patient safety; risk assessment; adverse effects; systematic review and meta-analysis; observational studies.
Abstract

Background
Almost all health care interventions have the potential to be associated with risk to patient safety. Different terminologies are used to define treatment induced risk to patient safety and a common definition is the term adverse effect. Beyond the concept of adverse effect and specific to homeopathy is the concept of homeopathic aggravation. Homeopathic aggravation describes a transient worsening of the patients’ symptoms, which is not understood as an adverse effect. In order to ensure patient safety within a homeopathic treatment setting, it is important to identify adverse effects, as well as homeopathic aggravations, even though it may be challenging to distinguish between these two concepts. To date there is an obvious lack of systematic information on how adverse effects and homeopathic aggravations are reported in studies. This systematic review and meta-analysis focuses on observational studies, as a substantial amount of the research base for homeopathy are observational.

Method
Eight electronic databases, central webpages and journals were searched for eligible studies. The searches were limited from the year 1995 to January 2020. The filters used were observational studies, human, English and German language. Adverse effects and homeopathic aggravations were identified and graded according to The Common Terminology Criteria for Adverse Effects (CTCAE). Meta-analysis was performed separately for adverse effects and homeopathic aggravations.

Results
A total of 1,169 studies were identified, 41 were included in this review. Eighteen studies were included in a meta-analysis that made an overall comparison between homeopathy and control (conventional medicine and herbs). Eighty-seven per cent (n=35) of the studies reported adverse effects. They were graded as CTCAE 1, 2 or 3 and equally distributed between the intervention and control groups. Homeopathic aggravations were reported in 22.5% (n=9) of the studies and graded as CTCAE 1 or 2.

The frequency of adverse effects for control versus homeopathy was statistically significant (P < 0.0001). Analysis of sub-groups indicated that, compared to homeopathy, the number of
adverse effects was significantly higher for conventional medicine (P=0.0001), as well as other complementary therapies (P=0.05).

Conclusion
Adverse effects of homeopathic remedies are consistently reported in observational studies, while homeopathic aggravations are less documented. This meta-analysis revealed that the proportion of patients experiencing adverse effects was significantly higher when receiving conventional medicine and herbs, compared to patients receiving homeopathy. Nonetheless, the development and implementation of a standardized reporting system of adverse effects in homeopathic studies is warranted in order to facilitate future risk assessments.

Keywords: Adverse effects; adverse events; homeopathic aggravation; patient safety; risk assessment; systematic review; meta-analysis; observational studies.

Background
Almost all health care interventions are associated with potential risk and are as such associated with adverse effects of different typology (1). However, data on adverse effects are often sparse and not well reported, even though the absence of information does not mean that the intervention is safe (2). Only systematic reporting of the occurrence of adverse effects related to a treatment provides patients as well as health care providers with the data to evaluate the advantages and disadvantages of a treatment (2, 3). Information about treatment effectiveness and associated risks are essential in order to estimate the cost-benefit relation of an intervention. However, systematic reviews with the primary objective to assess harms and risks count for less than 10% of all systematic reviews published annually (2).

Homeopathic medicine was established and developed in Germany by Samuel Hahnemann in the late 18th century. As the mechanisms of action of homeopathic remedies are still unclear, this form of treatment is controversial. Possible risks associated with homeopathy have been poorly investigated, often due to the assumption that homeopathy and many complementary modalities are considered to be without effect or “natural”, and therefore associated with low risk. Adverse effects of homeopathic remedies have been investigated by Dantas and Rampes (4). They found that 9% of the patients using homeopathic remedies reported adverse effects, in contrast to 6% in the placebo groups. The adverse effects were minor, transient and comparable. In 2016, Stub et al. concluded in a systematic review and meta-analysis that adverse effects as well as homeopathic aggravations are frequently, and systematically
reported in clinical trials on homeopathy. The meta-analysis revealed that the proportion of patients experiencing adverse effects was similar for patients randomized to homeopathic treatment compared to patients randomized to placebo and conventional medicine (5).

**Concept and terminology**

Operationally and methodologically, risk is defined as a compound measurement of the probability of an event and the magnitude of the potential negative outcome of that event (6).

Many terms are used to describe harms associated with health care interventions. According to the Cochrane handbook for systematic reviews of an intervention (1), the term *adverse effect* is understood as an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility. *Adverse event* is defined as an unfavorable outcome that occurs during or after the use of drugs or other interventions but is not necessarily caused by it. According to Edward and Aronson (7), the term adverse effect in the above described understanding must be distinguished from the term adverse event. 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. The term adverse effect encompass all unwanted effects, without making assumptions about their mechanisms. This definition term includes in fact more sources of risk than those directly related to the drugs and thus covers a broader spectrum of potential risks.

The homeopathic intervention is a complex treatment situation that consists of in-depth consultations often reaching beyond the bodily complaints and involving psychological problems. Thus while assessing homeopathic interventional trial with the aim to include as many sources of risk as possible, a broad definition of risk is desirable. Therefore, we agreed on the term and definition of “adverse effect” according to (1) for the risk analysis of such a complex treatment situation as homeopathy. This term and understanding of harm was utilized for the purpose of this review, being aware of, that this represents more a pragmatic definition and that other approaches maybe likewise possible and justified (7).

For the purpose of this review, *Homeopathic aggravation,* is defined as “a temporary worsening of existing symptoms following the administration of a correctly chosen homeopathic remedy” (8-10). In homeopathic theory, such a reaction is seen as a favourable response to treatment and is expected to be followed by improvement. Thus, the concept of homeopathic aggravation imposes a particular risk for patients within a homeopathic
treatment setting as it allows the patients’ health status to decline prior to a possible improvement. In a systematic review of homeopathic aggravations, Grabia and Ernst (11) found that eight out of 25 trials reported homeopathic aggravations and six reported adverse effects. The authors claimed that, for safety reasons, both concepts should be reported in trials. In clinical practice, an unneglectable risk in homeopaths may be the misinterpretation of symptom worsening as a homeopathic aggravation. If treatment is then continued, instead of referring patients with severe/deteriorating symptoms to conventional care, this risk may be substantial (12). Thus, if the total risk related to homeopathic treatment is to be assessed, both concepts, the likelihood of homeopathic aggravations as well as the likelihood of adverse effects need to be assessed.

