Do homeopathic medicines induce symptoms in apparently healthy volunteers? The Brazilian contribution to the debate on homeopathic pathogenetic trials

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Abstract

Homeopathic pathogenetic trials (HPT) are designed to identify specific and characteristic symptoms in apparently health individuals exposed to homeopathic medicines, so that the latter might be indicated following comparison to the patient's symptoms. The original methodological guidelines for HPTs were established by Hahnemann, who advocated rigorous methods likely to lead to conclusions free from any conjecture. With the advances in scientific methods, new guidelines were formulated to improve the methodological quality of HPT. Relevant scientific contributions were made by Brazilian researchers in this field, resulting in original studies or innovations in methods. The validity and reliability of the clinical information acquired from HPT are fundamental for the success of homeopathic clinical practice.

Keywords

Homeopathy; Homeopathic pathogenetic trials; Materia medica; Homeopathic clinical logic

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> "Nempe primum in corpore sano medela tentanda est, sine peregrina ulla miscela; odoreque et sapore ejus exploratis, exigua illius dosis ingerenda et ad omnes quae inde contingunt, affectiones, quis pulsus, quis calor, quae respiratio, quaenam excretiones, attendendum. Inde ad ductum phaenomenorum, in sano obviorum, transeas ad experimenta in corpore aegroto..."
> Albrecht von Haller, *Pharmacopoeia Helvetica,* Basel; 1771, p. 12. (apud Hahnemann, note to *Organon of medicine,* § 6).

Introduction

Homeopathic pathogenetic trials (HPT) are **experimental studies** to investigate the effects of potentially toxic or pathogenic substances serially diluted and agitated according to the recommendations in homeopathic pharmacopoeias on volunteers in good and stable state of health. HPT seek to produce valid and useful information on objective and subjective changes (mental, general and local) that homeopathic medicines might cause in apparently healthy human beings. HPT are an evidence of the scientific nature of homeopathy since its inception.

HPT are one of the pillars of homeopathy and a significant source of the symptoms, particularly mental, needed for prescription of homeopathic medicines. The symptoms collected in HPT are added to the ones resulting from poisoning and excessive exposure to toxics described in the literature and to the ones observed in clinical practice following use of medicines by patients. All three sources are used to compose the **homeopathic materia medica**, namely the main database for homeopathic prescription. The reason is that medicines are selected based on the comparison of the symptoms manifested by patients to the ones listed in the materia medica. Facing this scenario, the quality of the information used by homeopathic doctors when prescribing needs to be critically assessed, which is one of the goals of **homeopathic clinical logic** [1]. The latter is a field of studies developed by this author since 1990, i.e., before the formulation of evidence-based medicine. The main aim of homeopathic clinical logic is to critically assess homeopathic knowledge in order to make homeopathic medical practice more efficacious, efficient and **rational** and thus help practitioners achieve greater safety and accuracy in decision-making and professional action.

HPT might also be useful to demonstrate the actual induction of characteristic, valid and reliable symptoms in apparently healthy volunteers by highly diluted medicines despite the alleged implausibility still adduced by opponents of homeopathy. In the present article particular emphasis was given to the contributions made by Brazilian authors to HPT. In addition, more attention was paid to improvements in the methodological quality of HPT than to their results, i.e., sets of reported symptoms. Beginning by the guidelines originally formulated by Samuel Hahnemann (1755-1843) are described the changes introduced in the design of HPT to become more rigorous and controlled. In this way the issue of the induction of specific symptoms in apparently healthy individuals by homeopathic medicines will be more precisely elucidated.

Hahnemann's original guidelines for HPT

Homeopathy was born from Hahnemann's self-experimentation of Peruvian bark (*Cinchona officinalis* L.) which led him to suggest the application of the therapeutic

similitude principle to the drugs commonly used in his time. Here Hahnemann followed in the steps of Albrecht von Haller (1708-1777) and other respected doctors of his time, Anton von Störck (1731-1803) in particular. Starting in 1759, von Störck performed experiments on animals and on himself to then treat patients with extracts of plants, especially toxic ones such as hemlock, jimsonweed and aconite [2]. Hahnemann complied with the injunction to systematically test medicines first on apparently healthy individuals according to general rules to ensure the validity and reliability of the results. Along his life Hahnemann tested 67 medicines and published the pathogenetic effects (set of symptoms resulting from exposure to a natural or medicinal substance) of 101 drugs [3]. Initially he experimented with the medicines most commonly used by the contemporary doctors (the practice of whom, often poorly rational, he named allopathy, to distinguish it from enantiopathy and homeopathy). These experiments were named *Prüfungen* in German translated into English at that time as 'provings', and currently known as pathogenetic trials, following a suggestion made by this author [4]. To the results of the HPT conducted by him and his disciples, Hahnemann added data from accidental poisonings and iatrogenic overdosing.

In his compilation, Hahnemann used data from more than 50 volunteers, being that 8 participated in 20 or more HPT, including his son. Hahnemann was highly rigorous as concerns the volunteers, most of whom were students interested in learning homeopathy. Thus he made them solemnly swear in public that their descriptions were truthful. To ensure the precision of descriptions, the volunteers ought to carry a notebook at all times, on which they had to immediately register all sensations and changes upon occurring. Hahnemann distinguished his own self-reports from all others, to which he attributed more credibility, although he did not include precise descriptions of the circumstances under which symptoms appeared [5]. Fully aware of the main problems likely to lead to false results, he developed solutions to minimize this possibility.

One of such problems was the volunteers' **credibility** (*Organon of medicine*, § 126 [6]); thus he observed that volunteers were to be well-known friends and sympathizers of homeopathy, who could not be paid under any circumstance. Volunteers ought to be subjected to **careful supervision**, including in-person interviews to inquire on the experienced symptoms. By the same token, Hahnemann banned HPT at distance - i.e., without direct supervision but with reports sent by mail - as they would provide uncertain and doubtful descriptions, whence he rated them useless [6, § 143). Aware of the power of suggestion, he observed "in the investigation of these drug-symptoms all suggestion must be as rigidly avoided as in the examination of the symptoms of disease" ([6] §115).

In his HPT, Hahnemann employed **one single medicine** in its purest form and in moderate dose. With this he established the basis for the **reproducibility** of the results. Aware of individual differences ([6, §129) and of the need to test medicines in different people, he made recommendations on diet, lifestyle and use of medications, alcohol and caffeine-containing beverages to control for eventual confounding factors. According to him, only reliable symptoms were to be included in the homeopathic materia medica, therefore, "He who makes known to the medical world the results of such experiments becomes thereby responsible for the trustworthiness of the person experimented on and his statements, and justly so, as the weal of suffering humanity is here at stake" [6, § 139, note]. He believed a true materia medica was a compilation of the authentic, pure and reliable effects of simple medicinal substances [6, § 143] to the full exclusion of conjecture, traditional or imaginary ideas [6, § 144]. In the last chapter

of the 6th edition of *Organon of medicine* dealing with experimentation of drugs, Hahnemann invites careful and reliable observers to test on themselves. With the increase in the number of tests, he forecasted "The healing art will then come near the mathematical sciences in certainty" [6, § 145].

