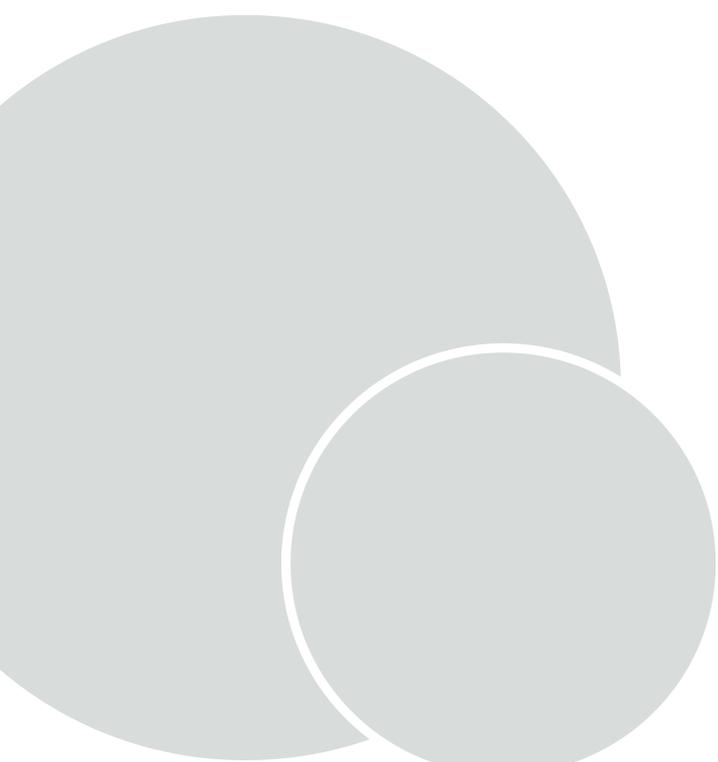


# The Current State of Homeopathic Research

- Healthcare research
- Randomised controlled clinical trials
- Meta-Analyses
- Basic research



With contributions from  
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May 2016

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# The current state of homeopathic research

This report on the current state of homeopathic research provides a summary on the research areas of healthcare research, randomised controlled clinical trials, meta-analyses and basic research.

It aims to contribute to the discussion within the field of homeopathy concerning the need for research, the relevance of individual research fields and methods, and their role in future research strategies.

We are also publishing this report on the current status of scientific research, moreover, for the benefit of medical science as a whole and the public.

Whilst the conventional development of medicinal products is based on research which must then stand up to medical practice, homeopathy is primarily a successful medical practice that must stand up to scientific research.

**Outcome** studies investigating homeopathic treatment under routine conditions have reported clinically relevant improvements in symptoms and quality of life, often comparable with those under conventional treatments, but with fewer adverse effects. In half of all health economic evaluations homeopathic treatment showed less costs. Methodologically, a causal relationship between drug therapy and therapeutic outcome cannot be deduced from those studies.

The **randomised controlled clinical trials investigated here**, studies with good methodology into individualised homeopathy with high potencies only, have indicated, like earlier studies, that classical homeopathy is superior to placebo, and that remedies in high potencies have a specific effect. A definitive scientific statement cannot be made at present given the heterogeneous nature of the data and the small number of studies of good quality.

A review of the **meta-analyses** of homeopathy reveals results which mostly are statistically significant compared to placebo, suggesting specific efficacy from potentised remedies. Depending on the selection criteria applied, different studies are thereby included in the analysis. The majority of the studies reported in all the examined reviews (also Shang et al.), including those with good methodology, suggest that homeopathic treatment is superior to placebo. These findings are in part markedly qualified by the authors of the respective meta-analyses in their (comment/discussion and) conclusion. The stated caveats, e.g. with respect to study quality, thereby do not always reflect the usual scientific standards, or they actually refer explicitly to the postulated implausibility of the efficacy of high-potency medicines.

There are a number of high-quality **basic research** studies that report specific effects also for high potencies, inclusive also of independently replicated experimental models. There are initial empirical results pointing to the physicochemical and pharmaceutical, as well as biological ways homeopathic remedies work, but no theory is fully developed yet.

A **summary analysis** of the clinical research data offers sufficient evidence of the therapeutic effectiveness of homeopathic treatment.

The results from numerous placebo-controlled trials and basic research experiments suggest, moreover, that potentised medicines offer a specific efficacy.

**Put in perspective**, there are many important open research areas – notably:

- Basic research into the optimisation of laboratory models and the understanding of the mode of action
- Independent replications of studies in clinical and basic research
- Exploration of the provision of homeopathic care in reality, also combined with conventional medicine
- Health economic analyses to evaluate the costs and benefits (cost effectiveness)

Board of the Scientific Society for Homeopathy (WissHom)  
Köthen (Anhalt), May 2016

# Clinical outcome research in homeopathy

Michael Teut

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## Background

Although randomised clinical trials (RCTs) are regarded as the “gold standard” in clinical research, they do have drawbacks: As a rule, they are conducted at selected research centres by selected physicians, with a selection of patients who in most cases have been enlisted.

Often, however, routine practice reveals many years later that the medicinal products are given to other patients in another context and with different concomitant conditions and medications to those in the registration trials, resulting in different outcomes and sometimes surprising adverse effects. The results from RCTs thus can only be generalized to the clinical routine to a limited degree.

For this reason, additional clinical studies that examine the effectiveness and safety of medicines under everyday routine care conditions and with everyday patients are important and increasingly demanded by health authorities. Such clinical studies, which are performed in everyday settings, are referred to as “clinical outcome research”.

In outcome studies homeopathy is usually studied as an integrated and complex therapeutic concept (e.g. consisting of a specific consultation, examination and medication). Prospective observational or cohort studies (without control group) describe medical care as it actually takes place in clinical reality. However, uncontrolled studies do not permit to assess about the efficacy of a specific intervention as the result may be influenced by other factors (e.g. the patients social status, income, lifestyle or other, concurrent therapies).

Prospective observational or cohort studies including a control group (e.g. homeopathy versus conventional treatment) permit to compare therapeutic alternatives in the routine care settings. However, the outcomes may be influenced by other relevant features or characteristics than the interventions in different patient groups (e.g. a more healthy lifestyle of the group undergoing homeopathic treatment, a different social, economic or educational status).

It is possible to statistically adjust for differences in the patient groups to a certain extent. If optimal comparability is desired, however, it is better to make use of randomisation technique: If patients are randomly assigned to treatment groups that reflect the routine setting (randomised, pragmatic study), efficacy can be judged most reliably.

Also health economic questions can be answered by outcome research. A cost analysis addresses only the costs of treatment, but not the outcome. A cost-cost analysis compares the costs of two alternative treatments – again, without taking into account benefits of the treatment. A cost-benefit analysis examines the benefit in monetary units; a cost-effectiveness analysis examines costs related to natural parameters (e.g. years of life gained). A cost-utility analysis examines costs in relation to benefits, reported as utility value, mostly in “quality-adjusted life years” (QALYs).

## Results

To date homeopathic outcome research has focussed largely on therapy administered by physicians. Most of the available clinical studies were performed in Europe and India.

The largest homeopathic cohort study to be conducted so far in German speaking countries included 3981 patients in the clinics of more than 100 homeopathic physicians in Germany and Switzerland over a period of eight years (1, 2). The most common indications for homeopathic treatment were long-term, chronic diseases: headaches and migraines in women; allergic rhinitis and hypertension in men; atopic eczema and recurrent infections in children. The pre-/post-treatment-comparisons of outcomes showed a reduction in the intensity of symptoms on average by almost 50%, and a marked improvement in quality of life. The intensity of the symptoms was evaluated by the physicians and patients on symptom scales (Numeric Rating Scale); quality of life was assessed using the SF-36 questionnaire. The decrease in symptoms was greatest within the first three months of treatment. The noted improvements in the symptoms and quality of life were long-lasting. In follow-up questionnaires the patients still reported lasting improvements eight years after starting treatment (2). Clinically relevant improvements were seen in this study for groups with the following diagnoses: Migraine and headache (3, 4), chronic rhinitis (5), back pain (6), geriatric patients (7), menstrual pain (8) and psoriasis (9). As this study was designed without a control group, the question arises whether the improvements reflect a therapeutic effect or the spontaneous course of the disease conditions. In this regard the term “regression toward the mean” is used to describe the shift of extreme values (e.g. when a disease is active) over time towards the mean value. A statistical analysis of the quality of life data from this large cohort study did not suggest a sole “regression toward the mean” effect (10).

An earlier prospective comparative observational study in the 1990s (11) already compared outcomes of patients on homeopathic treatment to those on conventional treatment in routine care. 465 patients with diseases of the upper or lower respiratory tracts and ears (including allergies) were included, 281 received homeopathic and 175 conventional treatment. After 14 days, 82.6% of the patients on homeopathic and 68% of those on conventional treatment were free of symptoms or greatly improved; 67.3% of the patients on homeopathic and 56.6% of the patients on conventional treatment improved within three days. Adverse effects occurred in 22.3% of the patients on conventional treatment, but only in 7.8% of the patients on homeopathic treatment. In 2007, the authors published the data from an even larger multinational prospective observational study including 1577 patients with acute respiratory and ear disorders: 857 patients received homeopathic treatment, and 720 patients conventional therapy. The improvements were similar in both groups after seven days, but recovery was more rapid in the homeopathic group (12).

In another comparative, prospective observational study (13), the outcomes of patients insured by a German health insurance fund receiving homeopathic treatment were compared to those on conventional medicine alone. A total of 459 patients took part. There was a more marked reduction of symptom severity (recorded by patients and physicians) in the homeopathy group compared to the conventional treatment group; in addition the costs were lower under homeopathic treatment.

In another prospective observational study including 1097 Norwegian patients given homeopathic treatment seven out of ten patients reported a clear and clinically relevant symptoms reduction during a six-month course of homeopathic treatment (14).

A prospective observational study conducted at a British hospital outpatient department in a population of 6544 patients revealed a clinical improvement in 70.7% of those under homeopathic treatment, and a good or very good therapeutic outcome in half of all patients (15).

A prospective observational study at an Italian hospital also reported at least a moderate clinical improvement in 74% of all included patients (16).

An observational study in 772 children conducted in six European countries and Brazil (17) reported a high level of treatment satisfaction and an increase in quality of life after two months of homeopathic treatment; adverse effects were observed in only 4.2% of the children.