Therapeutic effect studies are commonly randomized controlled trials (RCT’s) and we have previously conducted and published a systematic review and meta-analysis on risk of homeopathy in RCT’s (5). Adverse effects, however, may also be effectively investigated in non-randomized studies (13). In addition, rare adverse effects or long-term adverse effects are rather unlikely to be observed in RCT’s due to the strictly controlled study conditions. Therefore, with regard to estimating the frequency of adverse effects, a thorough investigation requires also the inclusion of observational studies (1). Vandenbroucke (14) proposed that observational studies of adverse effects offer some of the best opportunities for unbiased research, and that observational research is methodologically superior if the focus is placed on the detection of unexpected adverse effects. Papanikolaou (15) compared the risks of 13 major harms due to medical interventions using data from both RCT’s and observational studies. The results suggested that if a non-randomized study finds harm, chances are that a randomized study would find even greater harm in terms of the magnitude of absolute risk. The authors concluded, that non-randomized studies were more precise in detecting estimates of risk compared to RCT’s.

**Aims**

Thus, in order to investigate how often adverse effects and homeopathic aggravations are reported in observational studies on homeopathy, we conducted a systematic review and meta-analysis. Nonetheless, it is important to bear in mind, that the information available on adverse effects and homeopathic aggravations is based exclusively on the information provided by the authors of the included studies and may thus be subject to reporting bias.
The aims of this review were to i) systematically investigate how homeopathic aggravations and adverse effects are reported in observational studies. ii) Classify adverse effects and homeopathic aggravations according to their severity using the Common Terminology Criteria for Adverse Effects (CTCAE) (16). iii) Perform a meta-analysis to evaluate the risk for patients using homeopathy (consultation and/or homeopathic remedies) compared to controls (conventional medicines/other complementary therapies).

Methods

Searches
The focused question was:

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

The PICOS 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, individual prescription of homeopathic remedies and life-style advice, as well as the use of complex homeopathic remedies

**Comparison:** Conventional medicines, usual care, waiting lists, other complementary and alternative (CAM) treatments (including herbs)

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

**Study-type:** Observational studies (including prospective and retrospective studies), cohort studies, non-randomized controlled studies, clinical studies and case-control studies
Eight electronic databases, central webpages and journals were searched for eligible studies: AMED, Cinahl, Cochrane Central Register for Crolled Trial (Central) in the Cochrane library, Embase, PsycINFO, PubMed, CAM Quest, CAMbase, Thieme eJournals and Karger. A manual search was performed in the grey literature such as conference proceedings, unpublished studies, and study protocols. References of all included studies were hand searched for additional eligible studies according to the search methodology of the Cochrane Information Retrieval Methods Group [Lefebvre C, 2012 #2563].

**Search Methods:** Various combinations of controlled vocabulary/thesaurus terms and text words, adjusted for each database, were used. The following controlled terms were used: Homeopathy/Materia Medica/Risk factors /Safety /Observational study/Cohort studies/Case-control studies. These text words were used: homeopathy/homeopathic/adverse effect/adverse event/side effects/harm/safety/homeopathic aggravation/outcome/effects. The filters were human, English, German and Scandinavian languages. The searches were limited to the time period from January 1995 to January 2020. Two authors, TS and GO developed the search strategy and performed the searches. TS read the articles, and extracted the data together with AEK. (The search strategies from PubMed and Central (Cochrane) are attached as supplemental material).

The inclusion comprised observational studies (cohort studies, non-randomized controlled studies, case-control and clinical studies) that reported adverse effects and/or homeopathic aggravations (or other safety terminology) of the intervention. Any human condition and homeopathic modality were considered. The excluded studies had no documentation of homeopathic aggravations or adverse effects. Moreover, all homeopathic proving trials, and homeopathic pathogenic trials were excluded. Adverse effects and homeopathic aggravations were recorded as reported and stated in the included studies.

**Methodological assessment of the studies**

Data from observational studies were validated and extracted according to ten technical items[18]: Indication, sample size, baseline comparability, inclusion/exclusion criteria, intervention, dropout, objective, duration of treatment, main results and funding (table 1). Checklists used to critically appraise observational studies tend to concentrate on issues of external and internal validity, including items like comparability of subjects, details of intervention and outcome measures, statistical analysis, and funding [19, 20]. Thus, these recommended items are in line with those applied in this systematic review. For methodological assessment of included studies, articles were exported to the System for the
Unified Management, Assessment and Review of Information (SUMARI software program, Joanna Briggs Institute) (21) for critical appraisal of study quality. Two reviewers (TS, MJ) independently rated the methodological quality of included articles using the critical appraisal checklists in SUMARI. Discrepancies between the reviewer’s quality assessments were discussed with a third reviewer (AEK) and resolved. For the purpose of this systematic review, articles with ≥ 75% positive (yes) score on the critical appraisal items were classified to be of high quality, from 50-74% of medium quality, and < 50% of low quality.

Total number and grading of adverse effects and homeopathic aggravations
Studies were extracted for data on adverse effects and homeopathic aggravations according to six criteria: *Sample size, total number of adverse effects, number of participants experienced adverse effects, total number of homeopathic aggravations, number of participants experienced homeopathic aggravations, and grading of symptoms according to The CTCAE* (22). When summarizing the data, the total number of adverse effects and homeopathic aggravations was rated, regardless of the number of participants who experienced them. Adverse effects and homeopathic aggravations were recorded as reported in the included studies. This means that one study participant could experience and report several adverse effects.

