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

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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).

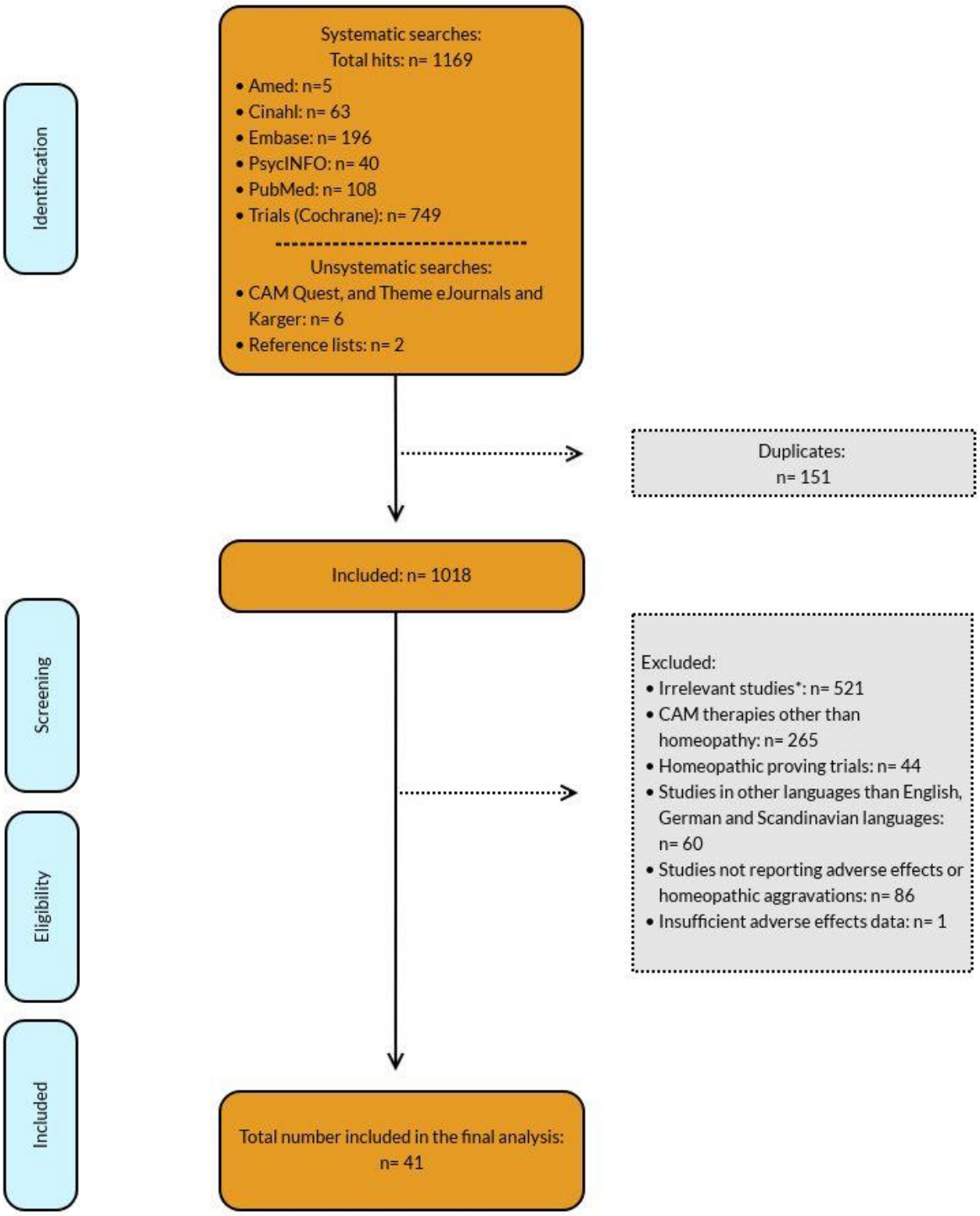

Figure 1: Flow diagram of the study selection

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,

32, 33, 38, 41-44, 60, 64, 66). 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%) (34, 40, 45-48, 56, 63, 65) 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 (42, 46-48, 60, 64, 65). The physicians classified homeopathic aggravations in six of the studies (49-53, 58). 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 (38, 41-43, 49, 59, 62);(32);(35); (36);(60);(27, 33, 39, 44, 57) and complementary therapy (herbs) in two studies (64, 66). Key data are summarized in table 2 (table 2).