Several observational studies are also available for diagnosis-related groups of patients:

- Comparative prospective observational studies into the routine treatment of children with atopic eczema have been conducted in Germany (18, 19, 20). Similarly good outcomes from both homeopathic and conventional treatment in terms of the skin and quality of life were reported, although homeopathic treatment was more expensive.
- A comparative, prospective observational study in cancer patients with different diagnoses in Germany compared conventional treatment plus homeopathy (259 patients) against conventional therapy alone (380 patients) (21). Quality of life was found to be better in the group receiving homeopathic treatment. Further studies in oncology revealed a high level of treatment satisfaction in the case of complementary homeopathic treatment (22) and a decrease in symptoms of oestrogen withdrawal in female patients with breast cancer under complementary homeopathic treatment (23). In a recent randomised pragmatic trial in Austria cancer patients were randomly assigned to receive either conventional therapy or conventional therapy plus homeopathic treatment (24). For the combination group a significantly better quality of life and far greater well-being was reported.
- A small comparative prospective observational study in patients with diabetic neuropathy revealed an improvement in clinical symptoms of patients on homeopathic treatment (n=45) compared to those on conventional therapy (n=32) (25). A prospective observational study in India including 336 patients likewise demonstrated a clinical improvement of neuropathy under homeopathic treatment within 12 months (26).
- The French EPI3-MSD cohort study reported that patients with musculoskeletal symptoms receiving homeopathic treatment from their general practitioner had similar outcomes to patients on conventional treatment, but that approx. 50% fewer were taking nonsteroidal antirheumatic drugs (27).
- Clinically relevant improvements were reported by other homeopathic prospective observational studies, amongst others, headaches (28, 29, 4), otitis media (30), male infertility (31), acne (32), chronic sinusitis (33,5), Chickungunya disease (34), menopausal symptoms (35), asthma (36), allergies (37) and injuries (38).

Health economic studies investigating homeopathy naturally reflect the costs within the national healthcare system. A systematic review performed in 2014 (39) summarises the results from 14 health economic analyses of homeopathy covering more than 3500 patients; ten studies included a control group. In eight out of 14 studies improvements in health and cost savings were reported; in four studies the outcomes corresponded to those of the conventional control, with equivalent costs.

Two studies found that the outcomes were comparable to conventional therapy, albeit with higher costs. One of the first studies into the costs of medical homeopathy under the integrated care contracts (Integrierte Versorgung) of the statutory health insurance funds in Germany revealed that the costs of additional homeopathic treatment were higher than those of patients receiving only conventional therapy, but yet without assessing the outcomes. Hence, the ratio of cost to outcome is not yet clear (40).

## Discussion

On the whole, outcome studies document relatively uniform results: In patients undergoing homeopathic treatment in routine care, relevant clinical improvements are observed, if compared to conventional care with often similar outcomes, but with fewer adverse effects and, in half of all health economic studies, lower costs.

It is important to understand that uncontrolled observational studies cannot examine whether high-potency homeopathic remedies are more effective than placebos. Outcomes from clinical routine are reported. Such outcomes have to be investigated with care and can be influenced by a number of factors – drug effects, suggestive effects, expectations, therapeutic consultations, regression toward the mean, and concomitant (non-homeopathic) therapies, amongst others.

The strengths of outcome studies, however, are that they allow to report on the outcomes of homeopathy in everyday conditions, portraying a good picture of the experiences gained by homeopathic patients and therapists in the daily routine.

## Conclusion

Under routine conditions, clinically relevant improvements in symptoms and quality of life are reported by the majority of homeopathic outcome studies. From a pragmatic perspective it can be concluded that patients experience a clinical benefit. Methodologically, however, a causal relationship (efficacy) between drug therapy and outcomes cannot be investigated in these studies.

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# Results of original RCTs with individual homeopathy and high potencies versus placebo and standard treatments

Klaus von Ammon, Loredana Torchetti, Martin Frei-Erb

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## Purpose

To compile an overview of the specific effects of individually prescribed ultramolecular medicines (classical homeopathy with high potencies  $\geq C12$ ) compared with placebo or standard therapy when used in patients requiring treatment.

## Method

A search for literature in published meta-analyses and the “Medline” database (search criteria: “homeopath\*” AND “RCT” AND publication date 01/01/2012-31/12/2014) resulted in high-quality (minimum criterion: Jadad<sup>1</sup> score  $\geq 3$ ), peer-reviewed original publications on randomised controlled trials (RCTs) into the effect of individually prescribed ultramolecular medicines (potency  $\geq C12$ ) which were collated for the purpose of a descriptive assessment. Books or book contributions, dissertations or conference articles were excluded from this analysis, as were pilot studies, studies that were not double-blind, studies with a dropout rate of  $>20\%$ , studies with laboratory or surrogate parameters, and prevention studies. The original studies were used, if possible, or the data extracted from meta-analyses.

## Result

Based on the publications by Linde 1997<sup>2</sup>, Linde and Melchart 1998<sup>3</sup>, Clausius 1998<sup>4</sup> and Shang 2005<sup>5</sup>, RCTs of good methodological quality fulfilling the minimum criterion of Jadad score  $\geq 3$  were identified. In addition, all peer-reviewed RCTs into classical homeopathy could be selected from Mathie 2013<sup>6</sup> and 2014<sup>7</sup>, and an updated Medline search (period 2012-2014) was performed. Altogether, 71 RCTs (without duplicate entries) were identified from the period 1982 to 2014. Of these, a total of 62 trials were ruled out (for details, see Table 1, page 20): 26 due to the use of molecular substances (potency  $< C12$ ), 14 pilot studies, 11 single-blind studies, five due to laboratory/surrogate parameters, and six for other reasons (two due to a lack of peer review, two due to the preventive use of homeopathy, and two due to a high dropout rate).

A total of 24 to 126 patients took part in the remaining nine trials (Table 2, page 21), with a mean number of 64 (SD=31, median 64). The clinical spectrum comprised three studies of diarrhoea, and one study for each of the other diagnoses. In four studies, homeopathy was used as an add-on to standard treatment (Frass 2005<sup>13</sup>, Jacobs 1993<sup>15</sup>, Jacobs 1994<sup>16</sup>, Jacobs 2000<sup>17</sup>). In all nine studies, homeopathy was compared against placebo. The clinical endpoint of the studies varied between five days and 1.5 years. The intention-to-treat (ITT) analysis is a standard.

In meta-analyses of RCTs, the study quality (risk of bias) is assessed by evaluating the internal validity. For this purpose, different instruments were used in the various meta-analyses: Linde 1997<sup>2</sup>, Linde and Melchart 1998<sup>3</sup>, and Clausius 1998<sup>4</sup> applied the – now outdated – Jadad score<sup>1</sup> (maximum 5 points, cut-off for low risk of bias  $\geq 3$ ) and their own scale to assess internal validity (maximum 6 or 7 points, cut-off  $\geq 4$  or  $\geq 5$  points; for details see Table 3, page 23). In the case of Shang 2005<sup>5</sup>, the study quality was judged on the basis of similar criteria to Jadad (higher quality = double-blinding and adequate randomisation). Mathie 2014<sup>7</sup> used today's commonly applied Cochrane method<sup>8</sup>, supplemented by differentiated classification of the bias categories. For the purposes of comparison, we evaluated the quality of the studies by Frei 2005<sup>14</sup> and Lökken 1995<sup>18</sup> using the Cochrane criteria and according to Mathie's classification. Some studies were thus evaluated with different tools. The methodological quality of most of the studies was found to be consistent in the various meta-analyses, with the exception of Jacobs 2000<sup>17</sup> (Shang low, Mathie high risk of bias) and Whitmarsh 1997<sup>19</sup> (high risk of bias in Mathie, and Shang, good quality in Linde and Melchart). Only the study by Jacobs 1994<sup>16</sup> was judged by Mathie to offer reliable evidence. In our opinion, the study by Frei 2005<sup>14</sup> can likewise be deemed reliable.

On the whole, whilst the study quality is not entirely optimal, it is satisfactory. Of the nine studies, only Frei 2005<sup>14</sup> revealed a low risk of bias according to the Cochrane criteria; in five studies the risk of bias was deemed uncertain, and in three the potential for bias was rated as high. The results of these studies must therefore be interpreted with certain reservations.

To compare the studies and subject them to meta-analysis, the results of the original studies were converted into effect size measures, such as into odds ratios (ORs). If the accompanying 95% confidence interval (CI) did not include 1, it was assumed that one group was superior to the other.

Of the eight RCTs with a calculated OR, six indicated that classical homeopathy was superior to placebo, whereas the situation was reversed in two studies (Table 4, page 23). Given the small sample sizes in all the individual studies, however, the confidence intervals were too wide to be able to suggest that the effect of homeopathy or placebo was clearly superior. The only exception was the study by Frass 2005<sup>13</sup>, the result of which clearly favoured homeopathy.

Whereas no OR was given in the case of Frei 2005<sup>14</sup>, the significance test to ascertain group differences was applied. It indicated superiority for classical homeopathy over placebo, even if such significance tests do not constitute measures of effect size and thus are not particularly suitable for making a summarised assessment.

By restricting the review to the studies with the best quality (reliable evidence) according to Mathie's criteria only, the OR in Jacobs 1994<sup>16</sup> then favoured classical homeopathy whilst the CI started precisely at 1. Homeopathy also appeared to be superior to placebo in Frei 2005<sup>14</sup>, even if no OR with CI was available for making a direct comparison.

## Discussion

As suggested by the majority of systematic reviews and meta-analyses performed to date, there is some evidence that classical homeopathy is superior to placebo. Also consistent with previous meta-analyses is the fact that the quality of the studies is not satisfactory right through. By applying very strict parameters (low or uncertain risk of bias, as per Mathie 2014<sup>7</sup>), the number of usable studies is reduced to six, with the remaining three revealing a high risk of bias in accordance with Mathie 2014<sup>7</sup>.

Given that these results were obtained from relatively few studies and small sample sizes, the following conclusions must be interpreted with caution (cf. Mathie 2014<sup>7</sup>).

The criterion of this review is the individual application of high potencies, which were used for different diagnoses with varying outcome measures and endpoints. In this respect the available data are inhomogeneous, allowing only for descriptive analysis.

It is surprising that all the studies were placebo-controlled, there were no comparative studies with standard therapy only, i.e. standard therapy without placebo, and that in a large number (4 out of 9) of studies homeopathy was used as an add-on. This reflects the experimental approach of most of the studies and invokes the question of transfer and applicability into daily practice. The broadness of the diagnostic spectrum, covering acute and chronic, mild (Lökken 1995<sup>18</sup>) to severe (Frass 2005<sup>13</sup>) conditions, is just as surprising. Apart from the three studies by Jacobs<sup>15-17</sup> into childhood diarrhoea, none of these studies has as yet been replicated.

To achieve more definitive results, future clinical studies should be conducted prospectively with larger sample sizes and methods that closely reflect the clinical routine.

