

Effectiveness, Safety and Cost-Effectiveness of Homeopathy in General Practice – Summarized Health Technology Assessment

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Key Words

Homeopathy · Health technology assessment · Upper respiratory tract infections · External validity · PEK

Summary

Introduction: The Health Technology Assessment report on effectiveness, cost-effectiveness and appropriateness of homeopathy was compiled on behalf of the Swiss Federal Office for Public Health (BAG) within the framework of the 'Program of Evaluation of Complementary Medicine (PEK)'. **Materials and Methods:** Databases accessible by Internet were systematically searched, complemented by manual search and contacts with experts, and evaluated according to internal and external validity criteria. **Results:** Many high-quality investigations of pre-clinical basic research proved homeopathic high-potencies inducing regulative and specific changes in cells or living organisms. 20 of 22 systematic reviews detected at least a trend in favor of homeopathy. In our estimation 5 studies yielded results indicating clear evidence for homeopathic therapy. The evaluation of 29 studies in the domain 'Upper Respiratory Tract Infections/Allergic Reactions' showed a positive overall result in favor of homeopathy. 6 out of 7 controlled studies were at least equivalent to conventional medical interventions. 8 out of 16 placebo-controlled studies were significant in favor of homeopathy. Swiss regulations grant a high degree of safety due to product and training requirements for homeopathic physicians. Applied properly, classical homeopathy has few side-effects and the use of high-potencies is free of toxic effects. A general health-economic statement about homeopathy cannot be made from the available data. **Conclusion:** Taking internal and external validity criteria into account, effectiveness of homeopathy can be supported by clinical evidence and professional and adequate application be regarded as safe. Reliable statements of cost-effectiveness are not available at the moment. External and model validity will have to be taken more strongly into consideration in future studies.

Schlüsselwörter

Homöopathie · Health Technology Assessment · Infektionen der oberen Atemwege · Externe Validität · PEK

Zusammenfassung

Fragestellung: Der Health Technology Assessment (HTA) Bericht zu Wirksamkeit, Zweckmässigkeit und Wirtschaftlichkeit der Homöopathie in der Schweiz wurde im Auftrag des Eidgenössischen Bundesamts für Gesundheit (BAG) im Rahmen des «Programm Evaluation Komplementärmedizin (PEK)» erstellt. **Material und Methoden:** Es wurde systematisch in internetzugänglichen Datenbanken sowie individuell in Zeitschriften, Referenzlisten und über Expertenkontakte gesucht. Die Studien wurden nach internen und externen Validitätskriterien bewertet. **Ergebnisse:** Eine grosse Anzahl von qualitativ hochwertigen Arbeiten der präklinischen Grundlagenforschung stützt die Auffassung regulativer und spezifischer Effekte homöopathischer Hochpotenzen bei Lebewesen. Die Auswertung von 22 systematischen Reviews zur Homöopathie ergab für 20 Arbeiten zumindest einen Trend zugunsten der Homöopathie. 5 Studien zeigten nach unserer Einschätzung einen deutlichen Beleg für die Wirksamkeit einer homöopathischen Therapie. Die Auswertung von 29 systematisch gesuchten Studien der Domäne «Upper Respiratory Tract Infections/Allergic Reactions» (URTI/A) zeigte insgesamt ein positives Ergebnis zugunsten der Homöopathie. 6 von 7 kontrollierten Studien wiesen zumindest eine Gleichwertigkeit mit konventionell-medizinischen Interventionen und 8 von 16 plazebokontrollierten Studien eine Signifikanz zugunsten der Homöopathie auf. Die Ausbildungsanforderungen an ärztliche Homöopathen und die Produktbestimmungen in der Schweiz gewähren ein hohes Mass an Sicherheit. Die klassische Homöopathie ist arm an Nebenwirkungen und mit der Verwendung von Hochpotenzen frei von toxischen Wirkungen. Eine allgemeine gesundheitsökonomische Aussage für die Fachmethode der Homöopathie als Ganzes kann nicht getroffen werden. **Schlussfolgerung:** Die Wirksamkeit der Homöopathie kann unter Berücksichtigung von internen und externen Validitätskriterien als belegt gelten, die professionelle, sachgerechte Anwendung als sicher. Zuverlässige Aussagen zur Wirtschaftlichkeit sind derzeit nicht möglich. In zukünftigen Studien sollten externe Validität und Modellvalidität stärkere Berücksichtigung finden.

Introduction

Background and Objective

This article is the summarized version of the Health Technology Assessment (HTA) report on behalf of the Swiss Federal Office for Public Health (BAG) in the Program for Evaluation of Complementary Medicine (PEK) on the effectiveness, appropriateness and cost-effectiveness of homeopathy in Switzerland; and further, on general questions as to demand and underlying conditions (for details see 'Use of Complementary Medicine in Switzerland' in this issue as well as the unabridged version of the HTA [1]). The topics were:

- Effectiveness: amount of evidence available on the effectiveness of homeopathy regarding (a) the entire method, on the basis of published systematic reviews and meta-analyses and (b) on an exemplarily selected clinical indication processed on the basis of published studies with different designs
- Appropriateness (demand/need and safety): (a) kind and frequency of undesirable effects described, (b) legal regulations regarding the safety of the remedies and (c) training and continuous education structured in order to ensure the safety of the application. (For demand and need see separate article in this issue.)
- Cost-effectiveness: results of economic studies of homeopathy in Switzerland and other countries

On Homeopathy

Homeopathy is still one of the most disputed methods in medicine, although it is based on over 200 years of clinical experience. The main points of criticism are the use of high-potencies, i.e. medicines containing no molecule of an active substance, and the mechanism of action, which is not yet adequately understood. In many respects the effectiveness of homeopathy is negated in a prejudiced manner and placed into the realm of placebo effect.

