Scientific assessment[1] of the motion V-01 "Real patient protection: end the advantages for homeopathy!"

Motion to the Federal Delegate Conference of Bündnis90/DieGrünen [The German Green Party] on 15–17 November 2019 in Bielefeld

Dr med. Harald J. Hamre, Dr med. Helmut Kiene
Institute for Applied Epistemology and Medical Methodology at the Witten/Herdecke University
Zechenweg 6, 79111 Freiburg, Germany

Summary

The motion V-01 contains false and misleading statements on homeopathy. In this document the central statements of the motion are contrasted with the relevant scientific evidence:

1. Proof of efficacy of highly-diluted (homeopathically *potentized*) solutions

The statement "*a change in the efficacy of a substance as a result of so-called potentization is not detectable"* is false. Effects of homeopathically potentized substances have been demonstrated in many laboratory experiments using various test procedures, and have also been confirmed in replication studies.

2. Efficacy in placebo-controlled clinical trials

The statement *"lack of efficacy of homeopathic treatment beyond the placebo effect has been repeatedly demonstrated in very large and high-quality trials"* is false. Efficacy has been found in many clinical trials and in corresponding meta-analyses, also in trials and meta-analyses of higher methodological quality.

3. "Dangers" of homeopathy

The statement regarding a "*health risk of delayed treatment if homeopathic remedies are used instead of medications with pharmaceutical active ingredients to treat dangerous or chronic diseases*" is based on speculative claims without evidence base and is therefore misleading. The failure to use necessary treatments is a general problem in medicine. Whether this problem is more common than usual in homeopathy is unclear. Evidence from case reports and comparative studies does not support this hypothesis.

There is a striking discrepancy: These statements are intended as a *"commitment to a health policy based on scientific knowledge",* but the actual evidence base is ignored, while unverified popular opinions are adopted.

[1] Written for the International Academy of Science in Homeopathy and Integrative Medicine, Berlin. English translation of the original German text, finalized by the authors.

1. Proof of efficacy of highly-diluted (homeopathically *potentized*) solutions

"In most cases, the manufacturing of a homeopathic remedy from a substance involves repeated dilutions of the substance with water or alcohol, followed by vigorous shaking after each dilution step (so-called potentization). A change in the efficacy of a substance as a result of so-called potentization is not detectable."

The statement "a change in the efficacy of a substance as a result of so-called potentization is not detectable" is false. Effects of homeopathically potentized substances have been demonstrated in many laboratory experiments using various test procedures and have also been confirmed in replication studies:

2007: In a systematic review of laboratory research (in vitro) with homeopathic high potencies, 67 experiments were assessed, a third of which were replications: three quarters of the experiments and even the replications showed high-potency effects.[1]

2010: In a systematic review, 107 biochemical, immunological, cell biological and zoological experiments were evaluated for reproducibility: in half of these (53), replication studies showed comparable effects.[2]

Currently published research shows high potencies to have positive and replicable effects, also in recent experiments of higher standards, using validated models.[3-7]

2. Efficacy in placebo-controlled clinical trials

"The lack of efficacy of homeopathic treatment beyond the placebo effect has been repeatedly demonstrated in very large and high-quality trials."

The statement is false. Efficacy of homeopathic treatment beyond the placebo effect has been found in many clinical trials and in corresponding meta-analyses, even in trials of higher methodological quality.

Since 1996, **six meta-analyses** of randomized, placebo-controlled clinical trials of homeopathy for any indications in humans have been published, thereof three on any type of homeopathy (Boissel 1996 and Cucherat 2000[8,9]), (Linde 1997 and 1999[10,11]) (Shang et al. 2005/Lüdtke 2008[12,13]), two on individualized homeopathy (Linde 1998[14]) (Mathie et al. 2014[15]) and one on non-individualized homeopathy (Mathie et al. 2017[16]).

For explanations on the methodology of randomized placebo-controlled clinical studies and their meta-analyses → see page 3

All **primary analyses** of these six meta-analyses showed a positive treatment effect of homeopathy beyond placebo. The treatment effects were statistically significant in five of the six meta-analyses[9,10,14-16], while in the sixth meta-analysis[12] the statistical significance was not explicitly mentioned but seems likely when considering the other published data.