This review did not consider any non-peer-reviewed studies into classical homeopathy, nor any studies that employed non-individualized methods of homeopathy – clinical, complex homeopathy, complex (integrative) treatments and isopathy – which are covered by the pool of experience in applied homeopathy.

## Summary

In the last 25 years, a number of good-quality studies into individual homeopathy and ultramolecular medicines have been published subsequent to peer review in high-level, Medline-indexed journals. The majority (7 out of 9) indicate that these medicines have a specific effect, even if the sample size of the individual studies was generally too small to demonstrate, on its own, that they were clearly superior.

A similar overview should be produced for non-peer-reviewed studies (n=15 in Mathie 2013<sup>6</sup>) and non-individually prescribed homeopathic treatment (n=279 in Mathie 2013<sup>6</sup>).

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**Table 1** Sources and primary exclusion criteria of RCTs not included in the overview

No.	Authors	Year	Sources						Primary reason for exclusion											
			Linde 1997	Clausius 1998	Linde & Melchart 1998	Shang 2005	Mathie 2013	Mathie 2014	Medline search (2012-2014)	Potency <C12	Pilot study	Single-blind	Lab/surrogate parameters	Other						
E1	Adler	2011						x												
E2	Adler	2013								x		x								
E3	Andrade	1991	x	x	x					x										
E4	Awdry	1996			x														x <sup>1</sup>	
E5	Bell	2004								x									x	
E6	Bell	2004								x									x	
E7	Bell	2004								x									x	
E8	Bell	2004								x									x	
E9	Brien	2011								x									x	
E10	Brigo	1991			x														x <sup>1</sup>	
E11	Carlini	1987			x					x										
E12	Cavalcanti	2003								x										
E13	Chakraborty	2013								x										
E14	Chakraborty	2013								x										
E15	Chand	2014										x								
E16	Chapman	1994	x	x	x	x														
E17	Chauhan	2014										x								
E18	de Lange	1994	x	x	x					x										
E19	Fisher	1986		x																
E20	Fisher	1989		x	x															
E21	Fisher	2001								x										
E22	Fisher	2006								x										
E23	Gaucher	1994								x										
E24	Gerhard	1997								x										
E25	Gmünder	2002								x										
E26	Halla	2005								x										
E27	Harrison	1999								x										
E28	Hitzenberger	1982		x						x										
E29	Jacobs	2001					x			x										
E30	Jacobs	2005								x										
E31	Jacobs	2005								x										
E32	Jansen	1992								x										
E33	Kainz	1996			x					x										
E34	Katz	2005								x										
E35	Kuzeff	1998			x					x										
E36	Mourão	2013										x								
E37	Mourão	2014										x								
E38	Mousavi	2009								x										
E39	Naude	2010								x										
E40	Oberai	2013								x										
E41	Paterson	2003								x										
E42	Peckham	2014										x								

E43	Rastogi	1999						x		x				
E44	Relton	2009						x			x			
E45	Relton	2012										x		
E46	Saha	2013								x				
E47	Sajedi	2008								x				
E48	Schreier	1997						x				x		
E49	Schwab	1990	x	x	x							x		
E50	Siebenwirth	2009								x				
E51	Sinha	2012											x	
E52	Steinsbekk	2005								x				x <sup>2</sup>
E53	Steinsbekk	2005						x						x <sup>2</sup>
E54	Straumsheim	2000			x					x			x	
E55	Thompson	2005								x				
E56	Thompson	2011						x					x	
E57	van Erp	1996						x						x <sup>3</sup>
E58	Walach	1997			x	x				x			x	
E59	Weatherley-Jones	2004								x			x	
E60	White	2003								x			x	
E61	Witt	2009						x						x <sup>3</sup>
E62	Yakir	2001								x			x	

**Remarks**<sup>1</sup> No peer review<sup>2</sup> Prevention<sup>3</sup> High dropout rate: E57 van Erp 1996: 26%, E61 Witt 2009: 53%**Table 2 Description of included trials**

No.	Authorship	Year	Diagnosis	n ITT	n PP	Duration	Study group	Control group
I1	Bonne	2003	Anxiety disorder	44	39	10 weeks	HOM	PLA
I2	Chapman	1999	Traumatic brain injury	61	50	4 months	HOM	PLA
I3	Frass	2005	Sepsis	70	67	180 days	Standard + HOM	Standard + PLA
I4	Frei	2005	ADHD	62	57	180 days	HOM	PLA
I5	Jacobs	1993	Acute diarrhoea in children	34	33	≤ 6 days	Standard + HOM	Standard + PLA
I6	Jacobs	1994	Acute diarrhoea in children	92	81	≤ 5 days	Standard + HOM	Standard + PLA
I7	Jacobs	2000	Acute diarrhoea in children	126	116	5 days	Standard + HOM	Standard + PLA
I8	Lökken	1995	Removal of wisdom teeth	24	24	5 days	HOM	PLA
I9	Whitmarsh	1997	Migraine	63	60	4 months	HOM	PLA

**Remarks**

ITT = intention-to-treat analysis; PP = per protocol analysis; ADHD = attention deficit hyperactivity disorder; HOM = homeopathy; PLA = placebo; standard = standard treatment

**Table 3 Risk of bias of the included trials**

No.	Authorship	Year	RoB Linde 1997: Jadad (5; ≥3) <sup>1</sup>	RoB Linde 1997: IV (7; ≥5) <sup>2</sup>	RoB Clausius 1998: MV (10; ≥5) <sup>3</sup>	RoB Linde & Melchart 1998: Jadad (5; ≥3) <sup>1</sup>	RoB Linde & Melchart 1998: IV (6; ≥4) <sup>4</sup>	Study quality Linde & Melchart 1998 <sup>5</sup>	RoB Shang 2005 <sup>6</sup>	RoB Mathie 2014 <sup>7</sup>	RoB after Mathie <sup>8</sup>
11	Bonne	2003								Uncertain (B3)	
12	Chapman	1999							Low	Uncertain (B1)	
13	Frass	2005								Uncertain (B2)	
14	Frei	2005									Low (A)
15	Jacobs	1993	3	3.5	7	3	3	B	High	High(C1.4)	
16	Jacobs	1994	5	6	9	5	5	A	Low	Uncertain (B1) <sup>9</sup>	
17	Jacobs	2000							Low	High (C2.0)	
18	Lökken	1995	5	6	5	5	5.5	A			Uncertain (B1) <sup>10</sup>
19	Whitmarsh	1997				4	4	A	High	High (C1.4)	

**Remarks**

RoB = risk of bias; IV = internal validity; MV = model validity; MA = meta analysis.

- <sup>1</sup> Jadad 1996: maximum 5 points (cut-off ≥3) for: 1) Randomisation; 2) Adequate randomisation; 3) Double-blind; 4) Adequate blinding; 5) Reporting of dropouts and discontinuations.
- <sup>2</sup> Internal validity Linde 1997: maximum 7 points (cut-off ≥5) for: 1) Randomisation; 2) Adequate randomisation; 3) Comparability of the groups before treatment; 4) Blinding of the patients; 5) Blinding of examining physicians; 6) Selection error after onset of treatment 7) Adequate statistical analysis.
- <sup>3</sup> Model validity Clausius 1998: maximum 10 points (cut-off ≥5): 1) Compliance with similarity principle (0-5 points); 2) Validated drug prescribing (0-1); 3) Level of trust in prescribing (0-1); 4) Medicine known to homeopathy (0-1); 5) Unum remedium (0-1); 6) Specialist homeopathic expertise of the physician (0-1).
- <sup>4</sup> Internal validity Linde & Melchart 1998: maximum 6 points (cut-off ≥4), precise criteria not determinable:
- <sup>5</sup> Study quality Linde & Melchart 1998: A) Good methodological quality likely; B) Major deficiencies unlikely; C) Significant minor or moderate problems; D) Not evaluable/major deficiencies.
- <sup>6</sup> Shang 2005: low risk of bias = double-blind, adequate randomisation (i.e. adequate generation of randomisation sequence and adequate masking of randomisation).
- <sup>7</sup> Risk of bias Mathie 2014: 7 Cochrane ranges 1) Adequate generation of randomisation sequence; 2) Adequate masking of randomisation; 3a) Blinding of participants and study personnel; 3b) Blinding of examiners; 4) Completeness of outcome data; 5) Selective reporting; 6) Other biases.  
A = low risk of bias in all seven ranges; Bx = uncertain risk of bias in x ranges, low risk of bias in all other ranges; Cy.x = high risk of bias in y ranges, uncertain risk of bias in x ranges, low risk of bias in all other ranges.
- <sup>8</sup> The studies whose risk of bias had not already been evaluated in the meta-analysis by Mathie 2014 were assessed according to the Cochrane criteria and evaluated using the Mathies classification.
- <sup>9</sup> Reliable study as per Mathie 2014, i.e. at least bias category ≥B1, and free of bias in the Cochrane ranges 1, 2, 3a and 3b.
- <sup>10</sup> Risk of bias in Lökken 1995 (as per Cochrane ranges): unclear in range 1 (i.e. unclear whether the randomisation sequence was adequately generated), and low risk of bias in all other ranges.

**Table 4 Results of included studies**

No.	Authorship	Year	OR Linde 1997 & Clausius 1998 (>1 favours HOM) <sup>1</sup>	CI Linde 1997 <sup>1</sup>	OR Shang 2005 (<1 favours HOM) <sup>2</sup>	CI Shang 2005 <sup>2</sup>	OR Mathie2014 (>1 favours HOM) <sup>3</sup>	CI Mathie 2014	Outcome of testing for group differences <sup>4</sup> :
11	Bonne	2003					0.87	0.28-2.73	
12	Chapman	1999			approx. 1 <sup>5</sup>	incl. 1	1.98 <sup>6</sup>	0.72-5.49	
13	Frass	2005					3.13	1.10-8.86	
14	Frei	2005							HOM>placebo <sup>7</sup>
15	Jacobs	1993	1.97	incl. 1	<1	incl. 1	n.i.	n.i.	
16	Jacobs	1994	2.24	incl. 1?	<1	incl. 1?	2.22	1.00-4.94	
17	Jacobs	2000			<1	incl. 1?	n.i.	n.i.	
18	Lökken	1995	0.72	incl. 1					
19	Whitmarsh	1997			approx. 1	incl. 1	1.72	0.69-4.34	

**Remarks**

OR = odds ratio; CI = 95% confidence interval; HOM = homeopathy; MA = meta-analysis

<sup>1</sup> OR and CI for Linde 1997 are depicted on a graph only; these ORs (without CIs) are reported for Clausius 1998, on the other hand,

<sup>2</sup> Shang 2005: OR and CI are presented on a graph only.

<sup>3</sup> n.i.= not included in the meta-analysis for Mathie 2014, as data could not be extracted.