Methodological improvements of HPT after Hahnemann

Hahnemann's guidelines for HPT were applied in Brazil shortly after his death in the tests performed by Benoît Mure (1809-1858) and his disciples at Homeopathic School of Rio de Janeiro from 1844 to 1848. According to Mure, such HPT were necessary due to diseases peculiar to Brazil and unknown in Europe, as well as of eventual differences in the effects of medicines compared to ones tested on Europeans. In the preface to his book *Patogenesia Brasileira* [8], dedicated to the Brazilian people, Mure wrote "Brazil contains even more curative agents adequate to combat without any exception the hateful manifestation of physical maladies" and

> ... Providence, which seems to have chosen the land of Santa Cruz to inaugurate the grand and happy changes for which humankind is [already] mature, finally allowed Hahnemann's disciples to start researches that will dry so many tears and that, instead of transient relief, [will] let them apply efficacious and definitive remedies to man's sufferings [8, p. 69].

In this book, Mure described the results of experiments (designated as 'pure experiences') with 36 new substances derived from plants (*Myristica sebifera*, *Hura brasiliensis*, *Ocimum canum*, *Janipha manihot* and *Cannabis indica*, among others) and animals (*Crotalus cascavella*, *Blatta americana*, *Elaps corallinus*, *Bufo sahytyiensis* and *Delphinus amazonicus*). He further described in detail the rules to be followed patiently and attentively by volunteers, including doses (1 drop of the 4th or 5th dilution daily until the onset of symptoms). He stressed that symptoms ought to be recorded carefully, in the chronological order of their appearance. Volunteers ought not to know which medicine they were testing or to discuss symptoms among them to avoid suggestibility. According to Mure, following Hahnemann:

> ... the homeopath has no need whatsoever of making imaginary suppositions on the nature of disease, but [he needs] to exactly know which the pains are, the affected parts, the time when the malady began; in one word, the facts, just the facts and only the facts that only the malady might provide him [8, p. 8].

In the chapter on clinical examination, Mure recommends practitioners to register all accessory circumstances attending each symptom, either ameliorating or worsening them. His injunction for symptoms to be described in a clear and understandable manner – using everyday terms and comparisons - is noteworthy. In regard to the various sensations, he wrote:

> For instance, there is heaviness, feeling as of a nail, a peg, needles, tearing, jarring, a band, blowing, gnawing, numbness, roughness, stiffness, clawing, a ball, a lump, stinging, throwing, cutting, pushing, boring, shaking, contusion, contraction, ripping, boiling, pinching; feeling of cramping,

> corroding, exploding, trembling, formication, voluptuous, flattering, strong will, itch, warm, burning, penetrating, crackling [8, p. 8].

Nevertheless, Mure's reported HPT exhibited the methodological flaws Hahnemann had been unable to foresee, which were detected and corrected soon afterwards by other homeopathic doctors, as described below (Table 1).

In 1853, the American Provers' Union – one of which directors was Constantin Hering (1800-1880), founder of the homeopathic school of Philadelphia – published criteria and recommendations for conducting HPT [9, sect. 1].

> " It is requisite that many experiments be made by as many individuals as possible, of all ages and sexes, of different constitutions, dispositions, and temperaments, in different climates, under the influence of different seasons, changes of weather, habits, and customs, peculiarities in dwellings, clothing, eating, drinking &c., &c."

Since experimenters were, as a rule, not used to perform such careful observation demanding attention to changes in sensations and functions, the guidelines recommended them to train and record any perceived changes in their bodies and minds along 1 or 2 weeks before the onset of experiments. In addition, they defined detailed rules and criteria relative to the substance to be tested, dose, diet and lifestyle, field notebooks and how volunteers ought to enter records – the volunteers being doctors and students, in particular. The authors emphasized that participation in HPT also could contribute to the skills needed for examination of patients, since

> "Skill in self-observation, or facility in distinguishing the minutest details of all the phenomena, objective and subjective, which are making their impressions on the nerves, enables the observer finally to link together cause and effect, with a continually increasing certainty" [9, sect. 8].

Again in USA, 5 homeopathic doctors established a group for medical research in Baltimore in 1881. They suggested that all tests with healthy volunteers ought to be preceded by a period of self-observation as training to achieve a better understanding of the pathogenetic nature of symptoms eventually manifesting in HPT. In addition, this group systematized an inductive, analytical and synthetic process for judgment of previously published pathogenetic data, considering only HPT conducted with 10 volunteers at least and symptoms reported for at least 2 volunteers, to improve the credibility and reliability of the materia medica, as expected by Hahnemann [10].

From 1901 to 1903, with the support of the American Homeopathic Ophthalmological, Otological and Laryngological Society, H.P. Bellows (otology professor at school of medicine, Boston University) chaired the first **multicenter double-blind trial** to compare the pathogenetic effects of *Belladonna* (mainly in mother tincture) versus placebo with 53 volunteers from 11 testing centers in USA [11]. Innovatively he introduced the double-blind technique to avoid suggestibility. In the preface to the book – which provides the full description of the study – Bellows compared the performance of HPT to the work of fishermen, who need to make their nets according to the fish they expect to capture, eventually with new and peculiar shapes as needed. In his view, the fish ought to be small, so that more rigorous criteria could be applied to

symptom selection, which would thus no longer fully depend on the personal judgment of HPT supervisors.

In the 1980s, a group of French doctors reanalyzed published HPT of some medicines frequently used by practitioners and mentioned in T.F. Allen's (1837-1902) *The Encyclopedia of Pure Materia Medica*), a reference work for homeopathic materia medica [12]. The results were similar to the ones reported by the Baltimore Investigation Club 100 years earlier: the number of symptoms was considerably reduced, and the rate of symptom confirmation for the 5 studied medicines was 22% [13].

Countless reports in the conventional and homeopathic medical literature show that 'normal', i.e., apparently healthy people, might report symptoms even when not taking medicines [14], or with the use of placebo in phase I clinical trials [15-16] and HPT [18,19]. A survey conducted with apparently healthy Brazilian medical students found a high incidence of changes in their state of health along 7-day retrospective observation; the largest proportion of symptoms was reported by the women [20]. The average incidence of symptoms was 7.2 per subject, varying from 1 to 20. Most changes were mild and transient; 38% were physical, 35% mental and 27% general, as a rule, similar to the ones associated with use of placebo in controlled clinical trials. Moderate or severe manifestations or the fact that almost 60% of them were intermittent show they might be difficult to interpret in HPT when not duly controlled and conducted with excellence.

