

Scientific evidence of the homeopathic epistemological model

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ABSTRACT

Homeopathy is based on principles and a system of knowledge different from the ones supporting the conventional biomedical model: this epistemological conflict is the underlying reason explaining why homeopathy is so difficult to accept by present-day scientific reason. To legitimize homeopathy according to the standards of the latter, research must confirm the validity of its basic assumptions: principle of therapeutic similitude, trials of medicines on healthy individuals, individualized prescriptions and use of high dilutions. Correspondingly, basic research must supply experimental data and models to substantiate the basic assumptions, whilst clinical trials aim at confirming the efficacy and effectiveness of homeopathy in the treatment of disease. This article discusses the epistemological model of homeopathy relating its basic assumptions with data resulting from different fields of modern experimental research and supporting its therapeutic use on the outcomes of available clinical trials. In this regard, the principle of individualization of treatment is the *sine qua non* condition to make therapeutic similitude operative and consequently for homeopathic treatment to exhibit clinical efficacy and effectiveness.

Keywords: Foundations of homeopathy; Medical education; Law of similar; Pharmacodynamic action of homeopathic remedies; Biomedical research.

Introduction

Founded in 1796 by German physician Samuel Hahnemann, homeopathy is a medical approach employed worldwide and that continually awakens the interest of users, medical students and doctors ever since [1]. The reason is that it allows for a safe and efficient therapeutic practice, while it seeks to comprehend and treat patients and their diseases within a globalizing and humanistic framework [2,3], which gives especial value to different facets of ill individuals in their uniqueness.

Regarding its institutionalization, the case of Brazil is one among the ones illustrating a high degree of development. Homeopathy was acknowledged as a medical specialty by the Federal Council of Medicine (CFM) in 1980 (Resolution CFM 1000/80) and the Brazilian Medical Association (AMB) confers the degree of specialist since 1990. Homeopathic physicians, thus, are a part of the medical community. Homeopathy is taught in *lato sensu* post-graduation programs (1,200-hours) hosted by institutions associated with the Brazilian Homeopathic Medical Association (AMHB). Homeopathic consultations are covered by medical insurance companies and since 1985 were also made available at the National Health System.

It is estimated that there are about 15,000 homeopathic medical practitioners in the country. In a survey carried out the last decade among Brazilian doctors by Fiocruz Foundation and CFM [4], homeopathy ranked 17th among 61 medical specialties regarding the number of doctors who defined it as their primary area of activity. After approval by the National Commission of Medical Residency in 2002 (Resolution CFM 1634/2002), homeopathy was included in the medical residency program of Federal University of the State of

Rio de Janeiro (UNIRIO, University Hospital Gaffré e Guinle) as an option for on-the-job-training [5] being an adjuvant to conventional treatment of disease in both outpatient clinic and wards. This unique example of integrated medicine allows for an ongoing dialog between distinct medical systems to the benefit of patients, since it offers them the best available means of diagnosis, treatment and prophylaxis of disease.

Despite the increasing demand of Brazilian population for homeopathy in the last decades, a survey made in 2008 showed that only 110 among more than 5,000 municipalities make it available through the public health network even when in recent years more than 300,000 homeopathic consultations were carried out within the National Health System (SUS), corresponding to 10% of primary care consultations in the evaluated period, as indicated by data from the Ministry of Health [6].

Initiatives for medical education made possible to teach the foundations of homeopathy at regular medical schools, either as mandatory or elective disciplines. In this way, information backed by scientific evidence and clinical practice helps dissolving a prejudice deeply rooted in medical culture [7,8].

Despite its use as a therapeutic option for more than two centuries in several countries, homeopathy remains marginalized from mainstream science and medicine because it is grounded on quite unorthodox notions that challenge the prevailing scientific rationality. The homeopathic approach to treatment is guided by the principle of therapeutic similarity, prescribes high dilutions of substances that when tested on healthy individuals elicited signs and symptoms similar to the ones exhibited by the patient. To become a homeopathic medicine, a substance must be subjected to specific protocols of testing on human beings and have its (mental, general and physical effects) described in the homeopathic materia medica (HMM).

By approaching human beings as complex entities, the homeopathic model assigns a dynamic nature to the biological body, where thoughts and feelings interact with organic systems and physiological functions in a way that makes each individual singularly susceptible to the various pathogenic agents and conditions. Resulting from this psychosomatic and globalizing conception of the process of becoming ill, homeopathic semiology takes into account the multiple facets of each patient to compose a symptomatic picture encompassing the peculiar traits of the multiple human spheres – namely, biological, psychological, social and spiritual – in order to establish an “individualized” diagnosis of remedies.