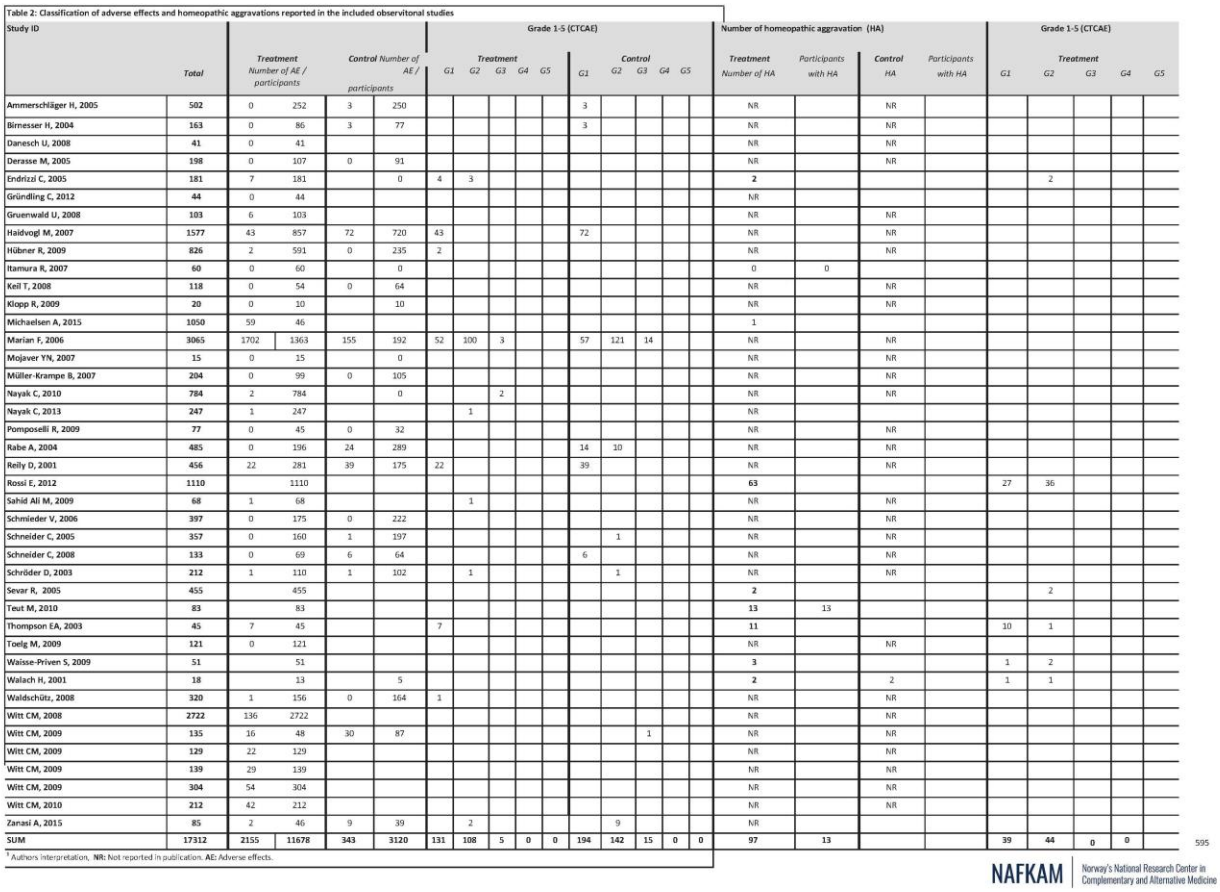

Table 2: Classification of adverse effects and homeopathic aggravations reported in the included observitonal studies