The results of the study just discussed point to the need for a rigorous experimental design and adequate techniques for control that will help distinguishing between symptoms common to volunteers and new or characteristic symptoms eventually caused by the tested medicine. The validity and reliability of HPT results clearly depend on 3 aspects: selection of a quantitatively sufficient sample of healthy and honest volunteers, use of sensitive and well-controlled experimental designs to minimize systematic flaws and application of clear preset criteria in the selection of the symptoms to be attributed to the tested medicine. In addition, the quality of supervision and the style in the interaction with volunteers should be carefully planned and described, as also should be the instruments for data collection and the measurement of effects. Finally, it is worth to remind the need to publish high quality reports for future reproducibility.

Strategies to minimize flaws, such as use of comparative placebo group, recruitment of volunteers not under relationship of dependence from investigators and blinded to intervention, supervisors blinded to intervention, matching of groups per gender, standardized instructions, pre-observation period with and without placebo, previous definition of guidelines for selection of pathogenetic effects, clear inclusion and exclusion criteria, randomization and moderate supervision were suggested by a Brazilian investigator in 1996 [4] as an attempt to avoid the inflation of pathogenetic effects arising in HPT as a result of the application of Hahnemann's guidelines. Table 1, extracted from [4] summarizes the main flaws, their implications and strategies for minimization.

Table 1 – Methodological flaws of Hahnemann's HPT and strategies for minimization

Methodological flaws	Consequences	Minimization strategies
No control group	Overestimation of drug effects (usual symptoms of volunteers + chance symptoms + drug symptoms)	Use of comparative placebo group
Volunteers are well-known friends and lecture attendees (sympathizers)	Overestimation of drug effects (placebo effected to please investigator/'master')	Use of non-subservient volunteers + comparison to placebo + blinding to intervention
Volunteers report use of drug to observe its effects on themselves	Overestimation of drug effects (expectations + conditioning effects)	Use of placebo + blinding to intervention + standardized non-biased instructions
Record of any change or symptom appearing during use of drug, even though volunteers observed similar symptoms much before use	Overestimation of drug effects (logic fallacy - *post hoc ergo propter hoc* + naturally occurring symptoms)	Use of comparative placebo group + comparison of symptoms between both groups starting from pre-observation period + preset criteria for selection of pathogenetic effects
No blinding of volunteers/supervisors	Overestimation of drug effects (selective perception + investigator effect)	Double blinding (volunteers and supervisors) + causal attribution by volunteers
Rigorous supervision and daily interviews (or every 2-3 days), daily record on a field notebook	Overestimation of drug effects (*Hawthorne* effect + recall bias)	Moderate supervision + improved volunteer selection + standardized questions
Abstinence of coffee, tea, seasonings and alcohol (or medication)	Overestimation of drug effects (effects of abstinence, expression of hidden symptoms)	Routine observation of volunteers + clear exclusion criteria for large alcohol/medication users
Vague definition of healthy volunteer – inclusion of non-healthy volunteers	Overestimation of drug effects (symptoms of past and current disease)	Prospective definition of healthy volunteer with clear inclusion/exclusion criteria + use of validated questionnaire
No random volunteer selection	Overestimation of drug effects (investigator effect)	Randomization

That study also evidenced the common and differential characteristics between HPT and phase I clinical trials. In both a restricted number of apparently healthy individuals is recruited to observe changes caused by medicines tested in controlled studies. However, HPT aim at producing (unpredictable or idiosyncratic) objective or subjective changes to be considered in the future prescription of the tested medicine, which are registered in full detail. In turn, phase I clinical trials are designed to assess the safety and pharmacokinetic profile of drugs, while little attention is paid to the modalities or full detail of symptoms, which are usually common and dose-dependent.

The relevance and impact of the study, originally published in English and translated into French, Spanish and Portuguese [20-22] reflects the significance of this debate within the homeopathic community. This debate was also of interest for other Brazilian investigators, whose contributions are summarily described in the next section.

Brazilian contributions

After Mure left Brazil, other doctors assumed the teaching and divulgation of homeopathy in Brazil, some of them conducting HPT with few volunteers (or self-experimentation). These HPT were published in homeopathic journals, such as *Annaes de Medicina Homeopathica* edited by Instituto Hahnemanniano do Brasil [24-26]. These HPT were usually conducted in an academic setting, with medical teachers and students, for considering, as in other countries, HPT as the core of educational strategies, i.e., learning through reflection in action (experiential learning).

This attitude survived to the present day in Brazilian undergraduate medical or graduate courses in homeopathy. The following description of the author's first experience in conducting a HPT illustrates the strategy on learning through reflection on doing.

Eleven students attending elective "Introduction to Homeopathy" during the 9th semester of undergraduate medical course at Federal University of Uberlândia (UFU) agreed to participate as volunteers in a HPT conducted in 1985. The medicine tested was *Lycopodium clavatum* 3cH, prepared from a Brazilian plant by Prof. Gilberto Luiz Pozetti, versus placebo [27]. Medicine and placebo were delivered as sucrose globules (5 globules upon waking up in the morning before breakfast, 14 days per phase). The placebo globules were not impregnated with the solvent (alcohol) used for medicine preparation. The study had double-blind, crossover design. Volunteers under continued pharmacological treatment or having used medicines in the past month were excluded. Volunteers were requested to perform self-observation along 7 days before the onset of the experiment on a notebook which included an informed consent form and blank pages to record symptoms along the study. Volunteers also had to inform on their general state of health and peculiar characteristics (mental, sleep, perspiration, appetite and usual cenesthetic phenomena, among others). Laboratory tests (blood glucose, uric acid, cholesterol, triglycerides, urinalysis) were performed before the beginning and end of each stage. The most striking symptoms reported by the volunteers are described in Table 2.

Table 2. Symptoms reported in a HPT of *Lycopodium clavatum* by UFU students (1985). The identification code for each volunteer appears between brackets

	Placebo	Lycopodium clavatum 3 CH
Mental symptoms	Depression (2,4) Causeless irritability (8) Irritability, < noise (8) Dream, he and his girlfriend were killing a university professor (8) Dream, violent fight, a friend was brutally attacking a karate black belt holder (8) Explosive behavior with a friend (8)	Anxiety and tachycardia, < 20:00 h (1) Sleeplessness (1) Feeling of helplessness, no protection (2) Anguish, < twilight (2) Mood changes (10) Weeping mood (9) Pessimism (9)
General symptoms	< 17:00 h (8)	< twilight (2)
Local symptoms	Dizziness in the morning (2) Acne-like eruption on the forehead and behind the left ear (1) Nasal watery discharge in the	Hiccup (11) Sore throat, starting at 17:30 h, left side, > warm food and beverages, with neck lymph node enlargement (2) Perianal itch, < bathing (8)

	morning (3) Stomachache, 17:00 h, > ice-cold milk, < after meals, with nausea (5) Headache, moderate intensity, < noise (5) Reddish rash on left ankle, as if by insect bites, itchy (9) Heartburn, < 8:30 h, > milk, triggered by anxiety (9) Rectal tenesmus (9) Normal evacuation in volunteer with usual constipation (10)	Itchy crack on the outer margin of the left foot (8) Itchy spot on the inner margin of the left foot sole (8) Mealy, itchy desquamation on the left plantar arch (8) Vesicles on the outer margin of the right foot (9) Abdominal distension and flatulence, < afternoon, 16:00-20:00 h (7) Abdominal flatulence (9)