For all six meta-analyses, **sensitivity analyses** regarding the methodological quality of the included trials were conducted. These analyses involved 1 to 9 study quality indicators in different combinations and with different scoring systems, resulting in a total of more than 50 sensitivity analyses. If we exclude sensitivity analyses using procedures or quality indicators that are not recommended (correction procedures based on funnel plot diagnostics[17,18], restriction to trials with a drop-out rate below a specific percentage[19]) or in which a quality indicator is

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Explanations on the methodology of placebo-controlled randomized clinical homeopathy trials and their meta-analyses

Homeopathic treatment can be individualized or non-individualized: **Individualized homeopathy** involves a comprehensive interview with the patients regarding the type of symptoms of their disease, other symptoms, etc., in order to select a suitable "individualized" homeopathic treatment. **Non-individualized homeopathy** follows other principles and requires less time.

In a **randomized, placebo-controlled clinical homeopathy trial,** the patient is **randomly** assigned to a treatment or control group, according to specific procedures. The random treatment allocation is intended to distribute other factors, which, in addition to the treatment, could influence the study outcome (e.g. the duration and severity of the disease to be treated) equally between both groups.

The treatment group receives a homeopathic remedy, the control group receives a **placebo** substance which looks and tastes as similar as possible to the homeopathic remedy etc. The purpose of the placebo treatment is that the patients should not know which treatment they are receiving, in order that any potential psychological factors which might influence the study results (e.g. the expectation of an improvement) are distributed equally between both groups, as well as other treatment components (e.g. interview with the patient, clinical examination, explanation and advice). For this reason, not only the patients should be "blinded" to whether they are allocated to the homeopathy or the placebo group, but if possible also the physicians, therapists and other people involved in data collection (**double blind trial**).

Clinical study outcomes are e.g. the number of improved patients or the extent of improvement (according to predefined criteria) in the two groups. The **treatment effect** of the homeopathic remedy is the difference between the two groups, i.e. the treatment outcome in the homeopathy group minus the outcome in the placebo group, according to specific calculation procedures such as subtraction, division, etc. The outcome comprises a measure of the size of the difference (effect size) and a measure for the **statistical significance**. A difference or treatment effect is said to be statistically **significant** if the likelihood of the difference occurring by chance is less than 5% ($p < 0.05$). Smaller as well as larger percentage values are possible. The usual 5% are used in the present text.

In **systematic reviews**, the outcomes of all retrievable studies on a specific research issue (in our case *"randomized, placebo-controlled clinical trials on homeopathic treatment for any disease in humans"*) are compiled and assessed.

Meta-analyses are systematic reviews in which the results of the individual trials – large and small trials, trials with statistically significant and non-significant results – are summarized into one quantitative average treatment effect, again with effect size and statistical significance.

In the **primary analysis** the summarized outcome for all trials included in the meta-analysis is calculated and presented.

With additional **sensitivity analyses** the researchers can examine whether the treatment effect in the subgroups of the trials with higher methodological quality is larger, similar or smaller than in all the trials (and then, where applicable, no longer significant). The methodological quality is assessed using different **quality indicators**, pertaining to random allocation of patients, blinding of patients and physicians, handling of missing data due to patient dropouts etc. Trials with higher methodological quality often, but not always, show smaller effects. This is often interpreted to mean that treatment effects are overestimated in trials with lower methodological quality. Other causes, however, can also lead to the same pattern, e.g. the "poorer trials" having larger treatment effects because they involved more experienced homeopaths, or vice versa. In addition, the restriction of analyzed trials to those with higher quality can lead to other changes that also affect the outcome of the meta-analysis, e.g. a change in the indication spectrum.[13] Accordingly, the outcomes of trials with higher methodological quality is not necessarily "more correct" than outcomes of trials that meet fewer quality criteria, and the results of primary analyses should always be taken into consideration.

incrementally modified without results changing from statistical significance to non-significance or vice versa, 19 sensitivity analyses remain.

In 7 of these 19 sensitivity analyses[5,10,11], **only one single quality indicator was used**; all 7 showed a significant positive treatment effect of homeopathy beyond placebo.