Study ID	Total	Treatment Number of AE / participants		Control Number of AE / participants		Grade 1-5 (CTCAE) Treatment G1	G2	G3	G4	G5	Control G1	G2	G3	G4	G5	Number of homeopathic aggravation (HA) Treatment Number of HA	Participants with HA	Control HA	Participants with HA	Grade 1-5 (CTCAE) Treatment G1	G2	G3	G4	G5
Ammerschläger H, 2005	502	0	252	3	250						3					NR		NR						
Birnesser H, 2004	163	0	86	3	77						3					NR		NR						
Danesch U, 2008	41	0	41													NR		NR						
Derasse M, 2005	198	0	107	0	91											NR		NR						
Endrizzi C, 2005	181	7	181		0	4	3									2					2			
Gründling C, 2012	44	0	44													NR								
Gruenwald U, 2008	103	6	103													NR		NR						
Haidvogl M, 2007	1577	43	857	72	720	43					72					NR		NR						
Hübner R, 2009	826	2	591	0	235	2										NR		NR						
Itamura R, 2007	60	0	60		0											0	0							
Keil T, 2008	118	0	54	0	64											NR		NR						
Klopp R, 2009	20	0	10		10											NR		NR						
Michaelsen A, 2015	1050	59	46													1								
Marian F, 2006	3065	1702	1363	155	192	52	100	3			57	121	14			NR		NR						
Mojaver YN, 2007	15	0	15		0											NR		NR						
Müller-Krampe B, 2007	204	0	99	0	105											NR		NR						
Nayak C, 2010	784	2	784		0			2								NR		NR						
Nayak C, 2013	247	1	247				1									NR								
Pomposelli R, 2009	77	0	45	0	32											NR		NR						
Rabe A, 2004	485	0	196	24	289						14	10				NR		NR						
Reily D, 2001	456	22	281	39	175	22					39					NR		NR						
Rossi E, 2012	1110		1110													63				27	36			
Sahid Ali M, 2009	68	1	68				1									NR		NR						
Schmieder V, 2006	397	0	175	0	222											NR		NR						
Schneider C, 2005	357	0	160	1	197							1				NR		NR						
Schneider C, 2008	133	0	69	6	64						6					NR		NR						
Schröder D, 2003	212	1	110	1	102		1					1				NR		NR						
Sevar R, 2005	455		455													2					2			
Teut M, 2010	83		83													13	13							
Thompson EA, 2003	45	7	45			7										11				10	1			
Toelg M, 2009	121	0	121													NR		NR						
Waisse-Priven S, 2009	51		51													3				1	2			
Walach H, 2001	18		13		5											2		2		1	1			
Waldschütz, 2008	320	1	156	0	164	1										NR		NR						
Witt CM, 2008	2722	136	2722													NR		NR						
Witt CM, 2009	135	16	48	30	87								1			NR		NR						
Witt CM, 2009	129	22	129													NR		NR						
Witt CM, 2009	139	29	139													NR		NR						
Witt CM, 2009	304	54	304													NR		NR						
Witt CM, 2010	212	42	212													NR		NR						
Zanasi A, 2015	85	2	46	9	39		2					9				NR								
SUM	17312	2155	11678	343	3120	131	108	5	0	0	194	142	15	0	0	97	13			39	44	0	0	

595

† Authors interpretation, **NR:** Not reported in publication. **AE:** Adverse effects.

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

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.

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).