Caption: <: aggravation; >: amelioration

On analysis, the symptoms reported by volunteer #8 stood out, both in the mental sphere (under use of placebo) and skin signs on the left foot, which are very similar to the pathogenetic effects of *Lycopodium clavatum* (prepared from European plants) described in the homeopathic literature. In addition, the most frequent time for aggravation was in the evening for both the placebo- and *Lycopodium*-related symptoms; also gastrointestinal symptoms listed in the materia medica of *Lycopodium* were frequent.

However, upon discussing the results with the students, one of them observed (and he was right) that he had been able to distinguish between the 2 phases of the study (*Lycopodium* or placebo) because he could feel the taste of alcohol in the medicine globules. This observation, which he probably mentioned to other volunteers during the experiment, invalidated the double-blind requirement, resulting in the decision not to publish the results of the HPT, which are thus now first communicated to readers and only for educational purposes. Another reason not to publish the results was that the symptoms that appeared during the first phase extended over the following one, whence the results were possibly contaminated due to a too short interval between interventions. Excess rigor? In any case, several years later volunteer #8 (who had moved to another town) started homeopathic treatment, being prescribed *Lycopodium clavatum* with excellent outcomes.

That was the first experience of this author in conducting HPT, described here to illustrate the complexity inherent to this type of study, which should always be conducted in a rigorous manner and very well controlled. This experience served as basis for a critical study published in 1986 on the methods used for HPT [28]. That study included a model for experimental design (including statistical handling and informed consent form) which was translated and published by a French journal [29]. At the end of the article the author warned:

> Either homeopathy incorporates the best scientific knowledge and methods in all its experimental actions, thus producing increasingly valid and reliable information, or it will remain forever associated to placebo, medical ignorance and even quackery [28, p. 40].

In 1995 the Research Committee of Brazilian Homeopathic Medical Association (AMHB), then chaired by Matheus Marim, developed a protocol for HPT (Protocolo Nacional de Experimentação Patogenética da AMHB/PNEP-AMHB) [30]. This protocol served as basis for multicenter studies conducted at institutions charged of the training

of homeopathic doctors. A concern with the reliability of the pathogenetic information led the Committee to also formulate a protocol for review of published HPT [31]. In parallel, and following different methodological guidelines, dozens of medicines were tested as self-experimentation or HPT by small groups of teachers and students from *Instituto Mineiro de Homeopatia*. These studies were published in *Revista do Instituto Mineiro de Homeopatia* and also periodically presented in scientific meetings [32]. Table 3 summarizes published HPT conducted by Brazilian investigators along the past 3 decades.

Table 3. HPT published by Brazilian investigators in the past 3 decades

Year	Authors	Summary
1988	Caixeta AB [33]	*Riboflavina* 30cH; 10 volunteers (5 male and 5 female); description of mental, general and local symptoms, especially cardiac, respiratory, urinary and gastrointestinal
1988	Marim M [34]	Double blind; *Stannum* in increasing dilutions (6cH, 12cH, 30cH, 200c, 1000c, 10000c, 50000c); previously all 21 volunteers (13 female and 8 male, private patients of the investigator, under homeopathic treatment for at least 2 years) used placebo; homeopathic medication was discontinued at least 90 days before the study; the average duration of participation was 13 months; laboratory tests and ECG performed before the study Symptoms corresponding to *Stannum* and the volunteers' constitutional medicine were reported by 87.9% of the sample. The author recommended seeking to understand the global, rather than partial responses
1992	Marim M [35]	Double blind, *Iodum* 6cH, 12cH, 30cH, 200c, 1000c, 10000c, 50000c and potentized placebo 30cH; random allocation; 14 volunteers Volunteers reported many symptoms not listed in the homeopathic materia medica. The author recommended excluding placebo from HPT
1997	Vieira AAL, Adams SR, Dornelles E, Santos MLS, Sartori O, Ramos UNO - Sociedade Gaúcha de Homeopatia [36]	Double blind; *Hydrocianicum acidum* 12cH, 200fc, 10000fc (group 1) and 30cH,1000fc, 50000fc (group 2); placebo at the beginning and end of the study; 11 volunteers (7 female and 4 male, students at graduate course in homeopathy; average duration of participation 7 months; laboratory tests and ECG were criteria for inclusion; weekly assessment by study supervisor Many mental symptoms were reported, as well as gastrointestinal, respiratory, cardiovascular and menstrual.
1999	Marim M, Ribeiro Filho A, Frota ES, Sommer M, Salmeron CRQ, Miranda FCR, Gamarra JS [37]	6 centers, followed PNEP-AMHB; *Brosimum gaudichaudii*, 12cH, 30cH, 200fc, 1000fc, 10000fc, 50000fc and placebo; 17 volunteers (10 male, 7 female), 25-30 years old; random allocation of 3 dilutions and potentized placebo; duration of participation 9 to 18 months; vial code only known by HPT director Placebo induced a number of symptoms comparable to *verum;* frequency of symptoms was highest after 1st vial, among women and with 50000fc. Mental symptoms were the most frequent, followed by sleep, stomach, head and limbs (repertory distribution)
1999	Marim M, Armani M, Forneck MEM, Rita R,	6 centers, followed PNEP-AMHB; *Bothrops jararacussu,* 6cH, 12cH, 30cH, 200fc, 1000fc, 10000fc, 50000fc; venom