A short glance at the history of homeopathy [2–5] may help to understand its characteristics. Birth of homeopathy is generally considered in 1796, when Hahnemann (1755–1843) formulated the so-called similarity principle due to his experiences with remedy provings on healthy volunteers: 'similia similibus curentur' (like shall be cured by likes). Since then our understanding of the similarity principle, as well as knowledge of remedies, has been deepened by numerous remedy provings, on the basis of toxicological knowledge and in particular, on the basis of clinical experience on millions of patients. To date, the homeopathic treasure of remedies has grown to over 1,000. The results of empirical observation, which is decisive to the quality of homeopathic therapy, may be found in the homeopathic pharmaceutical thesaurus (Materia Medica), in reference books on symptoms (repertories) based on it and in sets of rules on dosage and application.

It is crucial that homeopathic treatment is entirely individual for each person. The patient receives the remedy whose reme-

dy signature best corresponds to the totality of his/her individual symptoms and peculiarities according to the similarity principle. Individual symptoms are considered as externally perceptible signs (forms) of an internal, not more closely observable disease process (due to regulation disturbance, 'disturbed vitality'). With this concept homeopathy is in proximity of modern system-theoretical disease models. A further peculiarity of homeopathy is represented by the remedies, which are potentized (diluted and dynamized) often beyond Avogadro's number. Besides classical homeopathy, there are other methods, which, however, can only be regarded as homeopathic therapy in a limited sense. So-called clinical homeopathy selects the remedies on a clinical basis or that of 'tried and trusted indications' which are hardly individualized. In 'complex homeopathy' mixed medicines in usually low potencies are given against certain conventionally diagnosed symptoms and diseases. With isopathy the same substances, which cause disease symptoms are processed and used in homeopathic doses, e.g. potentized pollen-allergens for hay-fever. These methods are inconsistent with basic principles of homeopathy. For classical homeopaths such therapies may be acceptable for the alleviation of superficial acute diseases. But with longer and more frequent application these methods may mask the picture of symptoms, generating proving symptoms or impeding classical homeopathic treatment in future.

There are clear limits to homeopathic treatment: with a compelling indication for substitution therapy (e.g. insulin, surgical interventions) or with extreme pathologies in their final states, where regulative therapy is no longer sufficient and can be used, at best, for palliative alleviation.

Homeopathic Pre-Clinical Research

Background

Homeopathy has its own research tradition and since its inception has been based on empirical research within its system. This covers proving, accurate observation of symptoms, individualized choice of remedies in accordance with the similarity principle, evaluation of reactions and healing processes, observation of individual cases as well as collectives and technology specific to production of remedies. From a homeopathic point of view these activities represent the practice-relevant research and are decisive for the quality of homeopathic therapy. Detailed surveys on homeopathic research have been collected by Righetti [6], Halter and Righetti [7–9], and Matthiessen et al. [10].

In homeopathy, besides proving an effect, the question of explaining this effect plays a special role. It is in contrast to usual explanations of effects, relying on molecular, often receptor-mediated models for pharmaceuticals. In homeopathy regulative and/or energy-information studies appear in recent discussions. In the following we briefly summarize problems and the evidence of the pre-clinical studies.

Homeopathy is based primarily on observations on healthy and diseased humans. To that extent the entire pre-clinical research (e.g. on animals, plants, cells as well as purely physico-chemical investigations) cannot be called homeopathic in the true sense. Two of the three main pillars of homeopathy (the remedy proving of the healthy and the simile principle) are practically unaffected by pre-clinical research. The results are thus transferable to the therapeutic situation with limitations. The main object of basic research was and is primarily the principle of potentization. More recently basic research at university level has been increasing out of general scientific interest, and is now beginning to play a role in homeopathic pharmacy for quality control.

Physico-Chemical Basic Research

Since the 1950s experimental physico-chemical basic research has dealt with the question, whether a specific physical structure of the homeopathic remedy carrier (water, alcohol, lactose) can be demonstrated. The existing older literature had been screened scarcely (surveys to be found in [11–13]). More recent investigations with nuclear magnetic resonance and ultra-violet spectroscopy, as well as electrochemical and thermodynamic measurements, show differences between homeopathic potencies and controls (see e.g. [14, 15]).