<sup>4</sup> In the case of the study by Frei 2005 not yet included in a meta-analysis, a report is provided on the outcome of statistical testing for group differences.

<sup>5</sup> Outcome: impaired activity.

<sup>6</sup> Outcome: symptoms.

<sup>7</sup> Frei 2005: Crossover study to compare homeopathy against placebo; the linear mixed model delivers a significant within-person difference in favour of homeopathy (-1.67 points on the symptom-outcome scale, with a 95% CI of -3.316 to -0.016; p=0.0479).



# Methodological problems of randomised double-blind trials in homeopathic research

Klaus von Ammon, Curt Kösters

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RCTs (randomised controlled trials) are aimed at examining the efficacy of medical treatments. They entail experiments with (at least) two groups of patients or volunteers randomised to either the study group (under treatment to be studied) or the control group. The control treatment thereby comprises placebo or the best available therapy to date, or the study treatment is administered as an add-on to the best proven treatment. Multi-group comparisons can therefore be performed.

The aim is to control any external confounding factors (such as the study location, methods of administration etc.) as far as possible, or ensure that they do not differ between patients, so as to create the same conditions for the study groups. To control the “internal” – known and unknown – confounding factors amongst the subjects (e.g. expectations, predispositions, responsiveness), randomisation is used: it can thus be assumed that such factors are balanced out between the groups, or will differ only through coincidence, respectively. In such a way, the specific net effect of the treatment to be studied can be determined.

Such a study is deemed double-blind if neither the study subjects nor the investigators know to which study group a subject belongs. Triple-blind refers to a study design in which the rater also is unaware of the randomisation and the nature of the different treatments.

These types of study are generally chosen when investigating new medicinal products and are regarded as the “gold standard” – especially if the design is at least double-blind.

The RCT is surpassed at the top of the evidence pyramid (evidence-based medicine or EBM) only by a methodological review of such RCTs (meta-analysis).

With respect to the understanding of methodological problems, it must be noted that epistemologically RCTs are based on the paradigm of the classical natural science experiment. In such an experiment, all known variables are kept constant and only one input variable is modified. The resulting reproducible change in the output variables leads not only to the conclusion of a causal relationship between the input and output variables, but at the same time also permits this relationship to be quantified precisely.

If such an experiment cannot be fully reproduced in each individual case, it must be assumed that further, as yet unidentified variables exist. Before the experiment is sensibly repeated, these variables must be identified and eliminated.

The adaptation of this experimental approach to therapeutic research (and here in particular to pharmacotherapy) has brought with it methodological limitations, however:

- Biological organisms exhibit individual reactions – full reproducibility in an individual case generally cannot be achieved. Such a requirement has been abandoned in favour of a statistical statement concerning the differences in the respective group as a whole.<sup>1</sup>
- Repetition in an individual case is replaced through replication of the study as a whole.
- To keep the variables constant and to control them, randomisation is added – it should compensate for the potential internal “confounding factors”.
- On account of the rising number, the inconsistent results and incomplete reproducibility of studies and trials, they are summarised in meta-analyses.

What remains is the requirement that the greatest possible homogeneity be achieved within the study groups. Resulting problems in particular, but also further methodological problems, are still a topic of discussion, as is the value of this concept to medical practice.

In terms of medical practice, RCTs come under criticism for the following reasons, amongst others:

1. As experiments, RCTs represent an essentially different situation to that encountered in everyday routine medical consultation.
2. The behaviour of the principal investigator could – from the design of the study alone – be altered by his/her expectations (Rosenthal effect).
3. The individuals involved are aware of this difference and possibly behave differently (Hawthorne effect for study subjects).
4. Different reactions from one individual to the next cannot be reflected by the statistical statement.<sup>2</sup>
5. Any resulting statistically significant differences are no guarantee that the obtained findings are clinically relevant.
6. The applicability and relevance to routine practice with mostly multimorbid, old, (very) young, female, or pregnant patients, for instance, prove problematic, as the study subjects are often young men.
7. Adverse effects or interactions with other medicinal products cannot be monitored during the usually short period of study.
8. Long-term effects thus can only be recorded insufficiently and are systematically undervalued. Long-term effects can look very different, and under certain circumstances also contrast with the short-term effects.
9. Non-pharmacological treatment methods can be investigated only to a limited extent in double-blind studies.<sup>3</sup>

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<sup>1</sup> A probability of error must thereby be taken into consideration. A probability of error of 5% (or 1% and 0.1%, respectively) is now common.

<sup>2</sup> Georg Ivanovas raised the eloquent question in relation to a double-blind study into the influence of the firmness of a mattress on chronic back pain (Kovacs FM et al: Effect of firmness of mattress on chronic non-specific low-back pain: randomised, double-blind, controlled, multicentre trial. *Lancet* 2003, 362: 1599–604), namely whether all patients should sleep on a moderately firm mattress, including the 10% who experienced increased pain from such a mattress and were more comfortable on another. Similar issues resulting from individual reactions have also been seen with medicinal products, however.

<sup>3</sup> This proves problematic if, when writing a guideline on depression, the evidence pertaining to pharmacological measures must be weighed against that of psychotherapeutic interventions.

10. Complex therapeutic strategies with individualised elements (as is common practice today in pain therapy, for instance) cannot be investigated appropriately by means of the RCT.<sup>4</sup>
11. The applicability of this experimental approach to entire therapeutic systems has not yet been examined systematically, let alone validated.

The classic double-blind study is designed with a specific, almost experimental study scenario in mind: **one** medicinal product is tested in **one** indication. It is very well suited to the examination of such a focused question (with the mentioned limitations).

If this more or less successfully implemented strategy for conventional pharmaceutical research is adapted to homeopathic research, a number of other problems emerge which are inherent to the research subject and possibly, in turn, will necessitate adaptation of the research tool – and limit its validity or applicability, respectively. Some of these issues are already recognised<sup>5</sup>, but possibly have not yet been methodologically examined to an adequate degree.

Problems arise with the application of the methodological tool of double-blind RCTs in homeopathic research due to individualisation, due to the iterative approach to finding an appropriate agent and the assessment of the course, and due to the different way in which therapeutic success is evaluated in homeopathy.

Changes in symptoms can occur as a result of the natural course of the disease but also, in particular, as a reaction to a previously administered medicine. Successive approximation solutions are thus involved here, in the sense of an iterative approach.

The course during homeopathic treatment is evaluated largely on the basis of the change in well-being, as well as the relevant clinical symptoms. A marked improvement in well-being, albeit without any major improvement in the clinically relevant symptoms to begin with, is a justified reason for waiting – because experience has shown that an improvement in clinically relevant symptoms will follow.

## Problems due to individualisation

RCTs with adequate individual remedy finding and prescribing in line with classical homeopathic principles have seldom been conducted (*see contribution by Klaus von Ammon, Loredana Torchetti, Martin Frei-Erb: Results from original RCTs with individual homeopathy and high potencies versus placebo and standard treatments, with excluded studies therein*).

In a study with individual remedy selection (as is standard practice in classical homeopathy), the overall outcome is inevitably poorer than the result from the individual agent with the highest degree of probability if the different remedies available for selection do not offer the same – or at least roughly the same – degree of probability.

The degree of probability – if initially ignoring the involved therapist and his/her level of expertise – depends largely on the information available on the individual agents and their reliability.

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<sup>4</sup> In complex therapeutic strategies, the interplay of different treatments (e.g. pharmaceuticals, physiotherapy, relaxation techniques, psychotherapy, acupuncture) individually adapted to suit the patient in question are expected to deliver the therapeutic effect, rather than a single intervention.

<sup>5</sup> Gaus W, Högel J. Studies on the efficacy of unconventional therapies. Problems and designs. *Arzneimittelforschung*. 1995 Jan; 45(1):88–92.

The information available on the individual agents differs considerably, ranging from remedies with more than 1,000 known symptoms (originating mainly from drug proving and confirmed, moreover, by clinical experience – if taken together a criterion for high validity in homeopathy) to those with fewer than 10 known symptoms, which in addition result from clinical experience only and hence are of low validity in homeopathy.

In the clinical routine, this difference in the level of knowledge about medicines and the resulting, differing degree of probability are a much less serious problem (see above). The effect size of a study, which precisely evaluates an intervention, is therefore lower than the effect of an individual homeopathic treatment in clinical routine. Under the pressure of a study to offer the “optimal” prescription spontaneously (instead of the practical approach to approximation), a negative Hawthorne effect could in fact emerge.

Besides, therapists selecting medicines on an individualised basis cause an additional, fundamental methodological problem. The double-blind studies of conventional medicine themselves offer only limited reproducibility compared to classical physical experiments, because aside from the medicinal products as the actual study variables, the patients and their individual reactions are also involved. The therapists, as the third independent variable, additionally hamper replication – including replication by independent examiners, in particular.

Proposed solutions:

- Limitation of the choice of agents and introduction of a standardised treatment protocol is potentially suitable as a means of minimising the “therapist” variable. In an open pilot phase, the problem of differing probabilities can potentially be minimised. A restriction to the effectiveness of treatment vis-à-vis the results from everyday practice must probably be accepted. In case of simple, acute conditions this approach would appear to be justifiable based on experience to date; in chronic conditions the same would certainly then apply if at the same time an exclusion criterion is introduced for patients with symptoms that do not correspond to those of one of the approved agents – an exclusion criterion that at the same time clearly narrows the external validity (validity of the study for average patients).
- One innovative solution is the idea of an open treatment phase followed by the actual double-blind study with the inclusion criterion of “responder” (Bell: fibromyalgia<sup>6</sup>; Frei: ADHD<sup>7</sup>). However, a large proportion of the therapeutic effect already exhausted in the open treatment phase will no longer be captured by the double-blind study. Whether this concept can be successfully applied to other indications and other prescribing strategies also has not yet been fully explained or examined. Yet again, external validity is limited in this case by the inclusion criterion. In the design addressed specifically here, moreover, undesirable crossover effects (e.g. take-over instead of wash-out effects) cannot be completely ruled out. Provisionally, this concept must still be regarded as experimental by nature.
- An interesting, but certainly also still experimental – and largely untested – approach is the “N=1 study” with the option of consolidated meta-analyses.<sup>8</sup> In this case individualisation is not a methodological problem. Somewhat unclear in this study design is the documentation of changing prescriptions (see *Iteration* below); also unclear is the external validity.

<sup>6</sup> Bell I, Lewis D, Brooks A, Schwartz G, Lewis S, Walsh B, Baldwin C. Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. *Rheumatology*. 2004; 43:577–582.

<sup>7</sup> Frei H, Everts R, von Ammon K, et al. Homeopathic treatment of children with attention deficit hyperactivity disorder: a randomized, double blind, placebo controlled crossover trial. *Eur J Pediatr*. 2005; 164:758–767.