In 12 of the 19 sensitivity analyses, more than one quality indicator was used. All 12 analyses showed a positive treatment effect of homeopathy beyond placebo, the effect was statistically significant in nine analyses[10,11,13,15,16] and non-significant in three.[11,14,16]

- Three of the 12 sensitivity analyses had a low number of quality indicators (3 each). Nine of the 12 analyses had a high number of quality indicators (7 or 9); among these nine analyses, the treatment effect was significant in seven analyses[10,11,15,16] and non-significant in two.[11,16]
- Four of the 12 sensitivity analyses had particularly strict quality indicators. The treatment effect was significant in three of them[10,11] and non-significant in one.[11]
- Eight of the 12 sensitivity analyses belong to four meta-analyses from the period 1996-2008,[8-14] and four of the analyses belong to two meta-analyses from the period 2014-2017.[15,16] In these 21 years, the methodological standards for meta-analyses have advanced. The newer standards also involve aspects other than the quality indicators. The two most recent meta-analyses (Mathie 2014 and 2017[15,16]) were conducted according to newer quality standards: predefined analysis protocol, quality assessment of the trials using the Cochrane risk-of-bias appraisal tool, selection of main outcome measures from the trials for meta-analysis according to WHO recommendations, reporting compliant with PRISMA guidelines. Among the 4 sensitivity analyses from these two meta-analyses, the treatment effect was statistically significant in three analyses[15,16] and non-significant in one.[16]

Summary: Meta-analyses of placebo-controlled trials on homeopathy for any indication show positive treatment effects of homeopathy beyond placebo (6 out of 6 meta-analyses) that are statistically significant (explicitly in 5 out of 6, likely in 6 out of 6 meta-analyses). When restricting the meta-analyses to trials with higher methodological quality, the positive treatment effects remain predominantly significant (16 out of 19 sensitivity analyses), even in analyses with a high number of quality indicators (7 out of 9 analyses) or with particularly strict criteria (3 out of 4 analyses) and in the meta-analyses following newer, improved standards (3 out of 4 analyses).

3. "Dangers" of homeopathy

> *"Some emphasize the health risk of delayed treatment if homeopathic remedies are used instead of medications with pharmaceutical active ingredients to treat dangerous or chronic diseases."*

This statement is based on speculative claims with no basis of evidence and is therefore misleading.

Generally speaking, medical malpractice occurs in medicine, and patient compliance is not always ideal. The failure to use necessary therapy is a general problem in medicine. Whether or not this problem occurs more commonly when "*homeopathic remedies are used*", is an empirical question. Instead of speculations, we need to take a critical look at the actual evidence from, amongst others, comparative studies on homeopathic versus other treatment.

We found one **systematic review of published case reports and case series,** in which *"harm …associated with the use of homeopathy as a replacement of conventional treatments"* was addressed.[20] For this topic, eight publications with a total of 16 patients were identified in the world literature. According to

the authors of the review, a wide range of complications were caused by the use of homeopathy instead of conventional medicine. This is, however, not supported by the actual data. We checked the eight original publications for this topic: Only in one (!) of the 16 cases, complications from the non-use of an indicated medication in conjunction with use of homeopathic remedies could be reliably confirmed: One patient did not use previously poorly-tolerated malaria prophylaxis when travelling in an area with endemic malaria, and subsequently contracted malaria. Notably, the failure to use malaria prophylaxis can be a problem in travel medicine, also independently of homeopathy.[21,22]

Regarding the other 15 patients: In 6 cases there was definitely no homeopathic treatment at all or no non-use of conventional treatment. In 4 cases there was very probably no homeopathic treatment or the complications were not due to a lack of effective treatment but very likely caused by dietary restrictions in infants. In 5 cases it was unclear whether the alleged “homeopathic” treatment or the treatment by alleged "homeopaths" involved any actual homeopathic remedies.

In **comparative studies of homeopathic vs conventional treatment and placebo, respectively** (various indications: randomized trials[23-25], observational studies[26-33]) adverse effects or complications from homeopathic treatment were comparably frequent[23-26,28,30-33] or significantly less frequent ([27,29] + adults in[28]) than under conventional treatment or placebo.

Conclusion and comments

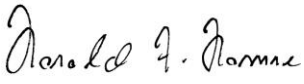
The three claims examined here:

- effects of potentization are supposedly not detectable,
- lack of efficacy of homeopathic treatment beyond the placebo effect has supposedly been demonstrated several times,
- homeopathic treatment is said to pose health risks from delayed use of conventional treatment,

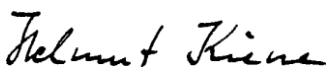
are false or misleading. The relevant facts have been presented above.

There is a striking discrepancy: These statements are intended as a *"commitment to a health policy based on scientific knowledge",* but the actual evidence base is ignored, while unverified popular opinions are adopted.

Freiburg, 8 November 2019



Dr med. Harald J. Hamre



Dr med. Helmut Kiene

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