	Adams S [38]	prepared in 2 ways: dilution in water and grinding in lactose followed by dilution in liquid; use of placebo (not potentized, impregnated with hydroalcoholic solution); 30 volunteers (20 male, 10 female); use of 1-5 vials; 26 volunteers used placebo (random allocation); meetings with supervisors every 7-15 days No qualitative or quantitative significant difference in the symptoms induced with diluted or ground starting material. Mental symptoms (and dreams), head, respiratory, gastrointestinal, musculoskeletal and general.
2002	Adams S, Azambuja R, Britto C, Sommer M [39]	2 centers, followed PNEP-AMHB; *Hura brasiliensis* 30cH, 200cH,1000fc,10000fc; 18 volunteers (doctors and veterinary doctors); supervision every 15 days; in some cases placebo administered in between dilutions, random allocation. Among many general (long-lasting mental and physical tiredness) and local (limbs, gastrointestinal, respiratory, head, chest) symptoms, authors emphasized a state of awkwardness, mental confusion and dullness as striking pathogenetic effect, thus broadening the pathogenetic image formulated by Mure
2003	Rosenbaum P, Waisse-Priven S, Paula A, Magalhães T [40]	PNEP-AMHB; *Lapis lazuli* 90K; 30-day pre-observation and record on notebook 15 days before onset; laboratory tests for inclusion 3 volunteers completed the study; symptoms in many body areas; placebo not used
2003	Rosenbaum P, Waisse-Priven S, Mansour MA, Estévez A, Nunes NA, Mangolini FS [41]	PNEP-AMHB; *Pyrite* 30K, 200K; 6 volunteers, 2 used placebo only in both phases; 2 used 30K only; and 2 30K and 200K in phases 1 and 2 respectively Symptoms described per volunteer in chronological order; final summary of symptoms
2004	Teixeira MZ [42]	*Sulphur* 30cH, 3 drops weekly, up to 4 weeks; medicine discontinued after appearance of new and striking symptoms; total duration 1-2 months; 21 volunteers, students attending discipline Fundamentals of Homeopathy, FMUSP; name of medicine hidden; approval by institutional research ethics committee
2009	Teixeira MZ [43]	33 volunteers (mean age 21 years old), students attending discipline Fundamentals of Homeopathy, FMUSP; *Arsenicum album* 30cH (n= 11, 6 female, 5 male), *Lachesis muta* 30cH (n= 9, 6 female, 3 male) and *Sulphur* 30cH (n= 13, 6 female, 7 male); weekly dose of medicine or placebo over 4 weeks + 4 additional weeks after crossover Only new or peculiar symptoms of *verum* and common symptoms with placebo were used for comparison with materia medica. Approval by institutional research ethics committee. Volunteers informed the name of medicines only at the end of the study
2005 e 2008	Albuquerque PEA, Carneiro SMTPG, Rodrigues MRL, Nechar RMC [44]	20 volunteers, doctors, in 2005 and 2008; blinding; *Serotonin sulfate* 30cH, 10 drops, twice daily up to 30 days; self-observation along 6 months before onset of study; record of observations 30 days before medication 370 symptoms distributed across all volunteers; 17 out of 32 symptoms of serotoninergic syndrome described in the literature occurred in the trial; authors recommended the medicine for fibromyalgia and chronic fatigue syndrome

2001	Fisher P, Dantas F[45]	2 HPT with the same method, *Acidum malicum* 12cH and *Acidum ascorbicum* 12cH, conducted at the Royal London Homeopathic Hospital; 20 volunteers per study, double blind, placebo-controlled; potentized placebo 12cH; double crossover, 4 phases; placebo and *verum* used at least twice by each volunteer; SF-36, laboratory tests and interview for inclusion; each medicine was used for 1 week, minimum 1-week interval between phases; interview at the end of each phase; 3 filters for blind selection of symptoms: volunteers first assessed possible causal relationship, then the supervisor after interviews, finally application of 9-item pathogenetic index developed for this HPT No adverse effects were reported; double blinding tested at the end of the study; 48% of hits for *verum* vs. placebo for *Acidum malicum* and 50% for *Acidum ascorbicum*; 22 possible symptoms of *Acidum malicum*, being 2 highly suggestive, and 16 symptoms of *Acidum ascorbicum*, 3 quite suggestive

Caption: ECG: electrocardiogram; fc: centesimal dilutions, continuous flux; PNEP-AMHB: National Protocol for Pathogenetic Experimentation, Brazilian Homeopathic Medical Association; FMUSP: Medical School, University of São Paulo

The first systematic review of HPT was published in 2007 [45]. It included studies published in 6 languages, from 1945 to 1995, with special emphasis on their quality. The review was designed and performed by this author, with collaborators from many countries. Coauthors from Brazil were Matheus Marim, then chair of AMHB Research Committee and responsible for PNEP, Hélio Teixeira, professor at UFU and Luc L.M. Weckx, professor at Federal University of São Paulo. The search was conducted in specialized databases (HOMINFORM – British Library of Homeopathy, HOMEOINDEX – Brazilian Library of Homeopathy), manual research in books and journals, contacts with pharmaceutical companies and experts and checking of cross-references, in addition to information provided by the reviewers, all of them experienced in pathogenetic or clinical research.

Two reviewers extracted that data, which were entered in an *ad hoc* form with 87 items to assess medicines, volunteers, ethical issues, sample, randomization, blinding, experimental controls, symptom recording, adverse effects, result interpretation, number of published HPT and global methodological quality of studies. The following rules were established for attribution of causal relationship of symptoms: a) short interval between occurrence and medicine use; b) intensity; c) duration; d) peculiarity or originality (idiosyncratic); e) volunteer's conviction that symptom was caused by medicine; f) comparison to symptoms induced by placebo; g) disappearance of older or current symptoms during trial; h) appearance in more than 1 volunteer (confirmation); i) association of concomitant modalities or symptoms; and j) reappearance on re-exposure. The data were extracted by 11 different pairs of examiners; the number of studies analyzed per pair varied from 2 to 45.

A total of 156 publications were reviewed, describing the pathogenetic effects of 143 medicines tested on 2,815 volunteers; 20,538 pathogenetic effects were reported. A total of 116 HPT were published in homeopathic medical journals, 13 in meeting proceedings, 11 as books and 16 as dissertations or in research institutions bulletins. More than half of the studies were published in English (54%), followed by German (21%), Dutch (11%), French (7%), Spanish (4.5%) and Portuguese (2.5%). The number

of HPT published in any language increased along the past decades, especially the last one analyzed (800% increase compared to the first decade).

The tested medicines were most frequently of plant origin (75) followed by animal products (29), minerals (18), composite chemicals (14) and conventional drugs (11). Two studies tested energy sources and 1 named the substance with code. The most frequent reason for substance selection was their medicinal effects (usually in the case of plant substances), followed by their toxic effects on humans; 30% of the studies did not inform the reason for selection. Preparation of medicines was described in 17 studies, but with full detail only by 7 (in some cases authors stated that preparation complied with the national homeopathic pharmacopoeia).

The global median number of volunteers was 15 (mean: 18) varying from 1 to 103. One single volunteer represented the full sample in 7 studies, 3 employed 2 experimenters, one being the report's author. About 57% of studies did not mention the volunteers' age and 34% did not report their gender. Age varied from 5 to 56 years old; 1,169 volunteers were male and 857 female. Homeopathic doctors were the main investigators and a large proportion of volunteers was of homeopathy students. Fifteen authors contributed with 52% of the studies.

The tradition notwithstanding, only 64 studies reported use of a notebook for symptom recording; 28 were open (blank pages) and 13 semi-structured (indicating symptom areas). Much relevant information for analysis and future replication was not provided or collected in a significant number of the analyzed studies.