<sup>8</sup> Teut M, Linde K. Scientific case research in complementary and alternative medicine-a review. *Complement Ther Med*. 2013 Aug; 21(4):388–95

- The solution that appears to come closest – whilst also the oldest: To permit consecutive prescriptions with consistent blinding (Walach, headaches<sup>9</sup>) is probably, methodologically, more problematic (see *Problems due to iteration* below).

## Problems due to iteration

To date no sufficient methodological evidence has been forthcoming to demonstrate that a double-blind study is a suitable experimental tool for evaluating several different successive and (within the meaning of iteration) coordinated prescriptions. Successive prescriptions permitted in a double-blind study could intensify the blurring of individual prescriptions.

It is recommended, therefore, to apply the double-blind study initially to individual interventions only (including repetitions of the same agent). This tends to restrict the applicability of the double-blind study in homeopathic research to simple, acute diseases, however.

## Problems due to the outcome

Unlike conventional pharmaceuticals, homeopathic remedies are not suitable for forcing the organism in question into a specific state – the postulated effect is stimulated self-regulation. The reactions thus induced are far more individual in their nature and course over time compared to the response to conventional pharmaceuticals. Assessment of the course in clinical practice is therefore much more strongly related, in the case of homeopathy, to the symptoms as a whole and also, in particular, to changes in well-being.

In the planning of a study this alternative approach to assessing the course must at least be considered – this requirement again tends to conflict, however, with the methodologically standardised, pre-defined examination times for the respective primary endpoints of a study.<sup>10</sup>

Also to be considered, however, are other clinical courses and how they can be given adequate consideration in the design of a study.<sup>11</sup>

These issues are also mostly relevant to chronic indications and largely negligible in the case of acute diseases.

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<sup>9</sup> Walach H, Häusler W, Lowes T, Mussbach D, Schamell U, Springer W, Stritzl G, Haag G. Classical homeopathic treatment of chronic headaches. *Cephalalgia*. 1997; 17:119–126.

<sup>10</sup> If headache is the primary endpoint, but the mood and energy levels of a patient initially clearly improve, then in practice (and from the perspective of the patient) this is regarded as a marked improvement – in a study it is not.

<sup>11</sup> The outcome of a study into the treatment of neurodermatitis, compared directly against ongoing cortisone treatment, is predictable: the effect of cortisone is faster and far better than that of a homeopathic treatment. Patients who seek homeopathic treatment for neurodermatitis are also aware of this fact. This is not the question that needs to be answered by a study, therefore. As far as the comparison between homeopathic treatment and cortisone therapy is concerned, it would be much more interesting if it were conducted in each case three weeks after discontinuing the last agent (in both study groups). In turn, however, the question arises whether this scenario also offers an appropriate and fair design from the perspective of conventional medicine.

## Other problems

Further phenomena characteristic of homeopathy, such as primary aggravation or a symptom shift (centripetal shift in symptoms vs. Hering's law), also have not yet been considered by the design or the analysis of studies, respectively. The individual development of such phenomena also conflicts at this point with the rigid scheduling of follow-up appointments required for the purpose of statistical analysis. But this, also, tends to be more relevant to chronic conditions.

Entanglement effects were suggested by Walach; hence, they should be accounted for planning a study. To date, however, neither the existence nor the power of such effects have been adequately examined or proven.

Appropriate research relating to these problems would be useful in the field of conventional pharmacology. The question as to possible substance-, remedy- or drug-specific effects in the placebo group (including proper storage of the products) has not yet been investigated. Clinical experience tends to suggest that this phenomenon is not particularly relevant.

Meta-analyses of diverse diagnoses in the strict sense of the definition (homogeneous total population) tend to be questionable from the basic perspective of methodology. Such vast meta-analyses could be practical as an extension to systematic review.

## Implications for homeopathic clinical research

Better and more extensive data are required with respect to routine homeopathic practice. Conclusions can be drawn from such data with a view to study planning: useful indications, effect sizes, appropriate study sizes and durations, along with data on the probability of selecting individual agents. Comprehensive and unselected case documentation will most likely deliver such data.

So far, study planning sometimes appears to be founded upon estimations and individual clinical advisers and their personal experience. There is room for improvement, accordingly, when it comes to communication between practice and research. And at least until valid data from everyday practice are available, extensive pilot phases are recommendable as part of study planning (see above).

The highly deficient development of theories in homeopathy should be stimulated. However, there is still a need for clarification with respect to individual research tools (appropriately modified RCT designs, e.g. by excluding non-responders and N=1; see above).

It is not possible to demonstrate at present, however, that a double-blind study, especially with primary blinding, is a suitable research tool for examining homeopathic treatment in any given indication – especially in chronic indications.

The justified, understandable and as yet inconclusively resolved question, namely “what contribution do context effects make to the clinical efficacy of homeopathy?”, in turn can be answered only, and exclusively, by (adequately elaborated) double-blind studies.

With this in mind, but also in the light of the long-standing and not only scientific debate surrounding homeopathy<sup>12</sup> – a debate that has long since become a vehement social dialogue on a global scale – the question arises whether research should not concentrate on the central point of this debate.

The clinical effectiveness of the method is not denied, even by sceptics and scientific critics. This debate does not (or at least not primarily) revolve around whether a homeopathic treatment is effective in one or another indication, but whether this clinical effectiveness can be attributed to and thus explained by a specific effect (efficacy) caused by the medicines applied (plausibility paradox, see footnote 13 below). High potencies, above all, naturally attract considerable attention.

Quite clearly, the relevant number of clinical studies performed in recent decades did not deliver a definitive conclusion<sup>13</sup>.

Perhaps the two essential questions raised here – “In which indications is homeopathic treatment effective?” and “What is the basis for the effect of homeopathic treatment?” – should be addressed separately. And the second question should be answered by developing independent treatment models. Distinguishing between questions and developing methodologically appropriate models are also suitable approaches when considering theoretical scientific aspects. RCTs in the field of conventional pharmacology address the question whether a specific medicine is effective in a specific indication. RCTs in homeopathic research address the (clinical) effectiveness of the method, the efficacy (specific effect) of the drug, and the mechanism of action.

These therapeutic models should then be replicated multiple times – by different examiners – ideally with a pre-defined number of replications.

Given the methodological problems arising from individualisation and iteration, the therapeutic models most appropriate here are those based on a limited number of agents which are prescribed according to a rigid regimen. Clinical situations in which, as a rule, the same agent is prescribed homeopathically, are ideal. For this reason alone, acute diseases/conditions must be clearly prioritised.

Very simple models (one condition/one agent) would also offer the advantage that they can potentially also be analysed and replicated by examiners who have no prior knowledge of homeopathy. A pre-defined number of replications would also permit a falsification criterion to be established. If the negative hypothesis applies, the results from replications should equate to the probability of chance.

Testing of the models in appropriate pilot studies is advisable, at least until a clinical database in the form of unselected case documentation is available.

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<sup>12</sup> In 2005, the esteemed scientific journal *The Lancet* officially announced “The end of homeopathy” in its editorial.

<sup>13</sup> “All relevant published reviews [...] reveal that the majority of the available studies produced positive results (this also applies to that by Shang et al.). At the same time, it cannot be denied that positive results are not as common from studies with good methodology as from those that are not so good. Naturally this means that positive results can certainly also be found in the good studies. The debate amongst clinical researchers therefore is not whether positive evidence is derived from placebo-controlled studies, but whether such evidence is sufficient to prove the efficacy of homeopathy in view of the low plausibility from the perspective of natural science.” (Prof. Klaus Linde, Munich Technical University, personal communication 2007).

Simple models that have already been tested are, for example:

- Treatment of childhood diarrhoea (Jacobs)<sup>14</sup>
- Treatment of respiratory patients with high-potency potassium dichromate (Frass)<sup>15</sup>

The treatment of hay fever with pollen (Reilly)<sup>16</sup> is also, in principle, a very suitable isopathy model, given its simplicity, for investigating the effect of potentised substances.

Beyond these therapeutic models, and without unduly influencing the therapeutic setting, the question of which indication is successfully treated by homeopathy can be answered scientifically to current methodological standards, depending on the indication, by epidemiological studies, cohort studies, randomised unblinded studies, and also by unselected case series. This applies in particular to chronic illnesses.

For reasons of logic, future meta-analyses will then be based predominantly on model studies that are easy to replicate, and their respective replication(s).

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<sup>14</sup> Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D: Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. *Pediatr Infect Dis J* 2003; 22(3):229–234.

<sup>15</sup> Frass M, Dielacher C, Linkesch M, Endler C, Muchitsch I, Schuster E, Kaye A. Influence of potassium dichromate on tracheal secretions in critically ill patients. *Chest*. 2005; 127:936–41

<sup>16</sup> Reilly D, Taylor M, Beattie N, et al., Is Evidence for Homoeopathy Reproducible? *Lancet*, December 10, 1994, 344:1601–6.

# Meta-analyses in homeopathic clinical research

Jens Behnke

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## 1. Introduction

The idea behind evidence-based medicine (EBM) is that one or more meta-analyses of high-quality, randomised clinical trials will furnish reliable data on the efficacy of a therapeutic method. A treatment for which sufficient positive data are available within this context is proven by the highest level of evidence, namely Ia.<sup>1</sup> In response to the question whether and to what extent a particular method should be used in the clinical routine, it is awarded recommendation grade A or a “strong” recommendation, respectively.<sup>2</sup>

As homeopathy is a topic of constant debate, both proponents and opponents frequently refer to the results from meta-analyses of the available clinical studies to support their respective stance in line with the highest scientific standards of EBM. With this in mind, an attempt will be made below to provide an outline of the most important global meta-analyses performed on clinical research into homeopathy. All relevant publications that are not limited to a single clinical indication are presented and discussed individually so as to formulate an overall opinion on this basis on the status of clinical research into homeopathy, insofar as this has been addressed by the given publications. The question that is relevant here is whether the clinical effects of homeopathy are placebo effects, or whether potentised medicines can produce specific effects.

### 2.1. Kleijnen, Knipschild and ter Riet (1991)<sup>3</sup>

This meta-analysis of homeopathy was published in 1991, namely during the era when EBM was in its infancy. The authors start by referring to what is often claimed: that homeopathy on the one hand is implausible, and on the other hand has not been investigated using modern methods (controlled studies). Kleijnen, Knipschild and ter Riet identified 105 evaluable studies that could be included in their analysis. Of these, 14 examined classical homeopathy involving the individual remedy selection, 58 the prescription of a single homeopathic agent following clinical diagnosis (proven indication), 26 a combination of remedies, and 16 isopathy. The studies were evaluated for their quality using an independent method and awarded scores, with the results being included in the final analysis with different weightings based on their score. A total of 81 studies indicated efficacy for homeopathy in excess of placebo effects. Of these, the majority were rated as methodologically good in terms of randomisation, blinding, patient number and similar methodological criteria (15 out of 22). Overall, Kleijnen, Knipschild and ter Riet (1991) criticise the fact that many studies tend to be of low quality, whilst at the same time noting the trend in favour of homeopathy, both in those with a sophisticated design and those which, in their methodology, are rather weak.

