A Systematic Review of Homeopathic Pathogenetic Trials from 1945 To 1995

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BACKGROUND

Homoeopathic pathogenetic trials (HPTs) are the basic method of homoeopathy. They are designed to investigate body and mind effects of potentially toxic or pathogenic substances, diluted and serially agitated according to homoeopathic pharmacopoeias, in non-patient volunteers in good and relatively stable health conditions. They are clinical trials designed to assess the effects of highly diluted medicines in healthy volunteers, the results are applied in practice on the basis of 'Similia similibus curentur'.

The methodology of HPTs was first proposed by Hahnemann. The controlled investigation of the pathogenetic power of medicines was one yardstick in Hahnemann's writings. Hahnemann recognized early in the *Organon*[1] the main methodological problems of HPTs, namely truthfulness of volunteers, to use medicines with different powers and to deal with individual differences. In attempting to minimize the effects of suggestion on volunteers Hahnemann recommended that "in the investigation of these drug-symptoms all suggestion must be as rigidly avoided as in the examination of the symptoms of disease". To obtain symptoms as accurately as possible, every subject had a pocket-size notebook to write down the sensations and changes immediately after they occurred. The volunteers were required to repeat the description of the changes without referring to this notebook during the personal interview: if the accounts varied he advised the director of the trial to confront the subject with both versions and invite him to choose and confirm the statement which is nearest to the truth. Prevention of guess-work, imagination and recording of findings only after close questioning were continuously stressed in different editions of the Organon. For him only reliable symptoms should be included in the homoeopathic materia medica.

However a critical analysis of Hahnemann's method to conduct HPTs raised many flaws and systematic errors[2], given our current knowledge, which could not be anticipated by Hahnemann at that time, leading to an over-estimation of medicine effects. Some of them are described below:

- Absence of control group
- Use of well-known friends and lecture audiences as volunteers ("believers")
- Volunteers informed that they were using a medicine to observe effects upon them
- Recording of all complaints, symptoms and changes observed during the action of the medicine even if the person has noticed similar symptoms in himself a considerable time before
- Absence of masking in volunteers or in supervisors of the trial
- Close supervision and daily (or 2-3 days) interview with subjects + daily recording in a pocket notebook
- Sudden prohibition of coffee, tea, spices and alcoholic drinks (or medicinal drugs)
- Vague definition of healthy volunteers ==> Inclusion of non-healthy volunteers
- No random assignment of subjects

Taken together these flaws are sufficient to cause serious doubts on the scientific acceptability of the specific pathogenetic symptoms reported in Hahnemann's writings. This was partially confirmed in a preliminary systematic review of HPTs published in the UK from 1945-1995, including 45 studies, which showed a great deal of variability in terms of the medicines tested, methodology, volunteers, sample size and outcome. This was reflected in great variability in the numbers, incidence and types of effects reported. There was also a clear association between the methodological quality of the trial and

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* *Originally published in the transactions of the conference "Improving the Success of Homeopathy 5: A Global Perspective", London 26-27 january 2006.*

the numbers of effects reported: better trials produced a lower incidence of pathogenetic effects (or none) compared to trials of poorer quality. Overall the analysis of reports revealed methodological shortcomings which could seriously compromise the validity, reliability and clinical applicability of the results[3].

To what extent have HPT incorporated new methods developed in scientific medicine in the five decades from 1945 to 1995? Can we rely on the conclusions drawn from HPT done during this period? A systematic review of published studies was therefore designed to assess the methods and outcomes of HPTs published in six languages (English, German, Spanish, French, Portuguese and Dutch) in the five decades from 1945 to 1995 and to help design and conduct future HPT to get more valid and reliable information.

METHODS

A criterion-based systematic review of HPTs was done in trials published in six languages from 1945 to 1995. The literature was exhaustively searched and only published reports of HPTs were included. Information was extracted by two independent reviewers, with experience in conducting HPT or clinical research, using a specially developed form with 87 items. Information on: medicines, volunteers, ethics, blinding, randomisation, use of placebo, adverse effects, assessments, presentation of data and number of claimed findings were recorded.