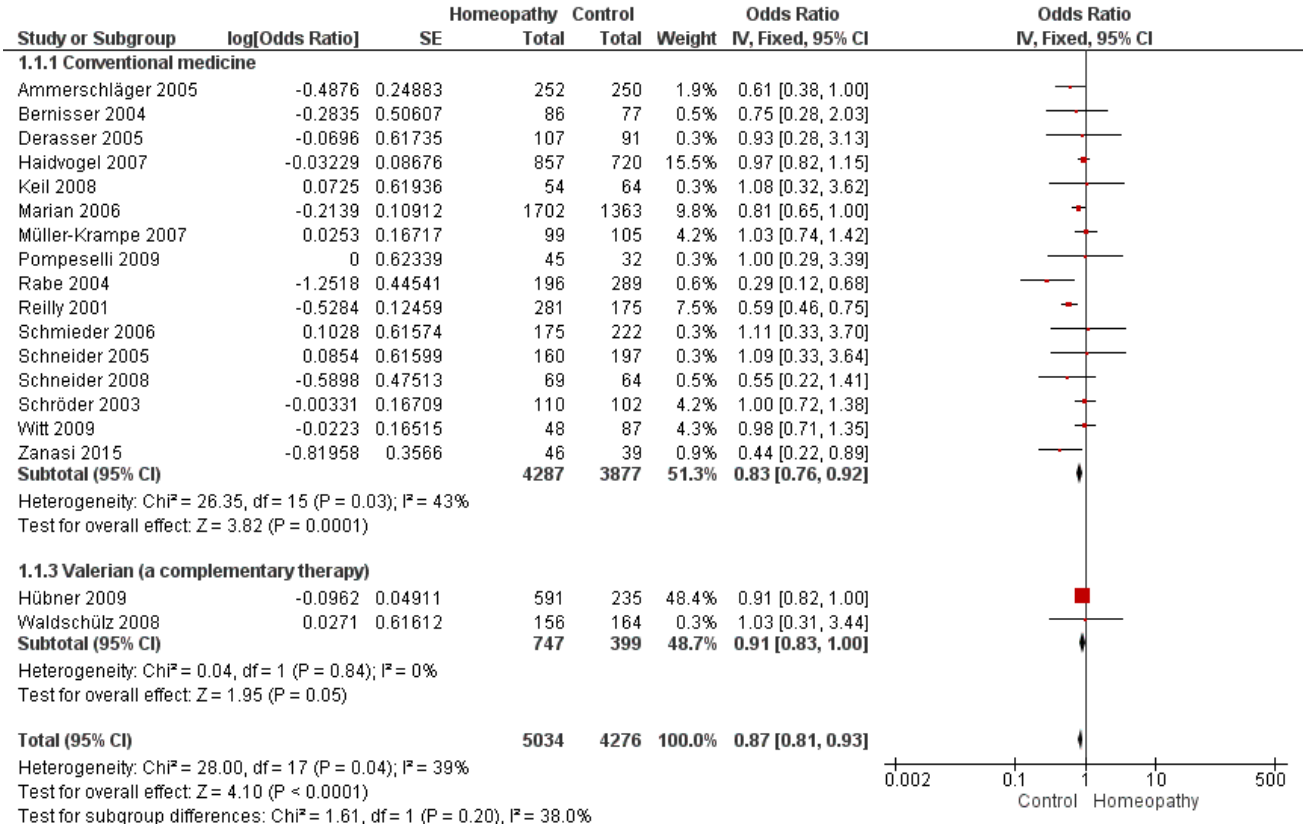

Figure 2: Forest plot for the observational studies, including sub-group analysis according to the category of controls

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.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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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