Botanical Studies

Plants were used as aids for the investigation of the homeopathic dynamization process since around 1920. For this area, too, only an incomplete search through the literature (e.g., Vickers 1999 [16] and Baumgartner 2000 [17]) was accomplished. Current results are: The effect of homeopathic potencies (also of high-potencies) on healthy plants is generally quite small (max. 2–3%), although statistically well founded. However, application of homeopathic potencies with stressed or ill plants show a larger reaction (up to 20%). The variability of plant development is generally smaller with addition of homeopathic potencies. Although indirectly, these results of botanical studies support the following two basic views of homeopathy: (1) The effect of homeopathic potencies is primarily regulative and thus more clearly observable in a diseased organism than in the healthy one; (2) Substances, also in more highly diluted (more strengthened) form, can induce specific reactions in living organisms.

Animal Studies

An often used and well reproduced standard model is represented by intoxication studies with a subsequent homeopathic or isopathic therapy. A meta-analysis [18] covering 105 intoxication studies shows clear clinically relevant and significantly positive effects of this isopathic therapy. Application of dynamized hormones could replace the (missing substantial-material) hormone effect in chickens [19] and frogs [20, 21]. These experimental studies on animals support the notion that homeopathic potencies act primarily regulatively.

In-Vitro-Studies with Human Cells

The human basophile degranulation test (HBDT) is the best studied human in-vitro model. It is based on the fact that with allergic reactions basophil granulocytes empty themselves (degranulate). In numerous studies and different variations the evidence of an influence of the HBDT with high homeopathic potencies of histamine, bees and other substances taking part in allergic reactions was demonstrated. Although these results are disputed, they were independently reproduced [22]. The effectiveness of homeopathy in clinical studies is assessed in the main part of this HTA.

Material and Methods

Literature Search

The following databases were searched: Current Contents/Clinical Medicine (2002 Week 23 to 2003 Week 22), Dissertation Abstracts (1990 to May 2003), Econlit (1969 to May 2003), EMBASE (1980 to 2003 Week 21), Evidence Based Medicine reviews (EBMR): CDSR, ACP Journal Club, DARE, CCTR; AMED (Allied and Complementary Medicine, 1985 to May 2003), BIOSIS Previews (1969 to 2003 Week 23), CINAHL (1982 to May Week 3 2003), Premedline + Medline (1966 to present) PASCAL, BIOMED (1987–2003), PSYINDEXplus – Lit. and AV (1977–2003/06), SIGLE (1980–2002/12), Social Sciences Full Text (1982–2003 (/04)). For continuation of search for individual questions reference lists of articles which had been determined in the first step were systematically examined for relevant publications. Furthermore, manufacturers and experts were contacted.

Effectiveness

(a) *Review:* 4 well investigated surveys on systematic reviews on homeopathy were available [23–26]. We thus used the oldest – and most extensive – compilation of Linde with 18 reviews as basis [25]. For reviews published after 2000 we scanned our self-generated database for homeopathic literature.

(b) *Domain selection:* For evaluating primary studies a specific domain was selected according to criteria of relevance and exemplariness in Switzerland, and sufficiently published material available.

Appropriateness: Safety and Demand/Need As Well As Cost-Effectiveness

Additionally, databases accessible via Internet – Toxline and/or pharmaceutical and Healthcare Industry News, Newspaper Abstracts und Mantis – were searched.

Inclusion and Exclusion Criteria

Reviews

Inclusion criteria: Published systematic review or meta-analysis satisfying the criteria: systematic search through adequate databases (at least Medline) with specification of inclusion and exclusion criteria or explicit specification, that a systematic search had been done.

Exclusion criteria: Irrelevant questions for the HTA, reviews on remedy provings; re-analyses, i.e. articles, which re-evaluate the data of other reviews and double publications.

Studies

Inclusion criteria: Study type: Each study design, which examined effectiveness, need, safety or cost-effectiveness of an intervention; Population: Populations and individuals treated for therapeutic or preventive reasons;

Intervention: All therapeutic interventions described as being homeopathic; Comparison: No restrictions regarding treatment of control group; Outcome: Only studies yielding a result relevant for the care of the patient (i.e., parameters on therapeutic effectiveness, safety need and cost-effectiveness); Study status: Published or at least completed intermediate evaluation; Language: English, German, Italian and French (no language restriction in database search).

Exclusion criteria: Irrelevant questions for the HTA, re-analyses, i.e. articles, which re-evaluate data from studies and double publications.

Two reviewers examined the lists of articles for clinical studies while one reviewer examined systematic reviews. On the basis of title and abstract (as far as available) relevant full-text articles were ordered.

Data Extraction and Evaluation

For treatment of the topics 'effectiveness', 'safety' and 'demand/need' questionnaires were provided as data extraction and evaluation instruments on basis of currently used published questionnaires and question lists [27–31], as well as the review by Wein [32]. An adjustment was made with aspects of external validity in connection with the special purpose of the PEK project [33–35]. The criteria for evaluation of external validity were compiled with assistance of specialists (Swiss Association of Homeopathic Physicians, SAHOP/SVHA), because usual quality criteria cannot simply be transferred to homeopathic studies without closer inspection, but have to be adapted. This applies for the complete individualizing or pre-selection of the remedy: observation of antidoting, inclusion and exclusion criteria on the basis of homeopathic parameters (e.g. block by medicines, drugs, serious organ diseases, or operation), individual remedy repetition according to reaction and period of effectiveness, adequate length of follow-up, especially for chronic diseases (see also 'Discussion'). Full-text articles for the clinical studies were processed by means of questionnaires for data extraction and evaluation by two independent reviewers and by at least one reviewer for systematic reviews and meta-analyses. After completion of the review process all data were compared and examined for consistency. Discrepancies during the evaluation were discussed and could be clarified in each case. This data-record formed the basis for descriptive summaries.