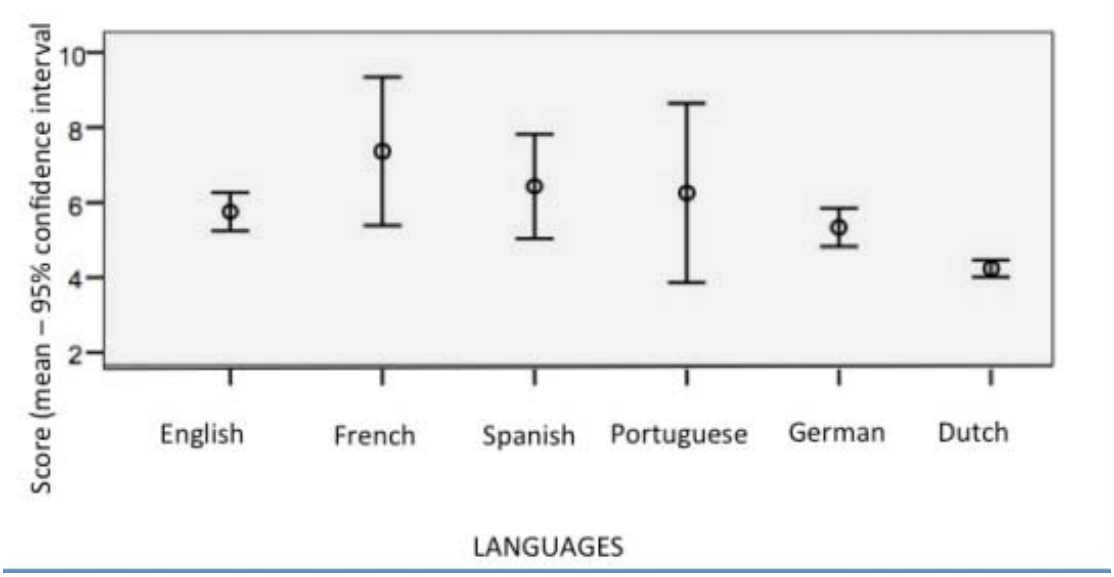
Methods and results exhibited wide variability. While the number of HPT increased along the analyzed decades, it was not attended by improvement of their methodological quality as assessed by a methodological quality index (MQI/Dantas Score) developed by the study main author. Scores (total range: 4 to 16) were attributed to 4 components: randomization, volunteer and investigator blinding, inclusion and exclusion criteria, and preset criteria for causal attribution of pathogenetic effects. Based on the scores, the studies were categorized in 4 classes: I (score 4 to 6), II (7-10), III (11-13) and IV (14-16). Kappa for the pair of examiners which analyzed the largest number of HPT indicated reasonable agreement for allocation concealment (k= 0.32), moderate for randomization sequence generation (k= 0.49), good for exclusion criteria (k= 0.65) and supervisor blinding (k= 0.69), and very good for randomization (k= 0.89) and inclusion criteria (k= 1.0).

Table 4. Methodological Quality Index for scoring HPT (Dantas score) [46]

	SCORE			
Component	1	2	3	4
Randomization	Not stated	Only stated, no details	Description of sequence generation or allocation concealment	Description of sequence generation **and** allocation concealment
Blinding	Not stated	Single blind	Double blind without verification	Double blind with post-trial verification
Inclusion and exclusion criteria	Not stated	1 partially stated	1 clearly stated or both partially stated	Clearly stated
Criteria for effect selection	Not stated	At least 1 defined	2 to 4 defined	More than 4 defined

On comparison of languages corresponding to more than 10 HPT, Dutch significantly differed from all others (p= 0.001, Dunnett's multiple comparison test, Fig. 1).

Figure 1. Mean methodological scores by language of publication

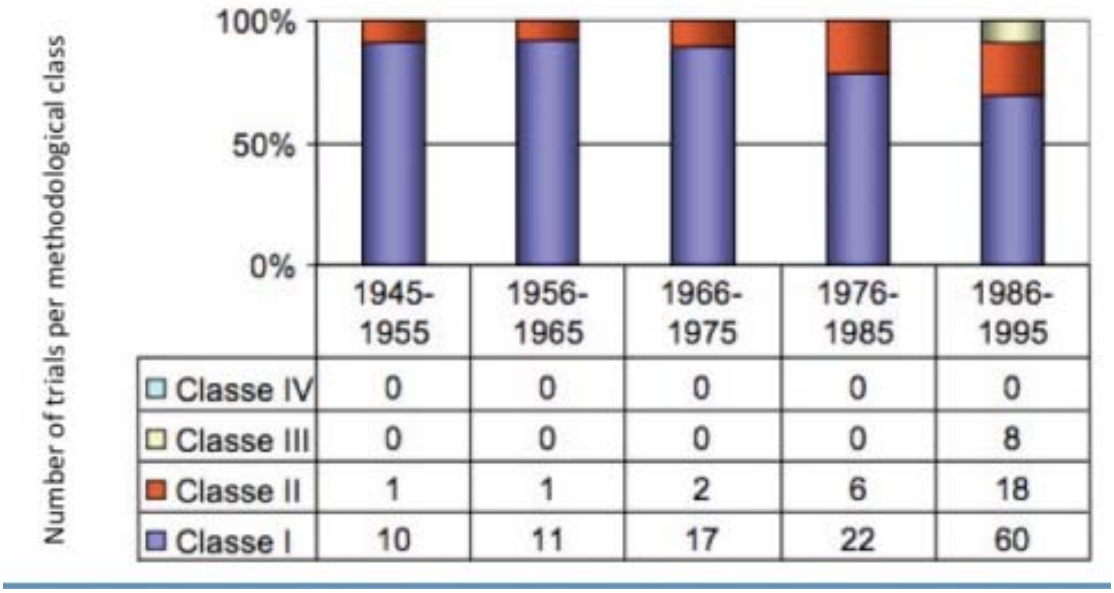


The average score of the analyzed HPT was 5.65, with large predominance of studies with low methodological quality (score 4: 41.5%; 5-6: 34.5%; 7-8: 14%; 9-10: 4.5%; 12: 4.5%; 13: 1.0%); 76% of the studies were included in class I. Only 15 studies described randomization, the first one published in 1961 and 9 from 1985 to 1995. Only 2 studies informed as to randomization sequence generation (computer software and random number table). Few studies clearly described how allocation was concealed. Volunteer blinding was described in 41 studies (26%) and supervisor blinding in 51 (33%); double blinding was described in 41 studies (26%) and exclusive volunteer blinding in 33 (21%). None of the studies checked the reliability of the blinding procedure by asking volunteers – and comparing their results - if they were aware of the use of placebo or verum during the trial.

Analysis showed that the number of studies with better methodological quality tended to improve along time (r_s= 0.218; p= 0.006) especially in the past 2 decades (Fig. 2).