Study ID	Indication	Participants		Criteria		Intervention	Dropout	Objectives	Duration of treatment	Main results	Funding
		Sample size	*Baseline comparability*	*Inclusion*	*Exclusion*	*Treatment vs Control (n)*	*Treatment vs Control (n)*		*Days*		
Ammerschläger H, 2005	Upper respiratory tract infection	n= 502 patients; n=153 physicians	Patients in the treatment group were significantly younger	Patients with clinically proven rhinositis and sinusitis	Patients with ongoing therapy with study medication or other rhinologica	Homeopathic complex remedy Euphorbium comp. (n=413) versus Xylometazolin (n=326)	n=161 vs. n= 76	Evaluate the effects of homeopathic treatment for upper respiratory tract infections	28	Both groups showed clinically relevant reduction of disease specific symptoms. Euphorbium was found to be non inferior to Xylometazolin.	Biologische Heilmittel Heel GmbH
Birnesser H, 2004	Epicondylitis	n=184	Small differences between groups	Diagnosed epicondylitis	NR	Traumeel S (n=86) vs NSAID (n=77)	n=6 vs n=15	Compare complex homeopathy with conventional medication	14	Traumeel was equivalent to NSAID, superior for rest pain and joint mobility	A grant from Biologische Heilmittel Heel GmbH
Danesch U, 2008	Asthma Bronchiale	n=41 patients; n=6 CAM-oriented physicians	A single group which was descriptively reported in publication	Patients with clinically proven asthma bronchiale and asthma associated vegetative symptoms	Patients that took Asthmavoven within the last four weeks	Adjuvant homeopathic treatment with Asthmavoven	NR	Evaluate the effects of Asthmavoven on vegetative symptoms in patients with asthma bronciale	28	Significant improvements in asthma associated symtoms and reduction of conventional medication	NR
Derasse M, 2005	Acute febrile infections	n=198	Greater frequency of rhinitis in homeopathy group	Children older than 11 years	Patients without symptoms	Viburcol (n=107) vs acetaminophen (n=91)	NR	Compare complex homeopathy with conventional medication	14	No significant differences between groups	A grant from Biologische Heilmittel Heel GmbH
Endrizzi C, 2005	Patients' experiences with homeopathic treatment	n=181	NR	One follow-up visit at the Campo di Marte Hospital	NR	Irrelevant	NR	Assess the harm of classical homeopathic treatment	365	Adverse reactions were observed at a rate of 2.68%	NR
Gründling C, 2012	Allergic disorders	n=44	A single group which was descriptively reported in publication	Patients diagnosed with neurodermatitis, allergic rhinitis, allergic conjunctivitis and bronchial astma, minimum age of 9	NR	Classical homeopathy in additional to conventional treatment (n=44)	n=8	To access the real-life efficacy of classical homeopathic treatment and the potential to reduce conventional medication dosage	112	All clinical symptoms were improved substansially.62% of the participants were able to discountine at least one medication	NR
Gruenwald U, 2008	Dust mite allergies	n=103 patients were enrolled; n=8 CAM-oriented physicians	A single group which was descriptively reported in publication	Patients with clinically proven dust mite allergy suffering from at least four symptoms	Patients with hypersensitivity against remedy ingredients, brain or liver diseases, alcohol abuse, epilepsy or pregnancy	Homeopathic treatment with Allergin D2 (Adhatova vasica)	NR	Evaluate efficacy and safety of Adhatova vasica on patients with dust mite allergies	8	83% of the patients showed improvements in dust mite allergy symtoms. Safety was rated very good in more than 90% by patients and physicians	NR
Haidvogl M, 2007	Acute ear and respiratory complaints	n=1,577	BMI, gender and age differed significantly between groups	Older than one month, one main chief complaint (onset < 7 d before)	NR	Individualized homeopathy (n=875) vs antibiotics, nasal preparations and analgesics (n=720)	n=345 vs n=109	Assess whether homeopathy was non inferior to conventional treatment	14	Significant differences between groups, in favour of homeopathy	The Holt organization, Karlsruhe, Germany