Review articles were analyzed according to modified questions and criteria of Glanville and Snowden [36] regarding question, data extraction, evaluation and synthesis.

Three levels of evaluation were distinguished:

(1) Description/documentation: The documentation was evaluated as 'good' if all aspects required for evaluation of internal and external validity were specified. Documentation was judged as 'bad', if possible bias-factors, which could have led to distortion or reduction of the validity, could not be appraised.

(2) Internal validity (IV): Evidence levels which take IV into account, were specified during the description of the study.

(3) External validity (EV): Among others EV was assessed with the following questions: Intervention: Are parameters relevant for EV raised for the evaluation (e.g. individualized therapy according to homeopathic similarity principle yes/no)? Population: Apart from the indications are there further relevant parameters raised? Performance: Were data raised for the state of training of the treating physicians? Outcome variables: Were distinctions made between clinical parameters, surrogate parameters and the quality of life? Results: Was the clinical relevance of effects considered? Safety: Were unexpected and adverse events (UAE) assessed and evaluated adequately concerning homeopathy, e.g. initial aggravation, Hering's law? Follow-up: Was the length of the follow-up noted and, related to the illness, adequately assessed?

Our results concerning effectiveness of classical homeopathy are synthesized in descriptive statistics. We weighted performance according to IV and EV criteria and differentiated results in terms of significance, trend or no difference in favor of or against the therapy.

For safety, data on frequency and degree of UAE were descriptively compiled with respective causality attribution assigned to them by author

and/or correspondent. Data were taken from studies processed under 'effectiveness', and through a specific search.

Studies on cost-effectiveness were arranged in tabular form and discussed and evaluated individually according to their content. (See also separate article on CAM costs in this issue.)

Results

Effectiveness – Reviews

22 reviews were included [37–58]. After examination of the title lists 60 studies were first selected, of which, however, 38 were again excluded. This was mostly because they were not systematic reviews. Of these there were 3 studies, which Linde [25] had originally taken into account. (For a comprehensive presentation see [1].)

Evaluation of Study Design

Nearly half of all reviews dealt with the general estimation of the homeopathic treatment, which, regarding the question we handled in this HTA, was highly relevant. This was, however, limited by the fact that the studies included exhibited restrictions concerning indications or interventions. Selection criteria were completely documented in 19 of 22 studies. Of these, 10 named as inclusion criteria 'RCT' or 'double-blind', 8, 'controlled studies' (without explicit criteria for randomization). Of these, however, 4 were placebo-controlled, usually accompanied with randomization. One study had no restrictions regarding the study type. 1 review exclusively selected studies against conventional therapy while 3 had open controls. In 2 studies (of 22) individualized classical homeopathic therapy was named as criterion.

In summary, 3 reviews showed high external validity in their study selection, either due to explicit inclusion criteria (individualization) or due to openness concerning included studies.

Evaluation of Data/Information Selection and Evaluation

The kind of information to be extracted from the studies closely depends on the criteria chosen for the determination of quality. In general, the emphasis lies almost exclusively on criteria of internal validity. Hence, in the 22 reviews only data on randomization, blinding and rate of loss (drop-outs, lost to follow-up) were extracted additionally to general data (PICO-statements to population, intervention, control, outcome parameters and results) in order to record the well-known bias-factors concerning selection, performance, attrition and detection. In the reviews data relevant for evaluating EV were scarcely documented and mostly not used for the respective estimation of quality.

15 of the 22 studies mentioned criteria for quality evaluation. Of these, 13 named internal validity, of which again 6 applied the Jadad score alone or in combination with other IV criteria. 2 studies included criteria of external validity, but authors hardly emphasized on these in the data synthesis.

Evaluation of Data Synthesis

Demotion of the actual study results is conspicuous in the authors' conclusions in 8 reviews. Those demotions justified by very strictly laid-out criteria of internal validity or by so-called vote counts were rescinded by us in 10 reviews. (This was done because in our opinion evaluation may be distorted, if factors of internal validity predominate, and may give – predominantly – false negative results). In contrast, 2 of the studies were judged lower than the evaluation given to them by the original authors.

Synopsis of study results shows 5 reviews with acknowledged significant effects for homeopathic therapy, 15 with trend and 2 with no advantage. 4 of the 5 positive reviews investigated the general effectiveness of homeopathy as a system [40, 48, 49, 51]. The fact ought to be emphasized, that in a follow-up study of [49] with higher external validity, i.e. an investigation of individualized classical homeopathy, evidence for its effectiveness could be furnished [51]. Of the 2 negative reviews one dealt with the more experimental model of muscles soreness [43], while the other review dealt with induction of labor [55] in a single clinical study with low internal and external validity, which did not furnish any difference between verum and placebo. These 22 studies seem to give sufficient evidence for effectiveness of homeopathy.

Detailed information is given in the online supplemental material to this article at www.karger.com/fok_s206_htahom (table 1).