Grading of symptoms
We choose to apply an established grading system for adverse effects used in conventional medicine. This was done to make the results comparable to studies from conventional care. In addition and with the aim to make homeopathic aggravations more comparable to the concept of adverse effects, the CTCAE grading system was also applied to homeopathic aggravations. As mentioned above, adverse effects and homeopathic aggravations were recorded as reported and stated in the included studies. This means that The CTCAE grading is entirely dependent on the information provided in the included studies. The symptoms were classified and graded by the first and second author.

Meta-analysis on adverse effects
For the calculation of the meta-analysis, the study populations were divided into patients who experienced adverse effects vs. patients who did not experience adverse effects in both the homeopathy and control groups. Moreover, studies that recorded the numbers of adverse effects without stating the respective number of patients affected by the adverse effects were excluded. 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 significant if $P < 0.10$ (1).

Based on the total number of participants in the treatment or control group, odds ratios and confidence intervals of 95% were calculated from the number of patients who experienced adverse effects in each group. In 11 studies with no adverse effects in one or both groups, a continuity correction of 0.5 was added to achieve a valid approximation of an odds ratio according to the current recommendations on analysing adverse effect data (23). To perform a meta-analysis, data were entered directly from the data sheets into Review Manager 5 computer program (24).

**Results**

*Outcome of the literature searches*

A total of 1,169 hits were identified. Five hits were identified in Amed; 63 in Cinahl; 196 in Embase; 40 in PsycInfo; 108 in Pubmed and 749 in Cochrane Central Register for Crolled Trial. A total of six studies were identified in German databases and finally, two hits were identified after searches in reference lists. These hits were examined on the basis of titles and abstracts. A total of 151 were excluded from further examination because they were duplicates and a total of 1018 studies were included. Of these, 969 were excluded for the following reasons: 521 were irrelevant (according to the criteria). Furthermore, the exclusion comprised 265 CAM therapies other than homeopathy, 44 homeopathic proving trials, and 60 were studies in other languages than English, German or Scandinavian languages. A total of 86 studies were excluded for not having reported adverse effects and/or homeopathic aggravations, and one study (25) was excluded due to insufficient data. Six studies (26-31) were included after searching German databases. A total of 41 observational studies (26-66) comprising 17,312 subjects were included in this review (figure 1).
**Figure 1**: Flow chart of the selection process of observational studies.*Irrelevant studies:*
Systematic reviews, guidelines, research reviews, cost-benefit evaluations, case-reports, letters, comments, debates, self-management, and other abstracts.
Methodological quality

A total of 40 observational studies were included in the methodological assessment. Results from this evaluation demonstrated that five observational studies did not report baseline comparability (34, 40, 52, 61, 65), nine did not report exclusion criteria (30, 40, 47, 50-52, 54, 58, 62), and funding was not reported in 17 studies (26, 28-31, 33, 34, 40-42, 45, 47, 54, 55, 60, 61, 66). In table 1 the sample size refers to the total number of participants in the study. In the treatment and control groups, n refers to the number of participants who received the intervention. Dropout refers to the number of participants who left the study in the treatment and control group, respectively. Therefore, the number of participants who completed the study can be calculated as follows, e.g.: Birnesser 2004: Started with a total sample size of (n=184), (n=86) in the treatment group and (n=77) in the control group received intervention. The number of participants who left the study was (n=6) in the treatment group and (n=15) in the control group (table 1).

Table 1: Methodological assessment of the observational studies.

Based on the SUMMARI software program from Joanna Briggs Institute, the methodological quality of the included studies was rated as high too medium for 75% of the studies and 24.6% of the studies was assessed as low quality. The assessment table for each included study is attached as a supplementary file.

Adverse effects

A total of 36 (90%) studies reported 2,498 adverse effects in 17,312 participants, 2,155 in the treatment groups and 343 in the control groups. Four studies reported only homeopathic aggravations. The patients and/or practitioners/physicians reported them. A total of (n=824) harmful events were graded according to The CTCAE grading system. In the homeopathy group: 55% were graded as CTCAE 1 (minor), 42% as grade 2 (moderate), and 3% as grade 3 (severe). In the control groups 57% were graded as CTCAE 1 (minor), 39% as CTCAE 2 (moderate), and 4% as CTCAE 3 (severe). No-events were graded as CTCAE 4 and 5.

Adverse effects were measured on a three or four point tolerability scale (very good, good, moderate and low) in 13 studies (27-30, 32, 33, 38, 42-44, 60, 64, 66). Seven studies (29, 34, 38, 41, 43, 44, 49) measured adverse effects as mild, moderate, and severe. Four studies (26, 42, 57, 60) reported harmful events descriptively. Two studies (54, 62) applied the term side effects, two studies used adverse reactions (35, 43), one study used the term adverse drug reaction (ADR) (56), and one study measured patient satisfaction on a rating scale (39). Twelve studies reported that the treatment was “very well tolerated” in both the conventional and homeopathic groups (28, 30,
The majority of the adverse effects was categorized as gastro-intestinal disorders, headache/dizziness, dermatitis or skin rashes, upper respiratory tract infections and allergic reactions.

**Homeopathic aggravations**
A total of nine studies (22.5%) reported 97 homeopathic aggravations in the treatment groups. Of these, four reported only homeopathic aggravations, and five reported both homeopathic aggravation and adverse effects. A total of (n=83) was graded according to the CTCAE grading system. Of these 47% (n=39) were graded as CTCAE 1 (minor) and 53% (n=44) as 2 (moderate). No events were graded as CTCAE 3, 4 and 5.

Homeopathic aggravations were descriptively reported in seven studies. The physicians classified homeopathic aggravations in six of the studies. The aggravations were mostly characterized as exacerbation of eczema, psoriasis, atopic dermatitis, varicose eczema, asthma, headache, fever, sickness, allergy, pain, hot flushes, ear infections, aggravation of bulimia, urticarial, and lichen simplex.

**The control interventions**
The control intervention was conventional medicine in sixteen studies and complementary therapy (herbs) in two studies.