For each medicine the name , dilution(s), method of dilution, presentation, dose, frequency per day, repetition of doses, total duration of the trial, number of active treatment periods and duration per volunteer (in days), source of the drug, mode of preparation and preparation responsibility was recorded. Regarding the study population we extracted the initial and final number, ethnic origin, sex, age, occupation, number of control volunteers, percentage of sensitive volunteers, inclusion criteria, exclusion criteria, assessment of health status prior to admission, training of volunteers, personality traits, physical characteristics, informed consent, method of recruitment.

The study method was assessed in terms of: approval of protocol by Ethical Committee, direction/coordination, randomization, sequence generation of subjects in the trial, allocation concealment, masking (blindness) of volunteers and of supervisor, use of placebo, pre-trial observation period with or without placebo, placebo distinguishable from verum, placebo potentised, comparative group, crossover, washout period (post-treatment observation), management of adverse effects, rules for stopping medicine, rationale and source of the medicine. The assessment of each trial was recorded in terms of: use of symptom diary, type of diary, initial interview (case-taking/ collection of previous symptoms), follow-up interview, use of laboratory investigations, use of psychological tests, withdrawal/dropout of volunteers, reason for withdrawal, withdrawal due to severe adverse effects, presence of adverse effects, pre-defined categories for assessment of the attributes of a symptom.

For the presentation of results we extracted information on the frequency of symptoms in the sample, description of complete symptoms, analytical presentation, chronology of symptoms, character of symptoms, location of symptoms, duration of symptoms, onset of symptoms, intensity of symptoms, modalities of symptoms, presence of concomitant symptoms, inclusion of prior symptoms that improved during the trial, detailed report of individual volunteers, use of symptom tables and charts.

The interpretation of the results by the authors was reviewed in terms of : pre-defined criteria to include medicine effects, use of descriptive statistics (measures of central tendency or dispersion of data), use of statistical tests and presence and number of significant findings claimed.

Finally, each reviewer was invited to make a subjective judgement: 'after reading and analysing all the points above, and based exclusively on the published report':

- Do you think the symptoms stated as belonging to the medicine can be trusted ?
- Would you apply the information given in it into your clinical practice to prescribe this medicine to a patient? For both questions the options were certainly, almost certainly, probably, possibly, with serious reservations, definitely not, can't answer or none claimed
- From a methodological point of view, you judge this report of proving as: completely reliable, very reliable, reliable, unreliable, completely unreliable
- Compared to the other reports you read, you think this is: below average, average, above average, much above average, excellent.

A final, open question asked about the main methodological criticisms of the reviewer to each study.

The methodological quality of published HPTs was assessed by a specially designed index, using mainly traditional indicators of quality in clinical trials, complemented by a personal judgement of reviewers for each study. Scores were organized in 4 methodological classes, where class I is the worst and class IV is the best quality HPT. Cutoff points of score for the different classes were 4,5,6 for Class I, 7,8,9,10 for Class II, 11,12,13 for Class III and 14,15,16 for Class IV. The Methodological Quality Index for homeopathic pathogenetic trials is shown below:

	SCORE			
Variable	**1**	**2**	**3**	**4**
Randomization	Not stated	Only stated, no details	Incomplete, description of sequence generation or allocation concealment	Complete, description of sequence generation and allocation concealment
Blinding	Not stated	Single blind	Double-blind without checking	Double-blind with checking after finishing the study
Inclusion and Exclusion Criteria	Not stated	One partially stated	One clearly stated or both partially stated	Clearly stated
Criteria for Selection of	Not stated	At least one stated	2 to 4 defined defined	More than 4 defined

Pathogenetic effects were defined as all clinical events and laboratory findings noted by volunteers during a HPT and recorded in the final report. In other words they are the findings claimed at the end of the trial by authors to be used by practitioners seeing patients with similar pictures. We counted as one pathogenetic effect a piece of information which could be included in an homoeopathic repertory as an independent subheading. For instance "boring headache ameliorated by pressure" was counted as one claim.