Effectiveness – Domain: Upper Respiratory Tract Infections and Allergic Reactions

The domain 'Upper Respiratory Tract Infections/Allergies Reactions' (URTI/A) was selected as conventionally defined indication area. Altogether 41 studies were found. 3 of these studies were double publications, 6 further articles did not concern URTI/A studies. Of the 29 studies, 11 were found in the abovementioned databases accessible to Internet, 16 by systematic examination of the reference lists and 2 studies via personal contacts. In the following presentation all data are based on the 29 evaluated studies [59–87].

Evaluation of Study Design, Setting and Population

The largest study examined 1,479 patients; the smallest an individual case (single case study). Altogether the studies contain results on 5,062 patients.

Of the 23 controlled studies 17 were randomized. We appraised the method of randomization for 10 studies as 'adequate', for 2 studies 'limited adequate' and for 5 studies it was 'not documented'. 6 studies were controlled but not randomized. 4 studies were prospective cohort studies, 1 was retrospective, and 1 publication represented a single case.

16 of 23 controlled studies were carried out with placebo comparison, in 7 studies the control group received conventional

therapy. 14 out of 15 studies were double blind (physician and patient) and 1 study was single blind (patient). Nearly all controlled studies were 2-armed, 3 studies were multi-armed: one 3-arm study with a non-homeopathic dilution as third treatment-arm, one 4-arm study with various combinations of complex remedies as 3rd and 4th arm, and one 6-arm study with various complex homeopathic and conventional remedies as comparisons.

Evaluation of Intervention and Control Therapy

Most studies contained individual (classical) homeopathic therapy (9 studies, of which 3 were placebo-controlled RCTs), 7 dealt with clinical homeopathy and isopathy, 5 with complex remedies, and 1 study could not be clearly classified. The priority of symptoms was considered in 6 studies, treatment according to similarity rules was performed in 9 studies. 2 studies clearly considered disturbing factors of the homeopathic therapy.

Evaluation of Objectives

Primary variable in 10 studies was a clinical outcome parameter. In 5 studies clinical parameters were measured in combination with the quality of life and in 3 studies in connection with 'costs'. In 8 studies surrogate and clinical parameters were noted, in 1 study only surrogate and in another only quality of life parameters. 1 study considered surrogate and clinical parameters as well as the quality of life for evaluation of results.

Evaluation of Results

Observational studies and individual cases revealed positive results for homeopathy. In comparison with conventional therapies 6 of 7 studies showed at least equivalence. 1 study (penicillin therapy for streptococcal tonsillitis vs. homeopathy) reported homeopathy being less effective. 8 of 16 placebo-controlled studies showed a significant result in favor of homeopathy. However, none of these 8 studies was done with an individualized therapy. 4 studies showed a trend, and 4 studies no advantage. In summary, 24 of 29 studies had a positive result in favor of homeopathy.

4 studies had a good external validity. 1 study with individualized therapy was significantly superior compared to conventional therapy, 1 study with clinical homeopathy and 1 with complex remedies showed significance compared to placebo. The 4th study consisted of a description of an individual case. Detailed information is given in the online supplemental material to this article at www.karger.com/fok_s206_htahom (tables 2–4).

Consumption of conventional medicines was registered as secondary outcome variable in some studies. Friese et al. [70] and Frei [61] could detect a plain reduction of antibiotics in each case of the homeopathic treatment group. In studies by Eizayaga et al. [63] and Matusiewicz and Rokiewicz-Piorun [85], additional homeopathic treatment for corticosteroid-dependent asthma led to a reduction in the use of conventional med-

icines. Furthermore, serious side-effects of the conventional medicaments were reduced. These results are also of economic interest, since the assigned homeopathic medication is substantially cheaper.

Safety

Homeopathic medicines are manufactured according to international pharmacopoeia (HAB 2000 [88]). The prescription of low-potencies of toxic mother-substances, particularly in complex preparations, ought to be well-justified and examined for its safety.

Treatment Responses

As far as UAE are concerned one must distinguish between effects, typical for homeopathy (primary aggravation) and those in fact unfavorable, above all pharmacologic-toxic, effects of the appropriate remedy. A first reaction at a functional level may be a part of the effects of individualized homeopathy with high-potencies. This may be so strong that it has become known as 'primary aggravation' and, in extreme cases, can exhibit the symptoms of a typical proving (remedy-testing). The frequency and the extent of these reactions depend on various factors. They are, however, generally not problematic in lege artis performed homeopathy.

As far as the URTI/A studies are concerned the documentation of UAE was 'adequate' in 13 studies while in 9 studies no data for UAE had been documented. An estimate of UAE as adverse or side-effects is generally difficult, likewise in homeopathy. A distinction between UAE and primary aggravation usually was not made. Primary aggravation was only documented in the study of Taylor et al. [76].

In an isopathic study up to 24% of primary aggravation was reported [75], apparently as a consequence of medications administered too frequently. In a flu-prevention study specific side-effects, which decreased with repeated application, occurred in 10% in contrast to 2% non-specific complaints with placebo [89].