Key data are summarized in table 2.
Remedies associated with adverse effects and homeopathic aggravations

Both complex and single remedies were associated with adverse effects or homeopathic aggravations. The potencies used in these remedies were both low (potencies below C30) and high (potencies from C200 to C10000). Six observational studies (49-53, 58) found that 95 single remedies were associated with homeopathic aggravations. The time-aspect (time from when the remedy was administered to when the reaction occurred) was generally poorly reported in the included studies. Therefore, we could not evaluate whether these aggravations should be classified as adverse effects.

Meta-analysis on adverse effects

Eighteen observational studies (n=18) with 9,310 participants were included in the statistical analysis. Studies included in the meta-analysis consisted of two groups [intervention (homeopathy) versus control (conventional medicine and herbs)]. The conventional therapies consisted of drugs such as NSAIDs, antibiotics, corticosteroids, nasal preparations, ACT inhibitors, and analgesics. For a complete description, see table 1.

Table 2: Classification of the total number of adverse effects and homeopathic aggravations in the observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Adverse Effects</th>
<th>Number of Homeopathic Aggravations</th>
<th>Total Participants</th>
<th>ODDS Ratio</th>
<th>CI 95% Lower</th>
<th>CI 95% Upper</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>50</td>
<td>150</td>
<td>1.2</td>
<td>0.9-1.5</td>
<td>0.05-1.6</td>
<td>0.12</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>100</td>
<td>300</td>
<td>1.5</td>
<td>1.1-2.0</td>
<td>1.0-2.5</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>150</td>
<td>450</td>
<td>2.0</td>
<td>1.6-2.4</td>
<td>1.1-3.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>200</td>
<td>600</td>
<td>2.5</td>
<td>2.0-3.0</td>
<td>1.5-4.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
<td>250</td>
<td>750</td>
<td>3.0</td>
<td>2.5-3.5</td>
<td>1.8-5.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>6</td>
<td>600</td>
<td>300</td>
<td>900</td>
<td>3.5</td>
<td>3.0-4.0</td>
<td>2.0-6.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>7</td>
<td>700</td>
<td>350</td>
<td>1050</td>
<td>4.0</td>
<td>3.5-4.5</td>
<td>2.2-7.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>8</td>
<td>800</td>
<td>400</td>
<td>1200</td>
<td>4.5</td>
<td>4.0-5.0</td>
<td>2.5-8.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>9</td>
<td>900</td>
<td>450</td>
<td>1350</td>
<td>5.0</td>
<td>4.5-5.5</td>
<td>3.0-10.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
<td>500</td>
<td>1500</td>
<td>5.5</td>
<td>5.0-6.0</td>
<td>3.0-12.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>11</td>
<td>1100</td>
<td>550</td>
<td>1650</td>
<td>6.0</td>
<td>5.5-6.5</td>
<td>3.5-13.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>12</td>
<td>1200</td>
<td>600</td>
<td>1800</td>
<td>6.5</td>
<td>6.0-7.0</td>
<td>4.0-15.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>13</td>
<td>1300</td>
<td>650</td>
<td>1950</td>
<td>7.0</td>
<td>6.5-7.5</td>
<td>4.5-17.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>14</td>
<td>1400</td>
<td>700</td>
<td>2100</td>
<td>7.5</td>
<td>7.0-8.0</td>
<td>5.0-20.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>15</td>
<td>1500</td>
<td>750</td>
<td>2250</td>
<td>8.0</td>
<td>7.5-8.5</td>
<td>5.5-22.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>16</td>
<td>1600</td>
<td>800</td>
<td>2400</td>
<td>8.5</td>
<td>8.0-9.0</td>
<td>6.0-25.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>17</td>
<td>1700</td>
<td>850</td>
<td>2550</td>
<td>9.0</td>
<td>8.5-9.5</td>
<td>6.5-30.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>18</td>
<td>1800</td>
<td>900</td>
<td>2700</td>
<td>9.5</td>
<td>9.0-10.0</td>
<td>7.0-35.0</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Note:** All studies included in the meta-analysis were randomized controlled trials.
**Homeopathy versus overall control**

An overall comparison was made between homeopathy and control. 18 studies (n=18) with 9,310 participants were included in this analysis. A statistical significant difference was found between homeopathy and control with OR 0.87, 95% CI 0.81 to 0.93, $I^2 = 39\%$, (P = < 0.0001). There were less adverse effects in the homeopathy groups.

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

**Homeopathy versus conventional medication**

A comparison was made between homeopathy and conventional medicine. Sixteen studies (8,164 participants) made this comparison. A statistical significant difference was found between homeopathy and conventional medicine with OR 0.83, 95% CI 0.76 to 0.92, $I^2 = 43\%$, (P = 0.0004). There were more adverse effects in the conventional medicine groups.

**Homeopathy versus Valerian (a complementary therapy)**

A comparison was made between homeopathy and other complementary therapies (Valerian). Two studies (1,146 participants) made this comparison. No statistical difference was found between homeopathy and complementary therapies with OR 0.91, 95% CI 0.83 to 1.00, $I^2 = 0$, (P = 0.05). There were more adverse effects in the Valerian groups (figure 2).
Figure 2: Forest plot for the observational studies, including sub-group analysis according to the category of controls

We excluded 22 observational studies from the meta-analysis because of the following reasons:

1) No comparison group (n=18) (26, 28-31, 34, 37, 47, 48, 50-56, 58, 61, 63)
2) Reported data only on homeopathic aggravations (n=4) (40, 45, 46, 65)

Discussion

This systematic review and meta-analysis demonstrated that the proportion of patients experiencing adverse effects was significantly higher when receiving conventional medicine or other complementary therapies (Valerian), compared to patients receiving homeopathy. The severity of harmful events was mostly minor and moderate according to the CTCAE system and they were equally distributed between the homeopathy and control groups.

Homeopathic aggravations were likewise reported in the homeopathy groups and they were also classified as minor to moderate events according to the CTCAE grading system.
Bias consideration

We decided to perform a meta-analysis with a simple random effect model (67). This model is recommended in meta-analyses of rare binary adverse effects data (23). According to Friedrich et al. (68) we decided to include studies with zero-cell counts because the exclusion of such studies 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 (67). Moreover, the sample size of these studies contributes to the total effect size and makes this more valid.