Inclusion criteria were not mentioned by 78% of studies; in the ones that did they were based on clinical history (94%) and laboratory tests (53%), followed by quality of life and psychological questionnaires (11.7% each). Assessment of the previous state of health of volunteers was not reported in 65% of HPT. A total of 134 publications (86%) did not indicate the criteria for selection of pathogenetic effects from other signs and symptoms that could not be related to the tested medicines. Among the criteria for selection used in the studies with higher methodological quality, the following stood out: occurrence in more than 1 volunteer (33%), intensity and peculiarity or originality (28% each). The methodological quality score exhibited positive correlation with sample size (r_s= 0.287; p< 0.001) and reviewer perceived reliability (r_s= 0.375; p< 0.001) but negative correlation with number of effects per volunteer (r_s= -0.204; p= 0.011).

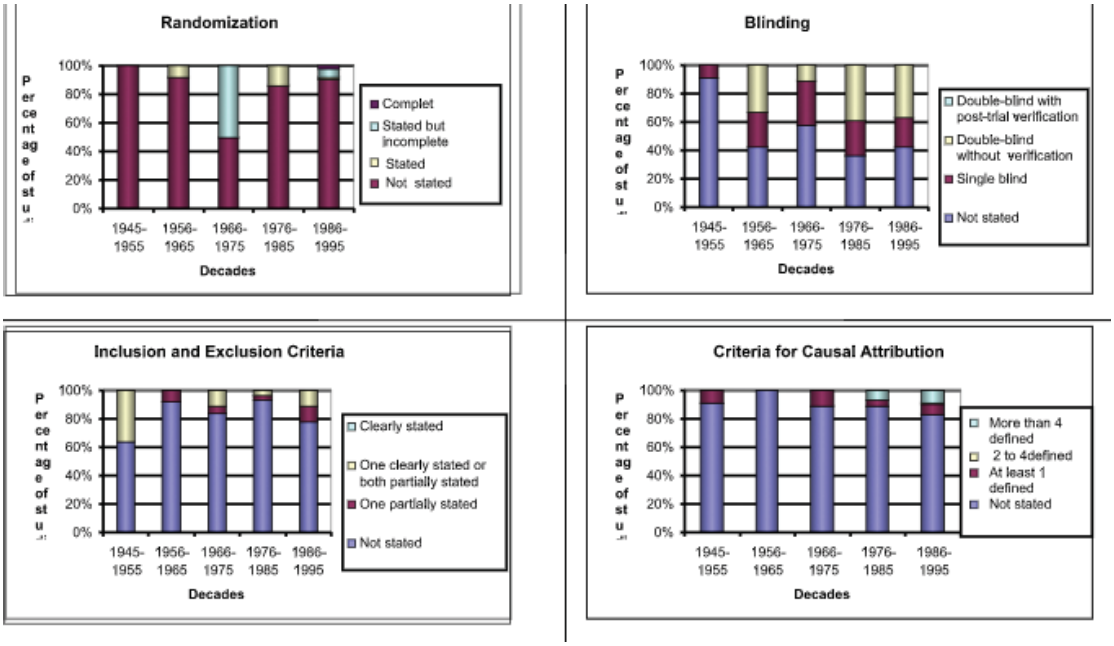
Figure 2. Evolution of methodological quality per decade, 1945 to 1995 (%)



	1945-1955	1956-1965	1966-1975	1976-1985	1986-1995
Classe IV	0	0	0	0	0
Classe III	0	0	0	0	8
Classe II	1	1	2	6	18
Classe I	10	11	17	22	60

The progression of the indicators considered in the Dantas score along the 5 analyzed decades showed increase of blinding, as well as of description of the criteria for causality attribution, especially in the past 2 decades (Fig. 3, [46]).

Figure 3. Progression of Dantas score components along 5 decades (%)



The studies had small sample size (median: 15) and volunteers were often somehow involved in homeopathy learning. There was positive correlation between Dantas core and sample size (r_s= 0.287; p< 0.001). The median duration of studies was 44 days among the 99 studies which reported this variable (mean: 82; mode: 14; standard deviation: 108). In some cases it was difficult to estimate the actual study duration due to lack of precise information. Study duration varied from 1 day to 18 months; in some

cases volunteers continued self-observation and reported symptoms several months after the end of intervention; these symptoms were considered pathogenetic effects. Study duration had positive correlation with average number of pathogenetic effects per volunteer (r_s= 0.216; p= 0.031). The studies with better methodological quality were shorter than the poorer quality ones; this difference was statistically non-significant. Placebo was used in 56% of HPT, but the corresponding symptoms were seldom used in comparisons and some investigators gradually gave up its use. Highly relevant information for analysis and future replication missed or was not collected in a considerable number of studies.

Most HPT were quasi experimental, before and after studies, with or without parallel group (placebo). Yet the recent trend to perform randomized, placebo-controlled experimental studies (14 studies including crossover) is noteworthy. Only 22 studies included pre-observation period before intervention (*verum* or placebo); 25 studies administered placebo during the pre-observation period, 5 of them both with and without placebo. Among the 11 studies with better methodological quality, 9 used the pre-observation period for training and later comparison of reported symptoms. A total of 56 studies used a comparative placebo group, although in some cases it is difficult to assert that comparisons were effectively made, as the intention underlying use of placebo was to sharpen the volunteers' attention. Only 48 studies conducted an initial interview with volunteers (ongoing complaints and past pathological history), but seldom reported their content and duration. Follow-up interviews were mentioned in 31 studies, while 117 did not make any comment in this regard.

All studies but 3 (2%) reported occurrence of pathogenetic effects attributable to the tested medicines, independently from the latter's type, dilution and number of volunteers. The mean number of effects per publication was 132, varying from 0 to 1,100 (median: 88). Each volunteer reported 7.3 symptoms, on average. Overall analysis of the studies showed high incidence of common and general symptoms, such as irritability, sadness, headache, skin problems, gastrointestinal symptoms and sleep problems. Most events occurred within the 1st week of medicine use, but some symptoms appeared very late (36 studies), several weeks after the onset of the study. As a rule, effects had short duration (hours to few days).

The average number of pathogenetic effects per volunteer exhibited negative correlation with lack of randomization (r_s=-0.203; p= 0.012), blinding (r_s=-0.171; p= 0.034) and sample size (r_s=-0.356; p< 0.001). Pathogenetic effects, usually mild and not posing serious risk to health, were reported by more than 80% of the volunteers, with tendency for negative correlation with the methodological quality of studies. The studies with better methodological quality generated less pathogenetic effects compared to the poorer quality ones.

In total, 769 volunteers behaved as controls; placebo was used in 56% of the studies. About 16% of the studies included a preliminary phase in which placebo was used. Placebo was described as fully indistinguishable from *verum* in 33 HPT (21%). Only 1 study from 1952 reported use of potentized placebo prepared according to the homeopathic pharmaceutical technique. Placebo was used for various purposes: control for comparison; instrument to sharpen the volunteers' awareness; and to rule out similar symptoms in the group using *verum*.