For treatment with very low potencies systemic toxic effects (e.g., of arsenic, lead and mercury) may occur with inappropriate application. The use of mother-tinctures, which should rather be assigned to the realm of phytotherapy, may provoke toxic symptoms [90]. The inappropriate use of homeopathic remedies, regardless of which kind, can lead to suppressions and possibly to a negative course of the illness. A systematic collection and confirmation for this kind of observations is particularly difficult and, to the best of our knowledge, has not yet been investigated scientifically.

Only a few publications investigating UAE are available: A meta-analysis of 3,437 patients in 24 placebo-controlled RCTs reported 63 UAE (1.54%) for patients treated with homeopathic remedies and 50 UAE (1.45%) for patients treated with placebo. The authors see no clear evidence for homeopathic

primary aggravation [45]. Dantas and Rampes [91] state a rate of 9.4% unwanted events using homeopathic remedies in contrast to 6.1% with placebo. They designate these as being minor and transient. The IIPCOS study indicated unwanted events in 8.3% of the patients, a third of which were classified as being 'heavy' and partially led to drop-out and/or therapeutic intervention. A correlation with the study medication was conjectured by only 3.4% of the patients [92, 93].

Interactions

Various substances, remedies and medicines have an inhibitory or blocking 'antidoting' effects on homeopathic therapy [94, 95]. Intensifying reciprocal effects have only sporadically been demonstrated (diphtheria serum [96]).

Treatment Omissions

The most frequent reproach in connection with homeopathic treatment is a delay of meaningful diagnostic or therapeutic measures, i.e., that patients with diseases which cannot adequately be cured with homeopathic remedies are treated too late or not at all with conventional medicine. Since our analysis is exclusively related to the activity of conventionally qualified physicians with additional homeopathic certification, treatment omissions – usually verified by anecdotal single-case descriptions but, as far as we know, not checked by any studies – probably play a subordinate role.

Cost-Effectiveness

Regarding cost-effectiveness, please also see the review article 'Complementary and Alternative Medicine Costs', in this issue. In many Western countries the costs of medical treatment show an increasing tendency far above the general cost of living. In Switzerland, estimates for entire costs of complementary medicine are in range of CHF 100–200 million. That corresponds to about 0.2–0.5% of entire health care costs (approx. CHF 50 billion, i.e. 50×10^9 in 2003) per year [97]. In poorer countries a similarly high burden with health care costs as they are incurred by the Western world is simply not being sustainable. Chile (end of the 19th century), Nigeria (1961), Romania (1969), India (1973), Brazil (1979) and Cuba (1992) integrated homeopathy into their health services [98].

Data and Studies on Homeopathy

A first tentative health economic study in favor of homeopathy was published by Bradford in 1900 [99]. In recent time several epidemiological investigations have developed models to account for entire direct and indirect costs of homeopathy and comparison with other treatments [65, 93, 100, 101].

Homeopathy has been investigated in Germany and Switzerland [102], Belgium [103] and France [104, 105]. Local and regional surveys are available in UK [106, 107] and Germany [108]. IIPCOS studies are based on indication [65, 92, 93].

Other studies investigated female infertility, rheumatoid arthritis, otitis media, atopies and allergies, dyspepsia and asthma. According to Gerhard et al. [109] direct costs saved on average due to infertility amount to over DEM 11,000.– per patient. In addition, hospitalization of conventionally treated female patients was six times more frequent. Furthermore, a systematic survey was carried out on a national level for the 'Federal Health Report – Demand on Alternative Methods' in Germany [110].

Cost comparisons have been done in detail so far only with children: De Lange de Klerk et al. [72] observed fewer recurrences and less consumption of antibiotics under homeopathic therapy, likewise Frei und Thurneysen (middle ear infection [61]), Keil (allergy [111]), Frenkel and Hermoni (atopy [112]), and Junker et al. (dystonia [113]).

Investigations of medical specialists' groups in Germany and Austria reported homeopathic treatment to divide costs in half per percent patients' improvement [114]. Investigations in hospitals are rare [115].

For individual cases it could be shown that, on an average, (individual) homeopathic physicians work (clearly) more cost-effective than their conventional colleagues [116]. A pediatrician causes half of the direct costs absorbed by the health insurance and clearly causes fewer hospital referrals than the average for the specialist group. Homeopaths cause only 15–60% of drug costs compared to their conventionally active colleagues. In addition, costs of side-effects virtually disappear. This also applies to predominantly homeopathic treatment in a hospital context [117]. In Switzerland, a model contract between a health insurance and homeopathic family doctors (gate-keepers) has led to patients' cost reduction of approximately 10% and a small net profit for the health insurance company, 1977–2003 [118].

Homeopathic doctor's higher direct expenses may be balanced during the course of the total treatment [100, 106]. Due to decreased costs of remedies and drugs and laboratory and technical services total costs tend to be lower, particularly on a long-term basis [107, 108].

Discussion

Effectiveness

The task of the HTA was to evaluate certified classical homeopathy on the basis of published data regarding their effectiveness, appropriateness (demand and safety) and cost-effectiveness in the context of PEK and to assess the situation in Switzerland.

The literature selection comprised Internet accessible databases and contacts with experts in Germany and Switzerland, as well as processing reference lists. One must assume that further systematic search in countries with a widespread use of homeopathy (e.g. Latin America, India) could elicit far more URTI-studies.