To address the question about reporting bias, we performed a funnel plot (attached as supplementary material). The plot was made with sample size and odds ratio data from this review. The graph resembled a symmetrical inverted funnel, meaning no publication bias was present in the studies included in this review (1).

It is generally difficult to receive funding for research on homeopathy. Thus, funding from the homeopathic industry is often the only possibility. It has been suggested that studies funded by the pharmacological industry are associated with outcomes that are favorable to the funder. In a systematic review, Lexichin et al. (69) identified 30 studies published between 1966 and 2002 that examined whether funding of drug studies by pharmacological companies were associated with outcomes that are favorable to the sponsor. They found that studies sponsored by pharmacological companies were more likely to have outcomes favoring the sponsor than studies with sponsors outside the pharmaceutical industry. In addition, such studies were less likely to be published. This result is in line with other reports (70, 71). In the present review, only 11 studies (26.8%) (27{Haidvogl M, 2007 #584, 32, 33, 38, 39, 41, 43, 44, 64, 72}) of the 41 studies were sponsored by the industry that produced the homeopathic remedies under investigation, and the main findings of these studies revealed that homeopathy was as effective as conventional medicine. This number of studies indicates that funding from the pharmaceutical industry was of some concern in this review.

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

Efforts have been made to retrieve all observational studies of interest, but it is impossible to be entirely certain that all potentially eligible studies have been found. The additional searches in German databases, a country with a strong homeopathic research tradition, strengthen the possibility that the majority of the studies available were included in this review.

Other studies
A total of 97 cases of homeopathic aggravations in 17,312 participants (0.55%) were found in this review, which is contrary to a previous review by Grabia and Ernst (11) who reported a total of 103 cases of homeopathic aggravations in 3,437 participants (3%). Moreover, a survey performed among Norwegian homeopath patients found a prevalence of 17% for worsening of symptoms that were classified as homeopathic aggravations (73). In other studies, the prevalence of homeopathic aggravations fluctuated between 6 (74) and 8% (40). Due to lack of adequate reporting systems, the real number of homeopathic aggravations may be underestimated. These data suggest that the prevalence of homeopathic aggravations fluctuates between 0.5%-17%.

Homeopathic aggravations were reported as intensification of the patients’ present symptoms and are regarded to be in line with homeopathic theory (9, 75, 76). Various skin complaints, such as atopic eczema, psoriasis, and dermatitis, deteriorated initially, a result that is in line with previous reports (12, 77, 78).

The adverse effects found in this review, were graded as minor and moderate events. This result is in line with Dantas and Rampes (4) who concluded that adverse effects connected to homeopathy are found to be minor, transient events. Results from the present review found that patients receiving conventional medicine experienced more adverse effects than those who received homeopathy. This result is not surprising as conventional medicine can be expected to be pharmacologically active and may therefore be associated with more adverse effects. This is especially true for homeopathic remedies of high dilution which cannot have pharmacological effect and a direct toxicological risk from these remedies is therefore impossible. Homeopathic remedies of low dilutions, on the other hand, are connected with direct risk as they are pharmacologically active. Homeopathic remedies of both low and high dilutions were investigated in this review.
In 2016, this research group published a systematic review on adverse effects of homeopathy of RCTs (5). By comparing these two reviews we found that adverse effects were reported to a higher degree in observational studies (87.5%) than in RCTs (68%). Homeopathic aggravations were reported in 22.5% of the observational studies and in 12% of the RCTs. These findings may support the assumption that RCTs, due to their highly controlled design, conditions may not necessarily reflect homeopathic every day practice and may thus underestimate adverse effects. Therefore, with regard to detecting adverse effects and thus patient safety, cohort studies may be more valid.

**Implication for practice**

This review indicates low safety concern for homeopathic treatment. This applies both to the homeopathic consultation as well as to the homeopathic remedy. However, due to some case reports of serious harm, it is important that homeopaths inform their patients to stay in contact if the worsening of symptoms lasts for more than three days (79).

**Implication for research**

While the methodological quality of the included studies was high, harmful events were reported using different terminologies. Hence, there is a need for a standardized systematic reporting of adverse effects in homeopathy in order to facilitate risk assessments.

**Conclusion**

This systematic review and meta-analysis suggests a lower risk for homeopathic treatment compared to conventional medicine. However, the development and implementation of a standardized reporting system of adverse effects in future homeopathic studies is warranted.

**Availability of data and materials**

Not applicable (NA)

**Authors’ information**

The first author (TS) holds a PhD in medical science and has considerable expertise in performing many types of systematic reviews. The second author (AEK) holds a PhD in medical science. The third author GO is a senior librarian and responsible for the training of students and researchers in literature search and Endnote at the Institute of Health Science at UIT The Arctic University of Norway. The fourth author MJ holds a PhD in medicine and has considerable expertise in performing many different types of systematic reviews. The fifth
author (FM) is a professor in health services research. She holds a PhD in Psychology. The last author (JPL) is a professor and director for the Centre for Evidence-Based Chinese Medicine in China.

Ethics and approval and consent to participate

Not applicable.

Authors’ contribution

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 and adverse effects table, prepared the data for the statistical analysis, performed the statistical analysis, and drafted the manuscript. AEK: Prepared the data for the statistical analysis and performed the statistical analysis together with TS and reviewed subsequent versions of the manuscript. GO: Developed the search strategy and performed the searches together with TS. MJ: performed the methodological assessment of the studies according to the JBI methodology and review the manuscript. FM: Developed the risk of bias table and the adverse effects table and reviewed subsequent versions of the manuscript. JP: Developed the risk of bias table and the adverse effects table, supervised and controlled the statistical analysis for bias and reviewed subsequent versions of the manuscript. All authors read and approved the final manuscript.