Hübner R, 2009	Nervousness/ restlessness	n=826	The Neurexan group tended to weigh less, fewer concomitant illnesses and had milder nervousness	Clinical symptoms of nervousness judged by the evaluating clinician	Using conventional or homeopathic medication for nervousness	Neurexan (n=571) vs Valerian (n=224)	n=20 vs n=11	Gather data on the effectiveness of complex homeopathy in a CAM setting	14	Significant improvement in the Neurexan group compared to the Valerian group	A grant from Heel GmbH
Itamura R, 2007	Chronic skin disease	n=60	NR	Diagnosed with skin disease by a dermatological specialist	NR	Individualized homeopathy in addition to conventional treatment (n=60)	NR	Patient-reported and clinically observed effects of homeopathy	More than 90	Homeopathy may provide a good response in patients with chronic skin disease	NR
Keil T, 2008	Eczema in children	n=118	Parents with higher education and use of CAM in homeopathy group	Previously not treated for eczema and itching by the study physician	NR	Individualized homeopathy (n=54) vs Corticosteroids (n=64)	NR	Assess whether homeopathy could improve eczema and QOL compared to conventional treatment	365	Eczema improved in both groups. No differences between groups. QOL improved more in the conventional group	The German sickness fund *Innungskrankenkasse* Hamburg
Klopp R, 2009	Multimorbid elderly patients	n=20 patients	Not reported in publication	Multimorbid male patients aged between 75-84 years	Female patients, intake of antibiotics or cytostatics within the last 4 weeks, known immune deficits and related diseases (cancer, diabetes)	Treatment with Spenglersan Kolloid G (n=10) versus placebo (n=10)	NR	Evaluate immunmodulating effects of Spenglersan Kolloid G	21	Significant effects with respect to immune modulating behaviour of white blood cells and improvements in local micro circulation	NR
Marian F, 2006	Patients' satisfaction and adverse effects in primary care. Data from two cross-sectional studies	n=3, 126 patients; n=170 GPs and medical homeopaths	Women and chronic patients answered more freguently than men and non-chronic patients	GPs' and homeopaths' who are members of the Swiss medical association for homeopaths	NR	Homeopathy: Approach and style not reported (n=1702) Conventional: Appropriate for the disease in question (n=1363)	n=61	Assess patients' satisfaction and adverse effects of homeopathic and conventional treatment	365	In primary care, patients' satisfaction with homeopathy was higher compared to conventional treatment	The Swiss Federal Office of Public Health
Michalsen A, 2015	To generate data on safety and treatment effect of a complex homeopathic drug	n=1050	A single group which was descriptively reported in publication	Patients older than 1 year with no upper limitation of age with symptoms of an acute catarrhal disease/common cold/flu-like infection and inflammation of the nose and throat	Allergy against any of the constituents of the study preparation,a diagnosis of tuberculosis, leucosis, collagenosis, multiple sclero-sis, HIV and autoimmune diseases. Children at an age below 1 year and pregnant or lactating	Contramutan N Saft (a complex homeopathic preparation)	NR	Assess safety and tresatment effect of Contrmutan N Saft	8	60 adverse effects were reported in 46 patients by the physicians. Adverse drug reactions were reported in 14 patients. Homeopathic aggrevation was reported in one patient. All events were of mild to moderaste intensity	The study was sponsored by Cassella-med (Cologne, Germany),the holder of the marketing authorization of the study preparation.
Mojaver YN, 2007	Trigeminal neuralgia	n=15	NR	Physician confirmed trigeminal neuralgia	Patients who use immuno - suppressive therapy, alcohol or drug abuse	Individualized homeopathy (n=15)	n=0	Evaluate individualized homeopathy in treatment of trigeminus neuralgia	120	A statistical significant reduction in pain intensity and frequency were found	NR