A substantial number of studies of pre-clinical research support the view of homeopathy, that high-potentized remedies can induce specific effects in living organisms or cells. Beyond that, homeopathic remedies seem to act in a regulative manner, i.e. compensatorily or normalizing.

Significantly positive results of homeopathic treatment are documented in many clinical studies. These results are, however, not always consistent, which frequently leads to restrictions in review conclusions. Discrepancies are frequently evaluated according to so-called vote counts, i.e. summing positive and negative results. The underlying paradigm considers studies as samples of a homogeneous group being subject to a more or less random scatter. With caveats this may apply to studies of the same type (repetition studies).

It is more important, however, by means of qualitative analyses, to look for factors, which could have caused discrepancies. In general positive results of studies exhibiting a low risk for false positivity should be rated more highly than negative ones, since they show potential effectiveness. In an ideal situation the conditions for effectiveness should be worked out. This is, however, hardly possible mainly due to incomplete documentation.

Possible relevant context factors, which have not yet been systematically examined or also have evaded such an assessment, are e.g. the susceptibility of an organism to homeopathic remedies (in contrast to conventional medicine a homeopathic remedy is not effective per se, but rather an effect only becomes possible through the interaction with the organism); the ability of the physician in handling homeopathic remedies; the conviction of the physician to use the correct therapy; the confidence of patients in their physician and therapy, and the individual regulation ability.

In all the reviews processed here no sufficient data have been presented on the factors listed above. And if only rudimentarily recorded, they were not included in the assessment of quality. Therefore, a more differentiated evaluation of the external validity of the respective reviews was hardly possible. In general they were also insufficiently taken into account in clinical studies.

As mentioned above we selected a descriptive procedure instead of a quantitative analysis due to the heterogeneity of the studies, which corresponds, in principle, to the procedure of Kleijnen et al. [48]. The decision was supported by the view of Wegscheider [119], who discusses the fact that meta-analyses, in contrast to RCTs, are protected neither against an open nor a hidden bias because choice of statistical study units occurs both retrospectively and selectively, while different end-points and inquiry methods are used and neither sample-planning nor a control of confounders takes place. If one were to evaluate RCTs using such methods, they would probably be excluded according to Cochrane's procedures.

Our positive estimation of effectiveness of homeopathy in the reviews is based particularly on the 4 extensive studies of Kleijnen et al. (1991), Linde et al. (1997 u. 1998) and Cucherat et al. (2000) [40, 48, 49, 51]. Our estimate of the bias risk deviates

from the authors' conclusion in some points: In their conclusions Kleijnen et al. were surprised about the extent of positive evidence, even among the best studies [48]. The restricted conclusions were based on plausibility arguments only. We do not share their conclusion due to the known positive pre-clinical results of homeopathy in living systems. In the review of Linde et al. [49] 89 studies were subject to a meta-analysis with a total odds-ratio (OR) of 2.45 (95% CI: 2.05–2.93) in favor of homeopathy. However, they again qualified this evaluation, because no clear evidence for the effectiveness of homeopathic remedies could be found for any single clinical condition. The criticism of this study, one which we also shared, consisted mainly of the fact that very heterogeneous data were combined into a total value. However, if one looks at individual study results, then nearly half (18) of the 39 qualitatively best studies find a significantly positive result in favor of homeopathy, so that one can conclude an effectiveness for homeopathy. In Linde et al. [51] 19 clinical studies of individual homeopathy were submitted to a meta-analysis. This resulted in a complete OR of 1.62 (95% CI: 1.17–2.23). After reduction on the 6 methodically best studies, however, a non-significant OR of 1.12 (95% CI: 0.87–1.44) resulted. The authors concluded that homeopathic remedies probably have a stronger effect than placebos. This is, however, not convincing evidence, due to the methodical quality of the studies. However, when in addition, studies in the category 'unlikely to have major flaws' (a further 6 studies) are taken into account, a significant value of 2.44 (95% CI: 1.30–4.59) for these was calculated. Cucherat [40] obtained in 17 studies a highly significant combined p-value of $p = 0.000036$ in favor of homeopathy. This value indicates the probability with which at least one result could not be accidentally positive. It became non-significant with the restriction to studies with a loss to follow-up <5% with $p = 0.082$. Since according to most evaluation guidelines values of 10–20% are tolerable, at which the result was significant, we sustained this significance evaluation.

Apart from the studies analyzed here there are surveys [6, 32, 120–122], which find a clinical effectiveness for many diseases, e.g. diarrhea in children, fibromyalgia, side-effects of radiotherapy and chemotherapy; further, mustard-gas poisoning [123], diphtheria epidemics (collated in [6, 120]), traumatology/dentistry [124–126] and obstetrics [127, 128]. The insights into clinical evidence of effectiveness in homeopathy research are still incomplete even though the reprocessing of 'old literature' has been attempted by some authors in recent years [120, 129]. From the viewpoint of homeopathy the fact is emphasized that among the studies, which have been excluded (cf. [1]) there are surveys and reviews, whose comprehensive data and results in favor of homeopathy are of far greater clinical significance than many of the studies discussed here.