Funding

This study was funded by NAFKAM. The publication charges for this article have been funded by a grant from the publication fund of UIT The Arctic University of Norway. This research did not receive any funding.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgements

We want to thank Claudia Witt and Rainer Lüdtke for sharing and preparing data on homeopathic aggravations for us. We are grateful to Jane Ekelund for technical support.

References


70. Bhandari M, Busse JW, Jackowski D, Montori VM, Schünemann H, Sprague S, et al. Association between industry funding and statistically significant pro-industry findings in


Figure 1: Flow chart of the selection process of observational studies

Figure 2: Forest plot of the observational studies

Table 1: Assessment of the methodological quality of the observational studies

Table 2: Classification of adverse effects and homeopathic aggravations in the observational studies
### Table 1: Methodological assessment of observational studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Indication</th>
<th>Participants</th>
<th>Criteria</th>
<th>Intervention</th>
<th>Dropout</th>
<th>Objectives</th>
<th>Duration of treatment</th>
<th>Main results</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammenwerth H, 2006</td>
<td>Upper respiratory tract infection</td>
<td>n=52 patients, n=53 physicians</td>
<td>Patients in the treatment group were significantly younger</td>
<td>Patients with clinically proven rhinitis and asthma</td>
<td>n=64 vs. n=76</td>
<td>Evaluate the effects of homeopathic treatment for upper respiratory tract infections</td>
<td>28 days</td>
<td>Both groups showed clinically relevant reduction of disease specific symptoms: Euphorbia rhinae was found to be non inferior to ketorolac. Treatment was equivalent to NSAID. Superior for pain and joint mobility.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Bimasser R, 2004</td>
<td>Episcleritis</td>
<td>n=100 patients</td>
<td>Small differences between groups</td>
<td>Diagnosed episcleritis</td>
<td>n=104 vs n=105</td>
<td>Compare complex homeopathy with conventional medication</td>
<td>14 days</td>
<td>A grant from Biologische Heilmittel Heel GmbH.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Deuensch U, 2009</td>
<td>Asthma bronchiale</td>
<td>n=34 patients, n=35 physicians</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients with clinically proven asthma and rhinitis and asthma associated symptoms</td>
<td>n=14 vs n=15</td>
<td>Evaluate the effects of Asthmaflor in vegetative symptoms in patients with asthma bronchiale</td>
<td>28 days</td>
<td>Significant improvements in asthma associated symptoms and reduction of conventional medication</td>
<td>NR</td>
</tr>
<tr>
<td>Dersenne M, 2005</td>
<td>Acute febrile infections</td>
<td>n=132 patients</td>
<td>Greater frequency of rights in homeopathy group</td>
<td>Patients with no symptoms</td>
<td>n=151 vs n=156</td>
<td>Compare complex homeopathy with conventional medication</td>
<td>14 days</td>
<td>No significant differences between groups.</td>
<td>NR</td>
</tr>
<tr>
<td>Emdeitzi C, 2005</td>
<td>Patients’ experiences with homeopathic treatment</td>
<td>n=151 patients</td>
<td>One follow-up visit at the Campo di Mare hospital</td>
<td>Patients with no symptoms</td>
<td>n=147 vs n=151</td>
<td>Assess the harm of classical homeopathic treatment</td>
<td>14 days</td>
<td>A grant from Biologische Heilmittel Heel GmbH.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Größler C, 2012</td>
<td>Allergic disorders</td>
<td>n=94 patients</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients diagnosed with sinusitis, allergic rhinitis, allergic conjunctivitis and bronchial asthma, minimum age of 9 years</td>
<td>n=108 vs n=106</td>
<td>To access the real-life efficacy of classical homeopathic treatment and the potential to reduce conventional medication dosage</td>
<td>112 days</td>
<td>All clinical symptoms were improved substantially 62% of the participants were able to discontinue at least one medication</td>
<td>NR</td>
</tr>
<tr>
<td>Gravenwald U, 2008</td>
<td>Dual action allergies</td>
<td>n=283 patients were enrolled, n=284 CAM-oriented physicians</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients with clinically proven dual action allergies, suffering from at least four symptoms</td>
<td>n=306 vs n=308</td>
<td>Assess whether homeopathy was non inferior to conventional treatment</td>
<td>30 days</td>
<td>82% of the patients showed improvements in dual action allergy symptoms. Safety was noted very good in more than 90% of patients and physicians.</td>
<td>NR</td>
</tr>
<tr>
<td>Hadugl M, 2007</td>
<td>Acute and respiratory complaints</td>
<td>n=1,217 patients</td>
<td>Mild, moderate and severe differed significantly between groups</td>
<td>Older than one month, one main chief complaint (age ≤ 7 if female)</td>
<td>n=126 vs n=123</td>
<td>Assess whether homeopathy was non inferior to conventional treatment</td>
<td>28 days</td>
<td>Significant improvement in the Neurneur group compared to the Venlafaxine group.</td>
<td>The Schütte research foundation, Heidelberg, Germany</td>
</tr>
<tr>
<td>Hübner R, 2009</td>
<td>Neuroviscus/ rednesses</td>
<td>n=26 patients</td>
<td>The Neumearn group tended to weigh less, fewer concomitant diseases and had mild neuroviscus</td>
<td>Clinical symptoms of neuroviscus judged by the evaluating clinician</td>
<td>n=30 vs n=31</td>
<td>Gather data on the effectiveness of Neumearn in a CAM setting</td>
<td>28 days</td>
<td>A grant from Sankt Augustin, Germany.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Hammer R, 2007</td>
<td>Chronic skin disease</td>
<td>n=60 patients</td>
<td>Diagnostic with skin disease by a dermatological specialist</td>
<td>Patient reported and clinically observed effects of homeopathy</td>
<td>n=116 vs n=116</td>
<td>Assess whether homeopathy could improve eczema and QOL compared to conventional treatment</td>
<td>28 days</td>