PRELIMINARY RESULTS AND DISCUSSION

156 HPTs reporting the effects of 143 medicines in a total of 2815 volunteers (769 controls) were double analysed by two reviewers. Most reports did not mention ethical approval. Use of placebo control was variable, overall in 56% of trials volunteers took placebo, placebo symptoms were often not used as comparators, some investigators progressively abandoned the use of placebo. The quality of reports was in general poor, and much important information was not available.

A growing number of HPTs was published along the decades, particularly in the last decade (800% more than in 1945). Table 1 shows included publications by language in the period from 1945 to 1995:

Time	Language						Total
	English	German	Dutch	French	Spanishl	Portuguese	
1945 - 1955	9	0	0	1	1	0	11
1956 - 1965	11	1	0	0	0	0	12
1966 - 1975	16	3	0	0	0	0	19
1976 - 1985	16	9	1	2	0	0	28
1986 - 1995	32	20	16	8	6	4	86
Total	84	33	17	11	7	4	156

Table 1. Number of included HPT per decade and language

HPTs were done mainly in Índia (36 studies) and United Kingdom (30), followed by German (17), Nederlands (17), Austria (16), France (13), United States (12), Mexico (9), Brazil (2), New Zealand (2), Norway (1) and Argentina (1).

There was a statistical difference among languages of publication of HPTs only when Dutch was compared to English and German languages. Figure 1 shows the mean methodological score by language:

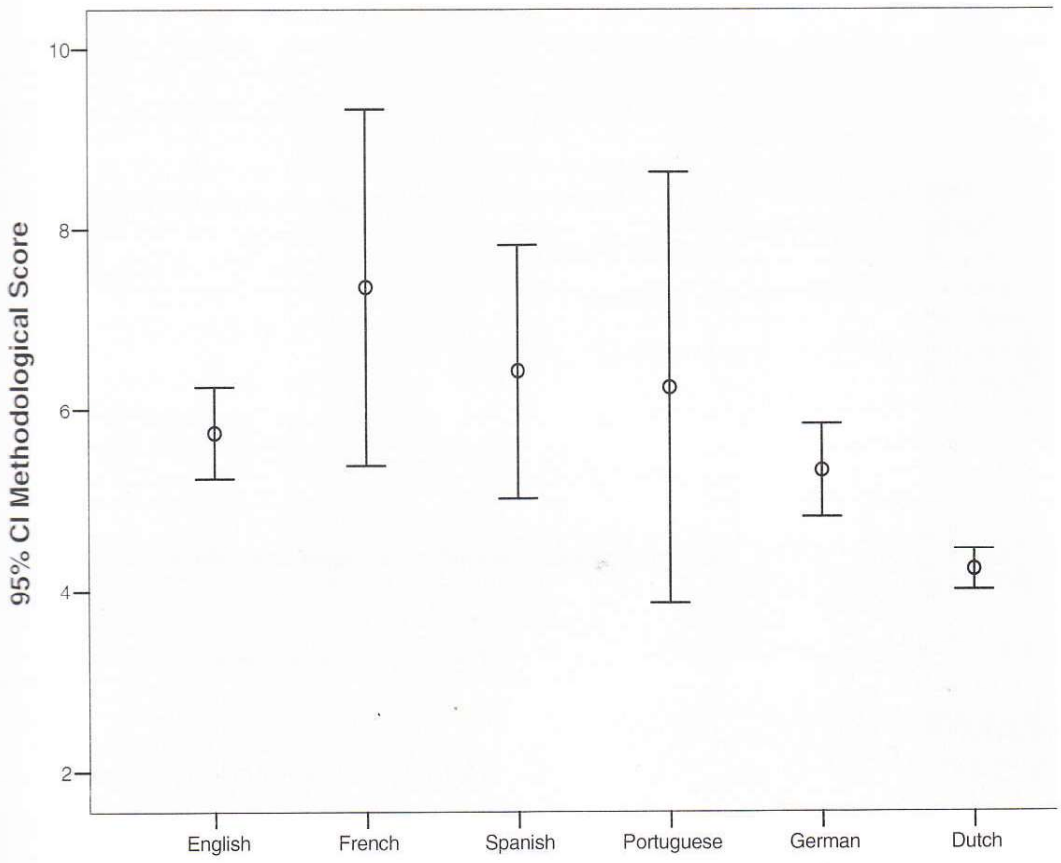

Figura 1: Mean of methodological scores by language of publication

Most HPTs were done in homoeopathic teaching or research centres under the supervision of medical doctors. Volunteers were mainly recruited in homeopathic medical schools (India) or post-graduated courses for doctors. Trial duration (mean 34 days) was very variable. Studies included from 1 to 103 volunteers (median 15). A single volunteer was used in 7 HPTs and in other 3 only two volunteers were included. 57% of the reports did not state age of volunteers and in 34% there is a lack of information on gender. Age range was 5 to 76 years. Male volunteers accounted for 1169 and female volunteers were 857. In 28 studies there were more female included than male, and this trend was increased in the last decade. Female volunteers tend to produce more pathogenetic effects than male. Ethnicity data were in general ignored in the reports.

Before-After studies were the most used designs, with or without parallel groups using placebo. There is a recent trend to use randomized placebo controlled trials, 14 of them used a crossover design. There was a large variation in methods and results, and in general the quality of the studies was very low. Almost all publications reported one or more pathogenetic effect. There was a strong tendency for more symptoms to be reported from HPTs of poor quality than from better studies.

65 publications tested medicines in single dilutions and 91 in different dilutions used by the same or different volunteers. In total 323 dilutions were used, mostly centesimal (192) followed by decimal (129) and fifty millesimal (2). 30c was the most frequently used dilution in our sample (66 trials) followed by 6c (33) and 6x (32). More than 50% of the tested medicines were not studied before the study took place.

Plants were the most common source for tested medicines (75), followed by animal (29), mineral (18), chemicals (14) and pharmaceutical drugs (11). Two publications studied energy sources and one study used a coded and unknown substance. Figure 2 shows the rationale for selection of the substances to be tested in HPTs:

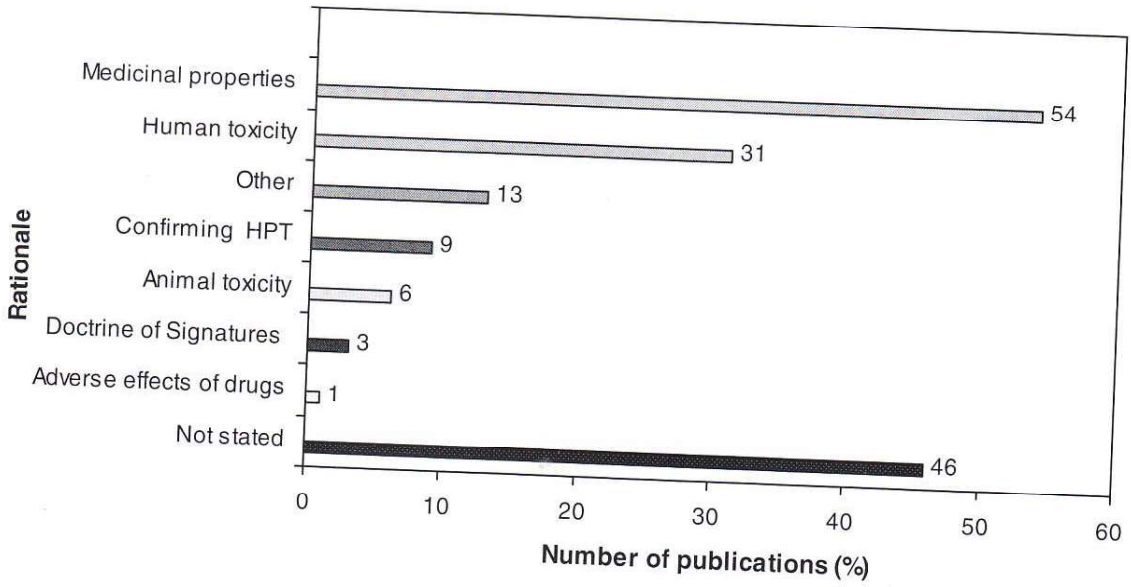

Figura 2. Rationale for conducting HPTs

There was a large variation in methods and results. Most studies were of poor quality and showed flawed designs, mainly absence of proper randomization, blinding, placebo control and criteria for analysis of outcomes. There was a significant trend for more symptoms to be reported from HPTs of poor quality than from better studies. There are some major outstanding methodological problems including lack of appropriate controls for proper evaluation of idiosyncratic effects and criteria to attribute symptoms to treatment.

Several factors may account for the great variability in the results. Among others the settings in which they were done, the lack of description of inclusion and exclusion criteria for volunteers, differences in study design and use of placebo, style of supervision, blinding, randomization (or suggestion), criteria for selection of pathogenetic effects and assumptions concerning attribution of symptoms to the medicine tested.

The identification and causal attribution of changes in healthy volunteers is very complex, it may be influenced by a large number of factors. It is strongly dependent on individual awareness and past experiences. In the absence of adequate control, clinical studies can yield results favouring investigators' assumptions if the study is not properly controlled, context is also important[4,5,6]. The importance of conditioning was demonstrated in medical students in an experiment where students were conditioned to expect sedative or stimulant effects but received only placebo in blue or pink capsules. Volunteers' behaviour pattern has also been shown to influence the reporting of subjective symptoms after placebo[7]. Most of the HPTs reviewed here were done in the context of homoeopathic courses with students learning homoeopathy. 7.2 body and mental changes were reported by healthy Brazilian medical students responding to a survey on symptoms they experienced in the last week[8]. In this situation two factors could bias the outcome towards increased

reporting of symptoms: the students, believers in the system and the production, in the past, of valid symptoms from HPTs; and the coordinator expecting the students to give him useful information after testing the substance.

The consistency of the effects across trials is another matter. Many investigators seemed to have taken for granted that every substance must elicit symptoms and for this reason felt it unnecessary to use placebo as a control or failed to include symptoms experienced by volunteers taking placebo. On the other hand the use of placebo exclusively for comparative statistical purpose excludes from consideration rare, idiosyncratic effects. Attempts by Martini in the 1930's to evaluate the occurrence of pathogenetic effects due to highly diluted substances in HPTs were, on the whole negative, a critical reappraisal of his results shows that no definite conclusion can be drawn[9].

Further methodological improvements for designing rigorous HPT are required. In the last decades several attempts to develop new approaches to test homeopathic medicines in healthy volunteers were done, either for testing new substances[10] or to confirm results[11,12]. It is urgent to improve the quality of reporting and it is imperative to have a consensus on minimal requirements for reporting HPT. The central question of whether homoeopathic medicines in high dilutions can provoke effects in healthy volunteers has not yet been definitively answered. We need a pure homeopathic materia medica, with valid and reliable information from HPT, to get better results in our clinical practice and research.

Acknowledgements

CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico do Brasil); Royal London Homoeopathic Hospital; Cecília Lomônaco de Paula and Gleice Margarete de Souza Conceição for statistical advise; Mary Gooch for help in literature search; David Riley for early cooperation in informing HPTs done in USA.

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