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<sup>1</sup> Cf. Cochrane (2014)

<sup>2</sup> Cf. Harbour & Miller (2001)

<sup>3</sup> Kleijnen, Knipschild and ter Riet (1991)

The authors conclude: “At the moment the evidence of clinical trials is positive but not sufficient to draw definitive conclusions because most trials are of low methodological quality and because of the unknown role of publication bias. This indicates that there is a legitimate case for further evaluation of homeopathy, but only by means of well performed trials.”<sup>4</sup>

## 2.2. Linde et al. (1997)<sup>5</sup>

In the light of the question whether the clinical effectiveness of homeopathy can be explained solely by placebo effects, Linde et al. (1997) conducted a meta-analysis of all placebo-controlled, randomised and/or double-blind clinical trials of homeopathy published in the renowned journal *The Lancet*. Of the 119 studies identified, 89 contained sufficient data to be included in the meta-analysis. Linde et al. evaluated this subset for its methodological quality using their own method of assessment, performed by two independent experts whose results were compared against one another. A high level of agreement was achieved in the assessment (interrater reliability:  $\kappa=0.76$ ). The average quality of the examined studies ( $n=89$ ) with regard to randomisation, double-blinding, handling of study dropouts, etc., was 52% of the maximum value on a generally accepted scale for evaluating the quality of clinical trials (Jadad Scale).

The analysis included 13 publications on individualised single-agent homeopathy (classical homeopathy), 49 that examined prescribing based on clinical diagnosis, 20 that used complex homeopathic remedies, and seven based on isopathy. Of the studies included, 22% examined moderate potencies (according to the definition by Linde et al. D9 – D23 or C5 – C11) and 37% high potencies (above D23 or C11, likewise as per Linde et al.), whereby both substance groups according to the authors theoretically contained too few molecules of the starting substance to exert any pharmacological activity (estimated total concentration per patient of less than  $10^{-13}$  mol/L).

The 89 studies included in the meta-analysis revealed that homeopathy was significantly superior to placebo (mean odds ratio 2.45; 95% confidence interval 2.05-2.93). In the case of the 26 studies rated as good methodologically, Linde et al. calculated lower, yet still significant efficacy versus placebo (odds ratio 1.66; 95% confidence interval 1.33-2.08). This result proved to be robust, moreover, in various sensitivity analyses (e.g. only the studies of the best quality with pre-defined endpoints which are listed in the MEDLINE database,  $n=5$ : odds ratio 1.97; 95% confidence interval 1.04-3.75). Correction of the results due to potential errors that could have arisen from selective reporting (publication bias) also did not eliminate the positive effects of homeopathy. Considering the initial question of their meta-analysis, the researchers ultimately concluded:

“The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo. However, we found insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition. Further research on homeopathy is war-ranted provided it is rigorous and systematic.”

The criticism arising from this meta-analysis was aimed primarily at the quality of the studies included, which Linde et al. (1997) evaluated using their own system and included, accordingly, in their final analysis. In response to this, the authors screened the material again and created subsets depending on the Jadad score attained by the studies, at which point they introduced an external assessment scale.<sup>6</sup> In this reanalysis it transpired that the superiority of homeopathy over placebo was lessened to

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<sup>4</sup> Kleijnen, Knipschild and ter Riet (1991)

<sup>5</sup> Linde et al. (1997)

<sup>6</sup> Linde et al. (1999)

some extent if studies of higher quality were considered, without disappearing completely and without this correlation being linear: The ten studies with the highest Jadad score of 5 demonstrated that the effect of homeopathic treatment was greater than in the 19 studies with a Jadad score of 3 and the 11 studies that achieved a score of 4. On the whole, it was found that homeopathy was significantly superior to placebo treatment in each of the six subsets created on the basis of the Jadad score. The argument that the higher the quality of the study design, the lower the effect of homeopathic treatment, was thus refuted.

### 2.3. Cucherat et al. (2000)<sup>7</sup>

This meta-analysis was undertaken as part of a report for the European Parliament. The authors conducted a systematic literature review and contacted pharmaceutical companies to identify randomised, placebo-controlled trials into homeopathy. Only those studies were considered in which potencies above C3 were used, or products designated by the manufacturer as “homeopathic”. A lack of blinding was not deemed to be an exclusion criterion. Only studies with a clearly defined primary endpoint were taken into consideration. Two experts were appointed to evaluate the quality of the studies. If their opinions differed, a third expert was consulted. Determination of the mean significance level (p-value) was used as the statistical method for meta-analysis, because the included trials were very heterogeneous as regards the treated diseases, prescribing methods and endpoints. A combined p-value of less than 0.05 signified in this case that the null hypothesis was incorrect and the homeopathic treatment thus differed significantly from placebo.

Of the 118 studies identified, 16 were included in the meta-analysis. The others, in the opinion of the authors, either had no clearly defined endpoint (92.9%) or were methodologically deficient. One of these 16 studies contained a total of three groups (standard treatment, homeopathy and placebo). Hence, 17 comparisons of “homeopathy versus control” were analysed in total. Of these 17 study outcomes, 11 (65%) delivered a result in favour of homeopathy; three suggested superiority for placebo that was below the significance level. As the overall conclusion from analysing all the studies that fulfilled their inclusion and exclusion criteria, Cucherat et al. thus reported a highly significant mean p-value of 0.000036, which demonstrates clear efficacy for homeopathy versus placebo. The authors concluded that this outcome was not significantly influenced by publication bias, as by their estimation 155 notional trials with a negative or non-significant outcome would have been required to increase the composite p-value of their meta-analysis to above 0.05. A subset analysis revealed, however, that the significance level in an analysis of only those studies with a dropout rate of less than 5% (n=5) was not achieved (p=0.082). Based on this conclusion, Cucherat et al. postulated:

“There is some evidence that homeopathic treatments are more effective than placebo; however, the strength of this evidence is low because of the low methodological quality of the trials. Studies of high methodological quality were more likely to be negative than the lower quality studies.”<sup>8</sup>

This cautious overall judgement is based on the definition of “methodological quality”, which in the given case is largely based on the rate of dropouts. Use of the same criterion as the main parameter for judging the quality of the study is questionable, however. What is essential to the reliability of the study outcome is not primarily the number of patients ending treatment prematurely, but rather the total number of cases, the correct randomisation of the subjects to the study groups, the blinding of patients and physicians, etc. In terms of the dropout rate the statistical method used to compensate for

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<sup>7</sup> Cucherat et al. (2000)

<sup>8</sup> Cucherat et al. (2000)

the resulting loss of data is mainly relevant to study quality.<sup>9</sup> To this end there are different approaches, some of which are suitable for rendering dropout rates of far more than 5% manageable.<sup>10</sup> The corresponding methods are standard practice in epidemiology, and the criterion chosen by Cucherat et al. for evaluating the study quality in their meta-analysis, along with the limitation of the conclusion of their meta-analysis that resulted, is therefore very unusual from the viewpoint of methodology.

## 2.4. Shang et al. (2005)<sup>11</sup>

This meta-analysis, published in the renowned journal *The Lancet*, triggered the loudest media echo of all scientific papers on the subject of homeopathy. The article was accompanied in the *Lancet* by an editorial announcing “The end of homeopathy”<sup>12</sup>.

Shang et al. (2005) referred more or less to the same pool of data as that at the time of publication by Linde et al. (1997); the final analysis included only eight out of the 110 studies initially reviewed, however. These eight studies were selected as the largest from a pool of 21 rated at first as demonstrating good methodology. The combined odds ratio of these homeopathic trials was 0.88 (95% confidence interval 0.65-1.19). For comparison, the authors initially selected 110 studies from the field of conventional medicine from a Cochrane database, of which six were rated as high quality and included in the final analysis with a combined odds ratio of 0.58 (95% confidence interval 0.39-0.85). Shang et al. concluded:

“Biases are present in placebo-controlled trials of both homoeopathy and conventional medicine. When account was taken for these biases in the analysis, there was weak evidence for a specific effect of homoeopathic remedies, but strong evidence for specific effects of conventional interventions. This finding is compatible with the notion that the clinical effects of homoeopathy are placebo effects.”<sup>13</sup>

This meta-analysis attracted criticism from various authors who pointed out a number of weaknesses:

Fisher<sup>14</sup> complained about the lack of transparency in study selection insofar as the original publication by Shang et al. (2005) contained no details of which eight studies were ultimately analysed. Such a situation is a glaring deviation from the scientific standards used in meta-analyses, as specified in the QUORUM guideline.<sup>15</sup> This guideline demands, amongst others, that all studies considered in a review – both those ultimately analysed and those excluded from final analysis – be presented in detail alongside the criteria for such a selection process so that the results of the meta-analysis and the path taken to obtain them can be understood. Although such a procedure is self-evident with any scientific publication, Fisher (2006) believes that close observance of such standards must be demanded, especially of reviews that contain far-reaching, definitive conclusions, such as the one by Shang et al. (2005).

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<sup>9</sup> Cf. Sakpal (2010)

<sup>10</sup> Cf. EMA (2010)

<sup>11</sup> Shang et al. (2005)

<sup>12</sup> The Lancet (2005)

<sup>13</sup> Shang et al. (2005)

<sup>14</sup> Fisher (2006)

<sup>15</sup> Moher (1999)

Fisher also doubts the accuracy of the fit of the 110 studies in conventional medicine against those in homeopathy. The latter were, on average, of much higher quality, as a result of which the probability of a positive result diminishes. Shang et al. failed, moreover, to conduct sensitivity analyses which would have revealed the extent to which the negative outcome depends on study selection.<sup>16</sup> Rutten and Stolper (2008) were of a similar opinion:

“Re-analysis of Shang’s post-publication data did not support the conclusion that homeopathy is a placebo effect. The conclusion that homeopathy is and that conventional is not a placebo effect was not based on comparative analysis and not justified because of heterogeneity and lack of sensitivity analysis.”<sup>17</sup>

Such a detailed sensitivity analysis was therefore produced by Lüdtkke and Rutten (2008) once it became known which eight studies had led to the presented result. It was found that the analysis of the 21 high-quality studies from the pool collated by Shang et al. (2005) demonstrated significant superiority for homeopathy over placebo. The negative conclusion ultimately presented by the authors is influenced essentially by one single, large study that examines the efficacy of one homeopathic remedy in the prevention of muscle soreness.<sup>18</sup>

Another weakness of the meta-analysis performed by Shang et al. is the heterogeneity of the very few selected studies in relation to the global statement derived from them as a result. The authors analysed a pool of studies that examined the efficacy of potentised medicines in the prevention of colds, treatment of warts, prevention of aching muscles, treatment of migraines, childhood diarrhoea, and severe brain injuries, jointly in only one study in each case. This is a method whereby consideration should be given to the possibility that homeopathy is an effective treatment for certain indications, but not for others. If one were to compare, as part of a meta-analysis, three clearly negative studies of conventional medicine in the treatment of cancer, soft-tissue injuries and rheumatic disease with specific drugs against a slightly positive study in the treatment of headaches with aspirin, its negative outcome would not likely be suitable for concluding that all conventional pharmacological interventions are generally ineffective.