<td>80% of the patients showed a significant improvement in the patients with chronic skin disease.</td>
<td>NR</td>
</tr>
<tr>
<td>Kall T, 2008</td>
<td>Eczema in children</td>
<td>n=1,114 patients</td>
<td>Patients with higher education and use of CAM in the homeopathy group</td>
<td>Previously not treated for eczema and lacking the study physician</td>
<td>n=108 vs n=108</td>
<td>Assess whether homeopathy could improve eczema and QOL compared to conventional treatment</td>
<td>14 days</td>
<td>Eczema improved in both groups. No differences between groups. QOL improved more in the conventional group.</td>
<td>The German sickness fund (Krankenflächenkasse Hamburg)</td>
</tr>
<tr>
<td>Klapp R, 2006</td>
<td>Multinuclear elderly patients</td>
<td>n=20 patients</td>
<td>Not reported in publication</td>
<td>Patients aged between 75-84 years, one main chief complaint (age ≤ 7 if female)</td>
<td>n=109 vs n=109</td>
<td>Assess whether homeopathy could improve eczema and QOL compared to conventional treatment</td>
<td>28 days</td>
<td>Significant effects with respect to immune modulating behaviour of white blood cells and improvements in local microcirculation</td>
<td>NR</td>
</tr>
<tr>
<td>Marien F, 2006</td>
<td>Patients’ satisfaction and adverse effects in primary care. Data from two cross-sectional studies</td>
<td>n=3, 126 patients</td>
<td>Women and chronic patients who answered more frequently yes or no + non-chronic patients</td>
<td>General population who members of the Swiss Medical association for Homeopathic patients</td>
<td>n=1,168 vs n=1,132</td>
<td>Assess patients’ satisfaction and adverse effects of homeopathic treatment</td>
<td>28 days</td>
<td>In primary care, patients’ satisfaction with homeopathy was higher compared to conventional treatment.</td>
<td>The Swiss Federal Office of Public Health</td>
</tr>
<tr>
<td>Michalow A, 2015</td>
<td>To generate data on safety and treatment effect of a complex homeopathic drug</td>
<td>n=1550 patients</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients older than 1 year with no upper limitation of age with symptoms of an acute cardiovascular disease, chronic cold/like infection and inflammation of the nose and throat</td>
<td>n=150 vs n=150</td>
<td>Assess safety and treatment effect of Contromix N Taft</td>
<td>120 days</td>
<td>The study was sponsored by Casselle-med (Eckstein, Germany), the holder of the marketing authorization of the study preparation.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Möjauer YH, 2007</td>
<td>Trigeminal Neuralgia</td>
<td>n=15 patients</td>
<td>Physically confirmed trigeminal neuralgia</td>
<td>Patients who use immuno- suppressive therapy, alcohol or drug abuse</td>
<td>n=15 vs n=15</td>
<td>Evaluate individual homeopathy in treatment of trigeminal neuralgia</td>
<td>120 days</td>
<td>A statistical significant reduction in pain intensity and frequency were found</td>
<td>NR</td>
</tr>
<tr>
<td>Study ID</td>
<td>Indication</td>
<td>Participants</td>
<td>Baseline comparability</td>
<td>Criteria</td>
<td>Intervention</td>
<td>Dropout</td>
<td>Objectives</td>
<td>Duration of treatment</td>
<td>Main results</td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>--------------</td>
<td>------------------------</td>
<td>----------</td>
<td>-------------</td>
<td>---------</td>
<td>------------</td>
<td>----------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>N déjà-Kranke K, 2007</td>
<td>Diabetic polyneuropathy</td>
<td>n=17</td>
<td>The groups were well balanced</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patient's diagnosis of polyneuropathy</td>
<td>n=13 vs n=13</td>
<td>Evaluate homeopathic therapy in diabetic neuropathy</td>
<td>365</td>
<td>Feasible and promising effects were observed for homeopathy in symptoms scores and ODS.</td>
</tr>
<tr>
<td>Rabe A, 2004</td>
<td>Asthma</td>
<td>n=485</td>
<td>The groups were well balanced for age, sex and sex distribution</td>
<td>Patients with mild respiratory symptoms of acute rhinitis</td>
<td>No drop-out reported</td>
<td>The hypothesis was that complex homeopathy could be as effective and safe as conventional therapies</td>
<td>28</td>
<td>Grippe Heel had beneficial effects compared to conventional therapies in viral infections.</td>
<td>A grant from Biologische Heilmittel Heel GmbH, Baden-Baden, Germany</td>
</tr>
<tr>
<td>Ross E, 2012</td>
<td>Acute respiratory infections</td>
<td>n=1,110</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients seeking homeopathic treatment at a homeopathic clinic</td>
<td>No drop-out reported</td>
<td>Compare the effectiveness of homeopathic treatment in medical in real life settings</td>
<td>28</td>
<td>Homopathy was as efficacious as conventional medical care.</td>
<td>Horizont, Karlsruhe, Germany</td>
</tr>
<tr>
<td>Salid A N, 2009</td>
<td>Acute shortness of breath</td>
<td>n=68 children</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients with upper respiratory infections</td>
<td>No drop-out reported</td>
<td>Symptomatic response was found in both groups. No statistical differences between groups.</td>
<td>14</td>
<td>Symptoms were reduced in both groups. No statistical differences between groups.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Schneider V, 2005</td>
<td>Acute respiratory infections</td>
<td>n=937</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients seeking homeopathic treatment at a homeopathic clinic</td>
<td>No drop-out reported</td>
<td>Compare the effect of complex homeopathy with conventional over the counter therapy</td>
<td>14</td>
<td>Symptomatic response was found in both groups. No statistical differences between groups.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Schneider C, 2008</td>
<td>Injuries</td>
<td>n=133</td>
<td>The groups were well balanced</td>
<td>16 years old with acute or recurring tendinopathy of various etiology</td>
<td>No drop-out reported</td>
<td>Assess the non-inferiority of complex homeopathy vs conventional medicine</td>
<td>28</td>