Study ID	Indication	Participants		Criteria		Intervention	Dropout	Objectives	Duration of treatment	Main results	Funding
		Sample size	*Baseline comparability*	*Inclusion*	*Exclusion*	*Treatment vs Control (n)*	*Treatment vs Control (n)*		*Days*		
Müller-Krampe B, 2007	Gastrointestinal cramps in children	n=204 < 12years of age	The group was incompletely balanced for age,weigth and higth	Newly or recurrent diagnosed gastrointestinal or urethal cramps	<12years of age undergoing treatment for such cramps	Spascupreel (n=99) vs Hyoscine butylbromide (n=105)	NR	Compared two different treatment options	7	Both groups improved in symptoms. No statistical difference was found between the groups	NR
Nayak C, 2010	Acute rhinitis in children	n=784	A singel group which was descriptively reported in publication	Children > 6 months old and < 15 years old with acute rhinitis < 7 days	NR	Group of 13 individualized homeopathic remedies	n=146	Evaluate a group of individualized homeopathic remedies for acute rhinitis	7	Indicated the usefulness of homeopathy in the management of acute rhinitis	The study received no funding
Nayak C, 2013	Diabetic neuropathy (DPN)	n=336 (247 were analyzed)	A single group which was descriptively reported in publication	Age over 30 years with diagnosed type 1 or type 2 diabetes, average blood sugar level less than 8% (HbA1c), sensory loss, diabetic distal symmetric polyneuropathy symptom score ≥ 3, patient meets prescribing criteria for one of the 15 preselected homeopathic medicines	Diabetic mononeuropathy and amyotrophy,polyradiculopathy,autonomic neuropathy,abnormalities of gait,absent stretch reflexes, wrist and foot drop, charcot joints, paralysis of cranial nerves,loss of arch with multiple fractures of tarsal bones,myocardial infarction less than 6 months, unstable angina, severe retinopathy, severe renal involvement or recurrent acute complications, HbA1c more than 8%	15 different homeopathic remedies	n=89	To eveluate the potential role of homeopathic medicines in themanagement of diabetic neuropathy	365	A statistically significant improvement in total diabetic distal symmetric polyneuropathy symptom scorewas found at 12 months from baseline. Most objective measures did not show significant improvement	NR
Pomposelli R, 2009	Diabetic polyneuropathy	n=77	The groups were well balanced	Patient with diagnosis of polyneuropathy	Patients with other severe chronic diseases (detailed list in publication)	Individualized homeopathy and conventional treatment (n=45) vs conventional treatment (n=32)	n=13 vs n=3	Evaluate homeopathic therapy in diabetic neuropathy	365	Feasible and promising effects were observed for homeopathy in symptoms scores and QOL	A grant from Belladonna Association (Milan, Italy)
Rabe A, 2004	Mild viral infections	n=485	The groups were incompletely balanced for age, eye and ear infections	Patients with mild or medium symptoms of acute respiratory viral infections	NR	Gripp-Heel (n=196) vs conventional therapies (n=289)	No dropout reported	The hypothesis was that complex homeopaty could be as effective and safe as conventional therapies	28	Gripp-Heel had beneficial effects compared to conventional therapies in viral infections	A grant from Biologische Heilmittel Heel GmbH, Baden-Baden, Germany
Reily D, 2001	Upper and lower respiratory tract and ear complaints	n=456 patients; n= 30 clinicians	The groups were well balanced apart from age	Older than one month, one main chief complaint (onset > 7 d before)	Patients with psychiatric disorders or severe chronic diseases (detailed list in publication)	Homeopathic remedies in D30 (n=281) vs antibiotics, antiasthmatics and nasal preparations (n=175)	n=30 vs n=14	Compare the effectiveness of homeopathy with conventional medicine in real life settings	28	Homeopathy was as effective as conventional medical care	HomInt, Karlsruhe, Germany
Rossi E, 2012	Homeopathic aggravations	n=1,110	A singel group which was descriptively reported in publication	Patients seeking homeopathic treatment at a homeopathic clinic	NR	Collected data from all patients consecutively visiting the clinic (n=441)	n=669	Evaluate the typology, intensity and frequency of homeopathic aggravations	420	Homeopathic aggravations manifested themselves 1-2 days after administration of the remedy	NR
Sahid Ali M, 2009	Acute Diarrhoeal Disease	n= 68 children	A single group which was descriptively reported in publication	Children with acute diarrhoe (minimum 3 unformed stools per day for at least 2 consecutive days)	Diarrhoe > 7 days, high-grade fever, severe dehydration, HIV, conditions requiring emergency procedures	Individualized classical homeopathy based on 11 out of 14 trial medicines (n=68)	NR	Evaluate the effects of homeopathic treatment for acute diarrhoeal disease	7	Diarrhoe index score improved significantly over time. 66 of 68 children were cured.	NR
Schmieder V, 2006	Upper respiratory infections	n=397	A slightly higher number of women in the homeopathy group. They were also shorter than those in the control group	Symptoms of upper respiratory infections associated with common cold	Patients with bacterial infections, asthma, treated with antibiotics or similar therapies	Complex homeopathy (n=175) vs conventional therapy (n=222)	NR	Compare the effect of complex homeopathy with conventional over the counter therapy	14	Symptoms were reduced in both groups. No statistical differences between groups	Biologische Heilmittel Heel GmbH
Schneider C, 2005	Acute symtomatic tendinopathy	n=357	The groups were well balanced	>18 years old with acute or recurring tendinopathy of various aetiology	Patients receiving other NSAID therapies	Complex homeopathy (n=160) vs conventional therapy (n=197)	NR	Assess the non-inferiority of complex homeopathy to conventional medicine	28	Symptoms were reduced in both groups. No statistical differences between groups	NR
Schneider C, 2008	Injuries	n=133	The groups were well balanced	New or recurrent injuries and trauma diagnosed according to international classifications	Patients already undergoing treatment for injuries, without data for three months, using unknown medication	Traumeel (mono or in combination with homeopathic theraphy) (n=53) vs conventional medication and functional treatment (n=50)	n=16 vs n=14	Assess the daily use, effectiveness and safety of complex homeopathy compared with conventional medicine	90	Traumeel was as effective as conventional medicine	Biologische Heilmittel Heel GmbH
Schröder D, 2003	Mild cardiac insufficiency (NYHA II)	n=212	The groups were well balanced, but there was a difference in sex distribution between groups	Patient diagnosed with mild cardiac insufficiency NYHA class II, necessitating therapy	Patients with unstable coronary heart disease, concomitant cardiac therapy	Cralonin drops (n=110) vs ACT inhibitor and/or diuretic therapy (n=102)	NR	Assess the non-inferiority of complex homeopathy to conventional medicine	60	Cralonin was non-inferior to usual ACE inhibitor/diuretic treatment	Biologische Heilmittel Heel GmbH
Sevar R, 2005	Chronic illness	n=455	A singel group which was descriptively reported in publication	Patients visiting a private homeopathic clinic	Not reported in publication	Individualized homeopathy (n=436)	n=19	Outcome audit for patients with chronic illness	365	Chronically ill patients may benefit from homeopathic treatment when integrated in their management	NR
Teut M, 2010	Homeopathic treatment of elderly patients	n=83	A singel group which was descriptively reported in publication	Patients > 70 years of age consulting a physician for the first time	Not reported in publication	Individualized homeopathy (n=83)	29	Determine the spectrum of diagnosis, treatment, course of illness in elderly who receive homeopathy	730	The study demonstrated substantial improvements following homeopathic treatment	Karl and Veronica Carstens Foundation, Essen, Germany