As the author of the first major meta-analysis of homeopathy, likewise published in the *Lancet*, Linde also agreed with many of the presented criticisms, as did other experts in the area of researching complementary medicine.<sup>19</sup> On the whole, it must be concluded that there were clear methodological weaknesses in the review by Shang et al. and that their conclusion is based on a relatively small number of studies that were selected according to questionable criteria.

## 2.5. Mathie et al. (2014)

The most recent meta-analysis of homeopathy was performed by Mathie and colleagues in 2014. It included only those studies with a method of treatment that could be classified as “individualised homeopathy”. This approach is based on the authors’ assumption that prescribing potentised medicines cannot necessarily be interpreted as an adequate criterion for it to be associated with a single coherent treatment procedure. Clinical homeopathy, complex homeopathy, isopathy, etc., differ at least from the individualised approach of classical homeopathy in that the latter regularly involves

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<sup>16</sup> Cf. Fisher (2006)

<sup>17</sup> Rutten & Stolper (2008)

<sup>18</sup> Vickers et al. (1998)

<sup>19</sup> Cf. Linde and Jonas (2005), and Bell et al. (2005)

much longer diagnostic periods. This situation could explain a serious difference compared to the other prescribing practices.

Mathie et al. thus take an initial step away from the concept of global meta-analysis, which attempts to answer the question whether any method that can be subsumed under the generic term of homeopathy is effective. This approach permits a more differentiated view of some of the available data than some previous reviews, even if Linde et al. (1997) already performed subset analyses which refer to different methods of prescribing potentised medicines.

Yet the limitation to 32 studies that examine individualised homeopathy is not the only characteristic feature of the meta-analysis by Mathie et al. The review of the quality of the individual studies, by assessing the risk of bias using a tool of the Cochrane Collaboration<sup>20</sup>, is also new. Their methodological guidelines represent the state of the art of EBM, especially with regard to systematic reviews and meta-analysis. In their methodology, therefore, Mathie et al. are at the height of the game with their approach.

Of the 32 included studies, 22 delivered sufficient data to warrant inclusion in the final analysis. These studies delivered a significantly positive result for homeopathy (OR 1.53; 95% confidence interval 1.22-1.91). The assessment of the retrieved study material performed by Mathie et al. (2014) with respect to the seven aspects (domains) of methodological quality (blinding, randomisation, selective reporting, etc.) according to the Cochrane criteria, however, meant that only three studies were graded as reliable. The combined odds ratio of these publications, at 1.98 (95% confidence interval 1.16-3.38), was higher than the average, but given the exclusion of the majority of the retrieved material the database was so small that the authors stated: „Though our conclusions can be made most securely from three trials with reliable evidence, this sub-set of studies is too small to enable a decisive answer to our tested hypothesis.“<sup>21</sup>

The main results of the meta-analysis by Mathie et al. confer, in their opinion, with those of previous, comparable reviews: Specific (minor) effects are identifiable with homeopathic treatment. These are robust, insofar as sensitivity analyses for different subsets of the analysed studies allow similar effect sizes to be identified. The quality of the evidence found was judged overall to be low or unclear. Hence, no definitive conclusions could be drawn. Consequently, more high-quality RCTs of individualised homeopathy are required in order to formulate reliable statements.<sup>22</sup>

### 3. Conclusion

In the light of the relevant global meta-analyses of homeopathy published to date it is clear, on the whole, that in four out of five cases potentised medicines tend to reveal specific efficacy in excess of placebo. The overall outcome is only negative (homeopathy = placebo) if a large amount (90%-95%)<sup>23</sup> of the available data is excluded from the analysis and/or dubious statistical methods are employed. In each of these cases measures are used that deviate from the usual scientific standards insofar as the desired increase in reliable data, by excluding studies with certain features, is not reasonably in proportion with the accepted narrowing of the database (for example, a dropout rate of <10% = 9 studies versus <5% = 5 studies; see above).<sup>24</sup>

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<sup>20</sup> Higgins & Altman (2011)

<sup>21</sup> Mathie et al. (2014)

<sup>22</sup> Ibid.

<sup>23</sup> Cf. Hahn (2013)

<sup>24</sup> Cf. Cucherat et al. (2000)

An exception here is the latest study by Mathie et al. (2014), which likewise judges a large proportion of the data found as (relatively) unreliable. In doing so, however, the authors refer to accepted standard procedures, and their study produces a positive result for homeopathy. The only study to ultimately conclude that the clinical effects of homeopathy can be explained entirely by placebo effects<sup>25</sup> reveals considerable shortcomings in terms of methodology.

In homeopathic research, the evaluation of data on the basis of (in)compatibility with certain theoretical preconceptions appears to play a significant role. As far as scientific theories are concerned, this phenomenon is referred to as plausibility bias.<sup>26</sup> Hahn (2013), for instance, analysed the inclusion and exclusion criteria of studies in meta-analyses of homeopathy with a negative or indifferent tendency, revealing, on the basis of statistical considerations amongst others, that they were probably formulated retrospectively. He suspects that this methodological approach was ideologically motivated, which would diametrically oppose the scientific demands of EBM.<sup>27</sup>

The authors of the reviewed publications, however, more or less agree that the available evidence does not permit any definitive conclusions to be drawn concerning the efficacy of potentised medicines in individual diseases – the reason being that independent replications of high-quality randomised, placebo-controlled, double-blind trials referring to one and the same indication are lacking.

Along with other considerations, this observation points the way for the future of homeopathic research: In this respect an evaluation of the available data from the perspective of model validity would be useful, along with the design of new, harmonised studies that then results. This could be achieved with meta-analyses which, with greater differentiation than hitherto, consider individual prescribing methods and/or, in particular, indications for homeopathic treatment. New data could also lead to reviews that cover material not previously considered, including non-interventional studies for example, and on this basis offer a more comprehensive picture of the evidence available on homeopathy.

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<sup>25</sup> Shang et al. (2005)

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# Status of basic research in homeopathy

Stephan Baumgartner

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Homeopathy is based on three principles: testing the remedy in healthy individuals, the similarity principle, and potentisation. Basic research in homeopathy focuses on scientific evidence for the similarity principle, and potentisation as a pharmaceutical process.

Criticism of homeopathy is aimed primarily at the process of potentisation, as from the perspective of natural sciences and pharmacology there are various arguments that question the meaningfulness of using potentisation as a pharmaceutical process. This includes, amongst others:

- The content of active substances decreases exponentially, to a large extent, on potentisation. With simple anorganic compounds (such as calcium, sodium, silicium), lower dilutions, which in practice correspond roughly to 6x-9x, cannot be produced beyond the ubiquitariness limit (ppm-ppb depending on the material used). With plant and animal extracts it can be assumed that as of a potency level equivalent to the inverse of the Avogadro number in terms of its degree of dilution (approx. 24x), the probability of tracing just a single molecule of the starting substance in the potentised drug rapidly reaches zero. For this reason, questions are raised concerning specific effects from drugs diluted to higher potencies.
- At lower potencies (to approx. 6x/9x), the substance content can deviate considerably from the nominally expected concentration – for instance due to minimal solubility in water (e.g. with metals), or due to adsorption at the vessel walls or dissolution from the same. From the viewpoint of natural science and pharmacology, this results in undefined concentrations in potentised drugs.

## Goals of basic homeopathic research

In response to the specificity argument, preclinical research into potentised drugs in recent decades has primarily addressed the question of the existence of possible specific effects from higher-potency drugs in biological models. Given the difficulties reproducing results achieved (1), the latter question has developed in the last 20 years into one concerning the development of apt scientific methods: methods that as far as possible should satisfy the object of the study in its specific properties and effects – also with a view to obtaining reproducible results (2). Another question concerned establishment of a correlation between potency level and effect, i.e. determining the dose-effect relationship. Only few studies addressed the question of pharmaceutical optimisation (e.g. number of shakes on potentisation) or resistance of the potentised drugs to environmental influences. With a view to identifying the pharmaceutical mechanism of action, studies were also conducted to determine any specific physicochemical properties of potentised drugs.

## Models and methods of basic homeopathic research

Scientific literature related to preclinical research into potentised drugs is comprehensively documented in the HomBRex database (3). In 2013, this database contained entries on 1,868 experimental studies discussed in 1,383 publications (3). Four large preclinical research areas with

potentised drugs can be distinguished: (A) physicochemical measurements, (B) *in vitro* assays (cell cultures, microorganisms), (C) bioassays with plants and (D) animal experiments, the latter accounting for more than 50% of all studies (4).

Research related to physicochemical studies into potentised drugs was last summarised in a review conducted in 2003 (5). The results from 36 studies were presented in 44 publications. The methods of analysis were divided into six categories: electrical impedance, electrochemistry, spectroscopy, nuclear magnetic resonance, Raman spectroscopy and methods with unknown principles (black box methods). Half of the studies used nuclear magnetic resonance, where reproducible results were also achieved across various studies. Based on the currently available data, there are no empirical indications of stable water clusters in potentised drugs (6, 7), which have been hypothetically demanded as carriers of potential drug information (8). In several independent studies that measured NMR relaxation times ( $T_1/T_2$ ), however, there were clear and consistent differences between potentised silicea products and relevant shaken controls which were interpreted as modified molecular dynamics in water (9). UV spectroscopy also revealed consistent differences between potentised substances and corresponding controls (10). A theoretical model that interprets such modifications as carriers of specific drug effects has not yet been devised, however (9). Since 2000, there has been a marked upswing in physicochemical research into potentised drugs. Hence, by the end of 2015 more than 150 publications had been identified as part of a systematic review, the content of which is currently being evaluated by an international study team. The research field is characterised by many different methods which in some cases are employed only in individual studies and often have not been replicated. Examples are the investigation for nanoparticles (11) or the reactivity of dyes (12).