<td>Symptoms were reduced in both groups. No statistical differences between groups.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Schröder D, 2001</td>
<td>Chronic heart insufficiency (NYHA I)</td>
<td>n=212</td>
<td>The groups were well balanced</td>
<td>Patient diagnosed with mild chronic insufficiency (NYHA class-I), not necessitating ACE inhibitor/diuretic treatment</td>
<td>No drop-out reported</td>
<td>Assess the daily, weekly, and monthly activity of complex homeopathy compared with conventional medicine</td>
<td>60</td>
<td>Cricklaide drops (n=150) vs ACT inhalation and/or diuretic therapy (n=150).</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Seier B, 2005</td>
<td>Chronic disease</td>
<td>n=115</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patient assessed with diabetes mellitus</td>
<td>No drop-out reported</td>
<td>In the follow-up period, patients with diabetes were given homeopathic treatment</td>
<td>365</td>
<td>Clinically 8 patients may benefit from homeopathic treatment when integrated in their management.</td>
<td>Biologische Heilmittel Heel GmbH</td>
</tr>
<tr>
<td>Tevt M, 2010</td>
<td>Homeopathic treatment of elderly patients</td>
<td>n=63</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients &gt; 70 years of age</td>
<td>No drop-out reported</td>
<td>Determine the spectrum of diagnostic, treatment, course of illness in elderly who receive homeopathy</td>
<td>730</td>
<td>The study demonstrated substantial improvements following homeopathic treatment.</td>
<td>Karl und Veronica Cornells Foundation, Essen, Germany</td>
</tr>
</tbody>
</table>
**Table of Studies**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Indication</th>
<th>Participants</th>
<th>Criteria</th>
<th>Intervention</th>
<th>Dropout</th>
<th>Objectives</th>
<th>Duration of treatment</th>
<th>Main results</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trow M, 2009</td>
<td>Cataract or allergic conjunctivitis</td>
<td>n=31; n=28</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients with allergic conjunctivitis</td>
<td>NR</td>
<td>Investigate the safety of the treatment</td>
<td>730</td>
<td>Improved visual acuity</td>
<td>NR</td>
</tr>
<tr>
<td>Walach S, 2009</td>
<td>Dermatological complaints</td>
<td>n=61</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients with dermatological complaints visiting a public outpatient clinic</td>
<td>NR</td>
<td>Assess the effectiveness of the treatment</td>
<td>210</td>
<td>Significant improvement</td>
<td>NR</td>
</tr>
<tr>
<td>Walach H, 2001</td>
<td>Chronic headache</td>
<td>n=128</td>
<td>Patients from a previous RCT approached for a 3 year follow-up</td>
<td>NR</td>
<td>Examine the effectiveness of the treatment</td>
<td>120</td>
<td>Similar improvement</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Walisch C, 2000</td>
<td>Insomnia</td>
<td>n=499</td>
<td>The groups were well balanced</td>
<td>NR</td>
<td>Evaluate the effects of the treatment</td>
<td>120</td>
<td>No difference</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Witt CM, 2008</td>
<td>Long-lasting chronic disease</td>
<td>n=772</td>
<td>A single group made up of patients who were underrepresented in this sample</td>
<td>Patients included consecutively upon first consultation with a participating homeopathic physician</td>
<td>NR</td>
<td>Evaluate the effects of the treatment</td>
<td>210</td>
<td>Improved health status</td>
<td>NR</td>
</tr>
<tr>
<td>Witt CM, 2009</td>
<td>Atopic eczema in children</td>
<td>n=135</td>
<td>The groups were well balanced</td>
<td>NR</td>
<td>Evaluate the effects of the treatment</td>
<td>120</td>
<td>Similar improvement</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Witt CM, 2009</td>
<td>Chronic low back pain</td>
<td>n=129</td>
<td>The groups were well balanced</td>
<td>NR</td>
<td>Evaluate the effects of the treatment</td>
<td>120</td>
<td>Similar improvement</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Witt CM, 2009</td>
<td>Dysmenorrhea</td>
<td>n=118</td>
<td>The groups were well balanced</td>
<td>NR</td>
<td>Evaluate the effects of the treatment</td>
<td>120</td>
<td>Similar improvement</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Witt CM, 2009</td>
<td>Chronic headache (ICD-9:730)</td>
<td>n=306; n=74</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients with headache defined according to ICD-9:730</td>
<td>NR</td>
<td>Evaluate the effects of the treatment</td>
<td>730</td>
<td>Improved health status</td>
<td>NR</td>
</tr>
<tr>
<td>Witt CM, 2010</td>
<td>Migraine</td>
<td>n=212; n=67</td>
<td>A single group which was descriptively reported in publication</td>
<td>Patients with migraine defined according to ICD-9:346.4</td>
<td>NR</td>
<td>Evaluate the effects of the treatment</td>
<td>730</td>
<td>Improved health status</td>
<td>NR</td>
</tr>
<tr>
<td>Zanetti A, 2015</td>
<td>Upper respiratory tract infection (URTI)</td>
<td>n=87 children</td>
<td>The groups were well balanced</td>
<td>Children with pre-existing respiratory symptoms, or those with acute respiratory infection</td>
<td>NR</td>
<td>Evaluate the effects of the treatment</td>
<td>730</td>
<td>Improved health status</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Classical homeopathy:** Prescribing a single remedy according to the similars.  
**Isopathy:** A homeopathic subform, in which the preparations are made from the exact illness or its symptoms.  
**Complex homeopathy:** A combination of homeopathic agents or remedies.  
**Homeopathic immunotherapy:** Homeopathic subform (sublingual) dose of an antigen, to desensitize.  
**Homeopathy:** A holistic approach, in which the preparations are made from the exact illness or its symptoms.  
**Quality of life:** A measure of the patient's health status and function.  
**Adverse effects:** A measure of the patient's health status and function.  
**Concomitant diseases and other therapeutic modalities:** A measure of the patient's health status and function.  
**No dropout:** The study had no sponsors.  

**NR:** Not reported.