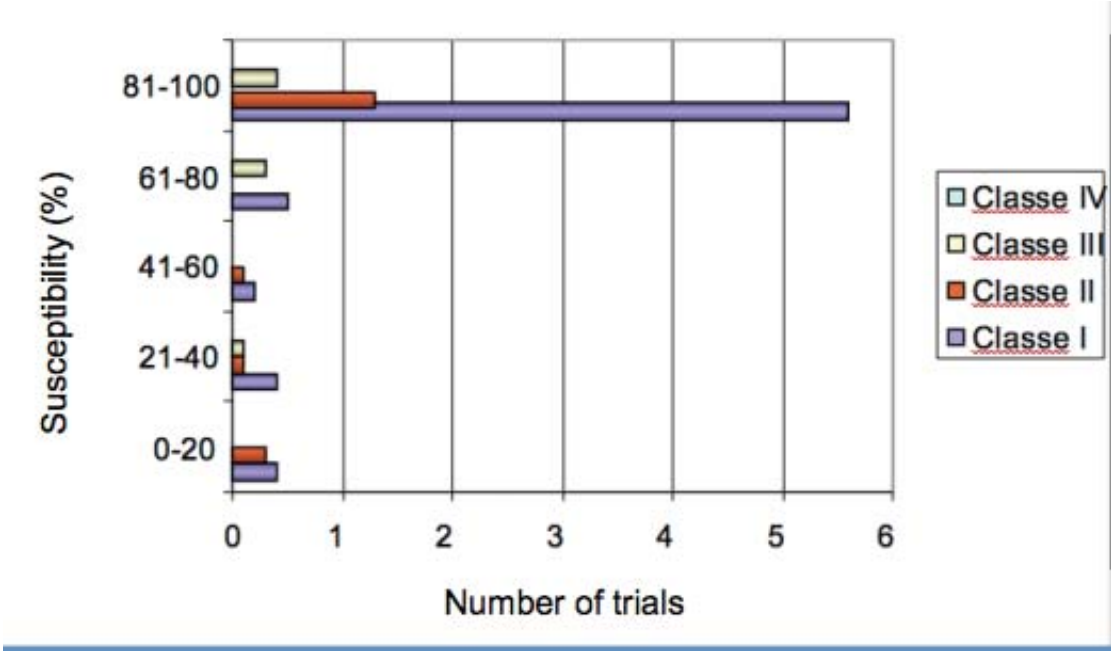
Instances of dropout were described in 34 studies, the proportion being usually very small. Half of the class III studies reported dropout, corresponding to 10% of the

volunteers (18/179) and attributed to adverse effects by only 1.1%. Relative to class II, 18.6% of the volunteers dropped out in 12/28 studies; dropout due to adverse effects was again 1.1%. Dropout occurred in 22/120 class I studies (18.3%) corresponding to 6.1% of volunteers; 2% of dropouts were attributed to adverse effects. However, within the context of HPT it is difficult to distinguish between adverse and pathogenetic effects, because per definition the latter are expected and desired, which runs against the traditional definition of adverse effects as undesirable cause of suffering.

A comparative analysis was performed of the main characteristics of the studies with higher methodological quality (score 12-13) with the same number of studies with the lowest score (4) randomly selected by means of the lottery method following matching per publication year. The results showed that the studies with poorer methodological quality did not report use of placebo, pre-observation period or attribution criteria and reported twice more symptoms than the better ones. It should be observed that the sample comprised only quasi experimental, before and after studies and all the volunteers given *verum* reported occurrence of pathogenetic symptoms.

The volunteers' susceptibility to exposure to homeopathic medicines was variable, although a high percentage of studies in which all volunteers reported pathogenetic symptoms was found in all the analyzed decades. Overall, 84% of the volunteers who took homeopathic medications during HPT reported 1 or more symptoms. Median for the 97 studies with information on volunteers' susceptibility was 100%. Only 1 study explicitly stated that no symptom could be attributed to the tested medicine.

Figure 4. Percentage of sensitive volunteers per methodological class



The results of the systematic review provide a picture of HPT conducted until 1995. In the following discussions, the authors were criticized for excessive rigor [47]. Yet, on the one hand, the review detected a trend to improvement in the methodological quality of HPT in the past decade, and did not include double crossover studies that used various filters for effect selection, as the one by Fisher and Dantas [45] and that reported symptoms probably associated with the tested medicines. On the other hand,

it does not seem reasonable or proportionate to believe that the thousands of symptoms reported in HPT are the fruit of fantasy, altered states of consciousness or merely imaginary. Despite the large component of subjectivity in HTP, whence their complexity, the efforts of groups of homeopaths over time to improve and make the results increasingly objective to make them valid and reliable, in addition to beneficial for patients, are noteworthy.

Final considerations

The validity and reliability of the information generated in HPT is crucial for successful clinical practice and research in homeopathy. HPT are an original contribution of homeopathy to experimental medical science for identification of predominantly mental, and secondarily physical changes induced by highly diluted and agitated medicines on apparently healthy individuals. Early detection of highly subjective sensory changes in a patient before the clinical manifestation of disease might be the key event for prescription of a homeopathic medicine able to quickly correct this prefigured deviation from normality still in the form of a feeling or sensation, resulting in the much desired secondary prevention. Such manifestations are usually not included in the reports of poisonings or in modern phase I studies of drugs, of which HPT might be considered to be precursors.

Since Hahnemann's times prescription of substances used as medicines able to cause deleterious effects on humans has been advocated without previous performance of HPT, which demand high organization skills, qualified human resources and financial investment. In Brazil, for instance, Costa used in 1960 streptomycin for treatment of vertigo based on the adverse effects of this drug [48]. More recently, Teixeira systematically suggested transforming modern drugs that induce rebound effect or paradoxical reactions into new homeopathic medicines likely to trigger curative body reactions [49].

In 1810, Hahnemann significantly entitled the first edition of the reference book of homeopathy *Organon of rational medicine* (*organon*, in Greek, denotes instrument or means for correct thinking and true science). As rational medicine, homeopathy cannot improve without systemic and systematic criticism of its notions and practices through open and soundly grounded discussions. Within this context, incorporation of the concepts of homeopathic clinical logic is particularly meaningful. Indeed, in the present article such concepts were used in the assessment of the relevant and sensitive issue around the reliability and validity of information collected in HPT.

Aude sapere! wrote Hahnemann as subtitle to the second edition of his *Organon*. Following Reilly's analogy [50] many pieces must still be discovered and adequately placed to complete the puzzle of homeopathy and gave meaning and coherence to the set of facts accumulated along more than 200 years by skilled and honest doctors who prescribe homeopathy and scientists who seek to unveil its secrets.

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