Study ID	Indication	Participants		Criteria		Intervention	Dropout	Objectives	Duration of treatment	Main results	Funding
		Sample size	*Baseline comparability*	*Inclusion*	*Exclusion*	*Treatment vs Control (n)*	*Treatment vs Control (n)*		*Days*		
Thompson EA, 2003	Symptoms of oestrogen withdrawal in breast cancer patients	n=43	A singel group which was descriptively reported in publication	Patients referred to a homeopathic hospital with breast cancer and symptoms of oestrogen withdrawal	NR	Individualized homeopathy (n=45)	No dropout reported	Investigate the homeopathic approach, the impact on mood and QOL in these patients		Homeopathy appears to be clinically useful. Mood disturbance and QOL were improved	NR
Toelg M, 2009	Katarrhal or allergic conjunctivitis	n=121 patients; n=28 CAM-oriented physicians	A single group which was descriptively reported in publication	Children younger than 16 years with clinically proven conjunctivitis	NR	Treatment with Euphrasia D3	NR	Evaluate efficacy and safety of Euphrasia D3 on children with katarrhal or allergic conjunctivitis	10	Efficacy was rated as very good in 93% of the patients, and safety was rated as very good in 99% of the patients and physicians	NR
Waisse-Priven S, 2009	Dermatological complaints	n=51	A singel group which was descriptively reported in publication	Patients with dermatological complaints visiting a public outpatient clinic	Lack of compliance with prescription, follow-up and discontinuation of other therapeutic modalities	Individualized homeopathy and general medical advice (n=31)	n=20	Assess the effectiveness of homeopathy on dermatological complaints	90	Significant improvement was observed in 59% of the patients	The study had no sponsors
Walach H, 2001	Chronic headache	n=18	Patients from a previous RCT agreed to be followed up for 1 year	Headache diagnosed according to International Headache Society and standard criteria used in headache/migraine trials	NR	Individualized homeopathy (n=13) vs placebo (n=5)	NR	Assess the long-term effect of individualized homeopathy (followed by an RCT of chronic headache)	365	This study demonstrated effects of homeopathic treatment in five of 18 patients	Robert-Bosch-Foundation, Stuttgart, Germany
Waldschülz R, 2008	Insomnia	n=409	The groups were well balanced	Mild to moderate sleep disturbance, diagnosed less than 4 weeks prior to the study	Concomitant diseases and intolerance to study medication	Neurexan (n=156) vs Valerian (n=164)	n=41 vs n=48	Assess the non-inferiority of complex homeopathy with a herbal product	28	Quality of sleep improved in both groups with no significant differences between groups	NR
Witt CM, 2008	Long lasting chronic disease	n=2722	A singel group male adults were underrepresented in this sample	Patients were included consecutively upon first consultation with a participating homeopathic physician	No restriction on diagnosis were made	Individualized homeopathy as a monotherapy or in combination with complementary or conventional therapies n= (2,722)	n=987	Evaluate health status changes under homeopathic treatment in routine care	2920	Substantial health improvement in patients under homeopathic treatment which lasted throughout the entire observation period	Karl and Veronica Carstens-Foundation, Essen, Germany
Witt CM, 2009	Atopic eczema in children	n=135 patients (1-14 years)	The groups were well balanced. Trend to longer symptoms duration in homeopathic group	Atopic eczema with at least 6 months' disease duration and fulfill 3 of 4 of the Williams' criteria. Between 2-7 at the three-Items severity score	Children with other dermal, medical and psychological diseases (detailed list in publication)	Individualized homeopathy (n=48) vs conventional medicine (according to German guidelines) (n=87)	n=15 vs n=35	Examine the effectiveness, safety and costs of homeopathic vs conventional treatment in usual care	730	Both groups improved in symptoms. No statistical differences between groups	Karl and Veronica Carstens-Foundation, Essen, Germany
Witt CM, 2009	Chronic low back pain	n=129 patients; n=48 homeopathic physicians	A singel group. 76 patients expected homeopathy to be helpful, 51 was uncertain and 1 was pessimistic	Patients with low back pain: lumbago, acute or chronic pain in lumbar or sacral regions	NR	Individualized homeopathic treatment (129)	NR	Evaluate homeopathy as a whole treatment system in usual care settings	365	Substantial improvements were found. Symptoms improved around half of the baseline and remained at this level	Karl and Veronica Carstens-Foundation, Essen, Germany
Witt CM, 2009	Dysmenorrhea	n=139 patients; n=57 homeopathic physicians	A singel group which was descriptively reported in publication	Patients were included consecutively upon first consultation with a participating homeopathic physician	NR	Individualized homeopathic treatment in addition to NSAID and contraceptive hormones (n=139)	NR	Presenting contemporary homeopathic health care and its outcome	730	Symptoms improved under homeopathic treatment. Use of conventional medication changed little	Karl and Veronica Carstens-Foundation, Essen, Germany
Witt CM, 2009	Chronic headache (ICD-9:784.)	n=304; n=74 homeopathic physicians	A singel group which was descriptively reported in publication	Patients with headache defined according to: ICD-9:784.0, ICD-10:R51 were included	NR	Individualized homeopathy, when needed, conventional medicine was prescribed (n=304)	NR	Evaluate homeopathy as a whole treatment system in headache in usual care settings	730	Substantial improvement was found assessed by health related QOL	Karl and Veronica Carstens-Foundation, Essen, Germany
Witt CM, 2010	Migraine	n=212, n=67 homeopathic physicians	A singel group which was descriptively reported in publication	Patients with migraine diagnosed after (ICD-9):346.9,ICD-10:G43.9	Patients with additional forms of headache	Individualized homeopathy,when needed, conventional medicine was prescribed (n=212)	NR	Evaluate the use and effects of homeopathic treatment for migraine in usual care settings	730	Relevant improvement was found, persisting throughout the observational period	Karl and Veronica Carstens-Foundation, Essen, Germany
Zanasi A, 2015	Upper respiratory tract infection (URTI)	n=85 children	The groups were well balanced	Patient aged between 4 and 15 years, cought induced by URTI lasting 5 days or less	Children with pre-existing respiratory problems, with antibiotic or other medical treatment that may effect the cough within 5 days	Homeopathic syrup [Stodal] (n=46) vs homeopathic syrup and antibiotics (n=39)	NR	Evaluate if the addition of antibiotics to a symptomatic treatment (homeopathic syrup) improved cough resolution in pediatric patients with acute cough due to uncomplicated URTI. Verify the safety of the treatments	28	Cough was significantly reduced in both groups.No significant difference in cough severity and resolution were found between the groups. The antibiotic group presented more adverse effects than the homeopathy group	The study was sponsored by Boiron SA, Messimy, France, the holder of the marketing authorization of the study preparation.

Classical homeopathy: Prescribing a single remedy according to the simile law. **Complex homeopathy**: A combination of a number of homeopathic agents or remedies. **Homeopathic immunetherapy**: Homeopathic (ultramolecular) dosis of an allergen, **Isopathy**: A homeopathic subform, in which the preparations are made from the exact illness or its biproducts, **QOL:** Quality of life. **AE**: Adverse effects. **HA**: Homeopathic aggravations. **NR**: Not reported in publication.