The studies examined here are concerned with epidemiological and economically significant diseases, which are partially neglected in conventional medicine research. Thus, the de-

mand of Wiesenauer et al. [78] for a stronger participation of general practitioners in research, has not lost its importance.

The domain URTI/A was selected due to conventional medical criteria. 8 out of 16 placebo-controlled studies revealed significant clinical effects in favor of homeopathy. They demonstrate effectiveness of homeopathy despite decreased external validity by randomization, selection of study participants as well as blinding, which are expected to reduce the significance of homeopathic effectiveness. The positive effect is even more clearly when compared with conventional therapies, where equivalence or superiority of homeopathic therapy occurred in all but 1 study. Altogether, positive results for homeopathy occur in 24 of 29 studies including results of observational and case studies.

The following restrictions as to transferability of study results in clinical everyday life as well as distortion factors may occur in the studies examined:

- Selection of the patients due to participation in randomized studies.
- Blinding raises concern about therapeutic setting and a loss of confidence, through which the effectiveness can be reduced.
- Individual assessment of symptoms in the course of therapy, which often leads to a modification of homeopathic remedies, is impeded by RCT standards, especially blinding.
- Insufficient training of the participating physicians in homeopathy in order to select and accomplish an effective homeopathic therapy. This concerns classical homeopathy in particular, since specific diagnosis has to be made according to different criteria in order to identify the effective remedy [63].

Despite these restrictions the available study results allow concluding an effectiveness of homeopathy.

From a homeopathic point of view despite the pleasing result the following points are worth mentioning: The large majority of studies mentioned in systematic and further reviews were carried out in sense of 'justification research'. Such methods ignore essential basics of homeopathy with inadequate non-practical methods. Thus, their external validity and/or model validity is small and the risk of false negative results high. The external validity was surrendered to a certain extent in favor of the internal validity. Therefore, these research results are of only minor importance for everyday practice. But, in principle as well as by example, they furnish proof of highly potentized remedies having a specific effect and clinical effectiveness when applied properly. At this point it is also important to stress appropriate study-design for the investigation of homeopathy [34].

Safety

Training requirements for homeopathic physicians and product regulations grant a high degree of safety of homeopathy in Switzerland. The risk of the omission of other meaningful treatments is low due to the high level of physicians' training.

With appropriate application, certified homeopathy has few side-effects and, with the use of high-potencies, is free of toxic effects.

Cost-Effectiveness

To what extent complementary medical therapies can be mapped onto usual methods of health economics has been the subject of recent discussions [130–132]. In principle, one can assume this is possible, if special conditions of complementary medical procedures are considered during the measurement of its effectiveness. This means that individual doctor-patient relationship, free choice of therapy by physician and patient as well as investigation of unselected groups of patients have to be maintained, thereby rather illustrating the situation in clinical practice.

Little data from health-economic studies are available on specialist fields of activity. In general complementary medicine is examined, whereby the definitions of CAM are broadly interpreted (e.g. diet or physical therapies). For homeopathy there are various studies from Germany, England and France, which show cost-effectiveness. A data-analysis in France [104, 105, 133] showed low costs of homeopathy.

Consideration of economic aspects of homeopathy has increased during the past years. Schüppel [132] concluded in a review that savings could be achieved with homeopathy. The question as to whether costs remain lower over a longer period of time compared to conventional treatment has to be evaluated in further studies. A general health-economic statement for homeopathy as a whole cannot be made on the basis of the available data. Individual studies, such as model projects of several health insurance companies in Germany, indicate a lasting effect and savings on indirect costs, e.g. a reduction of sick-days.

For discussion of Sommer et al. 1999 [134], concluding an additional burden through reimbursement of costs of several CAM procedures see article concerning cost-effectiveness in this issue.

Future Research

Homeopathy needs adequate and, compared to the state today, more extensive research structures. It is necessary to

develop research methods which take into consideration specific characteristics of homeopathy and integrate a well-carried-out homeopathic therapy in both, research and hospital. Professional and comprehensive worldwide processing of homeopathic studies is necessary as scientific basis for further clinical research taking into account historical evidence, retrospective studies and individual case-studies. Aspects of cost-effectiveness and external validity have to be more strongly considered in future studies. In addition, further systematic clinical studies with a sufficient number of participants and an adequate observation time would be desirable, if possible, in comparison with conventional medical interventions. For a detailed presentation of research problems the reader is referred to Righetti [6] and Halter/Righetti [7–9].

Conclusion

Pre-clinical research supports the view that high-potentized remedies can induce measurable effects in living systems. In clinical studies, taking internal and external validity criteria into account, effectiveness of homeopathy can be seen as clinically evident, and certified application as safe. From a methodological point of view positive evidence of homeopathic effectiveness is all the more remarkable, as in most research studies basic rules of classical homeopathy were violated. In those studies for purpose of scientific recognition internal validity is often more highly weighted than external validity, which may comprise an increased risk of false-negative results. Reliable statements on cost-effectiveness are not possible at present. In order to identify context factors, which influence homeopathic interventions, external validity and model validity will have to be considered more in future studies.

Acknowledgement

We thank Denise Bloch, René Gasser, Dr. Gunver Kienle, Dr. Peter Mattmann, Christina Vogt-Frank and PD Dr. Martin Wolf for co-operation and valuable discussion.

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