The study of potentised products by means of *in vitro* assays was last addressed in a review performed in 2007 (13). The 67 experimental studies that were evaluated can be divided into cell-free systems (e.g. enzymatic models), cell cultures, and models with cells from donated blood. Amongst the latter, those involving human basophils account for a considerable percentage (42%) of all the studies. The model used most frequently is inhibition of basophil degranulation by potentised histamine. Several replication studies and one multicentre study are available on this subject (14). It is noticeable from the studies with human basophils that effects could also be seen in various independent studies as a result of high potencies (beyond the inverse of the Avogadro number). The pattern of active and inactive potency levels within a given sequence of potencies (the “potency curve”) differed in each study (15), however – both between the different laboratories and on repeating the process at the same laboratory (16). As the basophils originated in each case from different blood donors, it is conceivable that the results depend on the individual donor. There is no empirical evidence of such to date, however.

Plant bioassays are the third research field with respect to the effect and efficacy of potentised substances. The status of the research was last examined systematically in 2009/2011 (17-19). In the three main fields, i.e. bioassays with healthy plants, intoxication models and phytopathological studies, a total of 167 experimental studies were counted in 157 publications. Of these, 48 fulfilled higher standards of quality and were analysed more closely (20). The test organism used most frequently was wheat, followed by duckweed and peas. The most commonly used stressor was arsenic. Silver nitrate was most often used as the potentised substance, followed by arsenic and gibberellic acid. In various studies, specific effects – also of potencies beyond the inverse of the Avogadro number – were observed. In the models that examined continuous series of potencies, a discontinuous relationship between effect and potency level was observed in all cases, i.e. effective and ineffective potencies alternated according to a defined, albeit different sequence depending on the study.

With respect to the fourth large research field, namely animal experiments, only reviews that offer a cursory description or are limited in terms of time or subject matter have been found recently – probably on account of the large number of scientific studies overall (4). The studies were in most cases performed on rats (35%) or mice (29%) (4). The employed research concepts were categorised by way of example using the rat (21). In most of the experiments a specific disease was artificially induced in the animals. In the majority of cases this entailed intoxication (e.g. with arsenic, lead, CCl<sub>4</sub>), induction of behavioural disorders (e.g. with ethanol, caffeine), inflammatory models (e.g. with carrageenan) or induced hormonal disorders. The animals were then treated either prophylactically or curatively with potentised medicines (before or after induction of the disease, respectively). A systematic review of 105 publications is available on the studies in experimental toxicology (22). A total of 26 studies were included in a quantitative meta-analysis. A mean protective index of 19.7% resulted for the examined indications (survival rate, excretion of toxins) after administering potentised substances, which were selected according to the isopathic principle. Aside from artificially induced disease models, there were two other model clusters in which the effect of potentised substances was investigated: development models and animal behaviour models. In case of the development models, studies repeatedly involved an amphibian model in which the effect of thyroxine 30x on the metamorphosis of *Rana temporaria* was examined. The inhibitory effect of thyroxine 30x on such metamorphosis was judged to be significant in a meta-analysis of 26 studies. The effect appears to be quite robust, moreover, as both internal and external reproducibility was rated as positive (23). A more recent review of animal behaviour models identified 18 publications that spanned a wide range of models and methods (24). There was an emphasis on the potentised drugs *Ignatia*, *Gelsemium* and *Chamomilla*. Potentised *Gelsemium* products, used in a number of studies, exhibited highly significant effects in behavioural experiments on mice which were of the same magnitude as conventional psychopharmaceuticals at substantial dosage (24).

In summary it can be stated that preclinical research into potentised drugs is characterised by a wide variety of methods and tested drug potencies. The large number of scientific publications also includes many studies of good quality that deliver empirical evidence of specific effects for potentised drugs, also for highly diluted potentised products.

## Research into the dose-effect relationship

The outcome of preclinical research into potentised products that has been most adequately confirmed empirically is the phenomenon of the non-linear relationship between the effect and potency level. To my knowledge, in every preclinical study that investigated several potency levels of the same substance, effective and ineffective potency levels were reported to appear consecutively according to a particular pattern (referred to, after Kolisko (25), as the “potency curve”) (17-19, 24). These patterns generally prove to be stable within one series of tests (26-28), but over time can also change (28) or differ between independent laboratories (14, 16). To date, no potency curve has been identified that remained stable either for the tested potentised substance, the experimental method, or a combination of substance and method. It is not possible to say at the moment whether this is due to as yet unidentified determinants or to a particular phenomenon that is inherent to the effects of potentised drugs.

## Research into the similarity principle

The principle of similarity has been investigated far less intensively than that of potentisation: the current status of research was last reviewed in 2011 (29). Research into hormesis clearly demonstrated that low doses of a stressor administered before or after an acutely toxic, higher dose of

the same stressor can ameliorate these harmful effects – both clinically and preclinically (29). Within the context of homeopathy, this may be regarded as empirical evidence of the isopathic principle. The best empirical evidence for applicability of the similarity principle (treating “like with like”) in the field of preclinical research has been obtained by a Dutch study team with studies into cell cultures. The cells in these studies were firstly exposed to a heat shock. Subsequent treatment with low doses of a series of different stressors revealed that the survival rate was better, the more similar the respective stressor was to the heat shock in terms of the spectrum of proteins that developed (30).

## Research into the biological mechanism of action

Difficulties reproducing the results from research into potentised substances could be caused by the fact that the experimental systems and/or parameters chosen to document the nature of the effect of potentised substances are inadequate. For example, it has been postulated that the activity of potentised substances is not aimed primarily at exerting a particular effect in a particular direction (irrespective of the system and its condition), but rather at having compensatory effects or promoting homeostasis. Translated into an experimental language, this means that primarily effects are not to be anticipated as regards the mean value of a population, which is reproducibly shifted in a certain direction, but that the scattering of the system is reduced. This is what was observed in a meta-analysis across various experimental systems in which the activity of potentised arsenic was investigated (31). Whether this phenomenon should be attributed specifically to the effect of potentised arsenic, or whether it is characteristic in general to the effect of potentised drugs, cannot be determined at present due to the lack of experimental data.

There are some indications that the status of an experimental system decisively influences the response to a treatment with potentised substances. The response of *Pisum sativum* to treatment with potentised gibberellic acid depends on the batch of seed, for instance (32). The metamorphosis of *Rana temporaria* is only influenced by potentised thyroxine if the amphibians originate from highland habitats (33, 34). *Lemna gibba* responds to potentised gibberellic acid only if the organisms are in a gibbous state (28). The therapeutic effect exerted by potentised *Lyopodium* in the phytopathological model system *Malus domestica* / *Dysaphis plantaginea* is especially pronounced if the stress from *D. plantaginea* is not too high (35). These examples clearly indicate that potentised substances are seen to exert an effect in particular if the test organisms are in a mildly, yet not excessively, stressed state. The degree of divergence from homeostasis evidently may only be so great that the organisms can regain a state of equilibrium on their own. This statement is to be taken as a working hypothesis at present and should be carefully examined in the process of developing further methods. After verification, it could be rated as evidence for a part of the biological mechanism of action of potentised drugs.

Another aspect of the mechanism of action is formulated in the hypothesis that potentised drugs exert their effect at the level of the ability of the whole organisms to regulate itself. Empirical evidence is available in this regard from a number of experimental oncology studies in animals. By systematically administering potentised drugs in the animals inoculated with cancer cells, the number and size of the developing tumours were decreased; treatment of the cancer cell lines with the same potentised drugs *in vitro* revealed no activity whatsoever (36-39). These results speak clearly in favour of an effect at the higher level of the organism as a whole. This aspect of the biological mechanism of action of potentised drugs must also be determined more precisely in future studies. The relevance to the design of preclinical models is evident: If the hypothesis fits, any efficacy in potentised drugs cannot be expected from studies in cancer cell lines (40).

## Reproducibility of basic homeopathic research

In 2010, a systematic review to address the question of the reproducibility of effects in basic research of potentised products identified 24 experimental models that had been used in a total of 107 studies and were repeated internally at the laboratory or externally (41). Repeat studies in 24 of these models revealed similar results in 22, differing results in 6, and no effects in 15 models. Independent reproductions delivered significant results with 7 models. It can therefore be stated that preclinical research into potentised drugs in the last 10 years has made clear progress: in 1999, no single experimental model was known in which the results could be reproduced independently (1).

## Outlook

Given the advances in methodology, the prospect of addressing diverse questions of scientific and pharmaceutical relevance is becoming more realistic. Consideration must first be given to determining the mechanism of action of potentised drugs, at both the pharmaceutical and biomedical level. From the pharmaceutical perspective, two concepts are conceivable: (1) consolidation and methodological expansion of the physicochemical studies for determining the specific molecular structure and dynamics of potentised drugs, and (2) physical interventions into potentised drugs, the effects of which can be investigated with appropriate bioassays and which then permit conclusions to be drawn on the mechanism of action. Furthermore, established test methods could be used to examine pharmaceutically relevant issues, especially with respect to stability under external influences (heat, pressure, sterile filtration, electromagnetic radiation, etc.) and also with regard to stability in general.

## Working groups and organisations

In Europe there are five working groups at present that focus closely on questions of basic research into potentised products. These working groups are based at the University of Witten/Herdecke (Germany, Dr Stephan Baumgartner), the University of Bern (Switzerland, Prof. Ursula Wolf), the Interuniversity College of Graz (Austria, Prof. Christian Endler), the University of Verona (Italy, Prof. Paolo Bellavite) and the University of Bologna (Italy, Prof. Lucietta Betti). Elsewhere, there are several university-based working groups in Brazil and India.

Notable organisations are the GIRI (Groupe International de Recherche sur l'Infinitésimal, [www.giriweb.com](http://www.giriweb.com)), a scientific association dedicated to basic research into potentised products, the Karl and Veronica Carstens Foundation as the supporters of the HomBRex database ([www.carstens-stiftung.de](http://www.carstens-stiftung.de)), and the HRI (Homeopathy Research Institute), as the organiser of conferences on the subject of homeopathic research ([www.homeoinst.org](http://www.homeoinst.org)).

## Summary

The following can be concluded on the status of preclinical research into potentised substances: Amongst the available specialist scientific publications, totalling more than 1,000, there is a significant collection of studies of high quality that has delivered empirical evidence of specific efficacy, also with highly diluted, potentised drugs. Likewise, there are several experimental models with which significant specific effects were observed for potentised products when replicated independently. The empirically ascertained modification of molecular dynamics in potentised drugs could give indications of the physicochemical and pharmaceutical mechanisms of action, which as a whole must still be determined, however. There is also initial empirical evidence of the biological mechanism of action, described by a regulatory reaction of the entire organism to deviations from homeostasis.

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