To answer to the frequent questioning about the existence of scientific evidence supporting the validity of the homeopathic model, this article makes a critical survey of the specialized literature describing some current basic and clinical lines of research validating the assumptions mentioned above so as to show its correspondence with the homeopathic traditional theoretical and practical model.

Homeopathic Epistemological Model

- ***Principle of therapeutic similitude***

Grounded on the study of the pharmacological properties of tens of medicinal substances used at that time, where he observed a secondary reaction (indirect effect) by the organism occur after the primary action (direct effect), Hahnemann enunciated an aphorism to describe the action of medicines in the human organism:

“Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed *primary action* [...]. To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of *secondary action* or counteraction.” (*Organon of Medicine*, §63) [9]

As illustrations of this natural law, Hahnemann listed the *primary actions of the medicines* employed in his time as promoting alterations in different organic systems and the following secondary action by the organism (vital reaction or conservation force). The latter acts neutralizing the primary disorders caused by drugs, i.e. it aims to bring back the state of balance of the internal environment that was altered by the therapeutic intervention:

“[...] Excessive vivacity follows the use of strong coffee (primary action), but sluggishness and drowsiness remain for a long time afterwards (reaction, secondary action), if this be not always again removed for a short time by imbibing fresh supplies of coffee (palliative). After the profound stupefied sleep caused by opium (primary action), the following night will be all the more sleepless (reaction, secondary action). After the constipation produced by opium (primary action), diarrhoea ensues (secondary action); and after purgation with medicines that irritate the bowels, constipation of several days' duration ensues (secondary action). And in like manner it always happens, after the primary action of a medicine that produces in large doses a great change in the health of a healthy person, that its exact opposite, when, as has been observed, there is actually such a thing, is produced in the secondary action by our vital force.” (*Organon of medicine*, §65) [9]

By giving to ill individuals substances that cause symptoms similar to the ones they elicit in healthy experimental subjects (*similia similibus curentur*), the application of the principle of therapeutic similitude seeks to stimulate a healing homeostatic reaction against disease by inducing the organism to react against its own disturbs. Described in the 1860s by Sorbonne physiologist Claude Bernard as “fixité du milieu intérieur” (fixedness of the internal environment), the term “homeostasis” was minted in 1929 by Harvard physiologist Walter B. Cannon to define the tendency or ability of living organisms to keep their internal environment constant through self-adjustments of their physiological processes.

Not a stranger to the history of medicine since the time of Hippocrates, at least, the principle of therapeutic similitude, reinterpreted as vital or homeostatic reaction, finds scientific support in modern pharmacology and physiology in the notion of “rebound effect” of drugs or “paradoxical reaction” of the organism. The latter appears after discontinuation or alteration of the doses of countless classes of modern drugs that act contrarily (antagonistically, antipathically, oppositely, palliatively, enantiopathically) to the symptoms of disease and it has been confirmed by hundreds of studies in experimental clinical pharmacology [10,11].

Seeking to ground the homeopathic epistemological model on modern scientific knowledge, for the last decade this author has been surveying the nomenclature, concepts and scientific studies of modern pharmacology and physiology looking for possible support for the principle of similitude in the basic fields of science. This study showed that in spite of the hundreds of scientific researches on the rebound effect of drugs published in very high impact-factor journals, whenever the mechanism of action of drugs is taught or discussed in medical and scientific circles, such natural phenomenon (notably, already mentioned by the homeopathic tradition 200 years ago) is virtually dismissed. In this way, due to the lack of information, practitioners lack an important tool to avoid the iatrogenic effect of modern drugs.

To illustrate: drugs classically used in the treatment of *angina pectoris* (β -blockers, calcium channel blockers, nitrates, etc.) with beneficial effects in their primary effect (anti-angina), might awaken an increase of the frequency and intensity of chest pain as secondary effect by the organism after discontinuation or irregular use of doses, which sometimes does not respond to any therapeutic means. Drugs used for the control of *arterial hypertension* (α -2 agonists, β -blockers, ACE inhibitors, MAO inhibitors, nitrates, sodium nitroprusside, hydralazine, etc.) might produce rebound arterial hypertension as a paradoxical reaction of the organism to the primary stimulus; *antiarrhythmic* drugs (adenosine, amiodarone, β -blockers, calcium channel blockers, disopyramide, flecainide, lidocaine, mexiletine, moricizine, procainamide, quinidine, digital, etc.) when treatment is interrupted may awaken a rebound exacerbation of basal ventricular arrhythmias. *Anticoagulant* drugs (argatroban, bezafibrate, heparin, salicylates, warfarin, clopidogrel, etc.), employed due

to their primary effect in the prophylaxis of thrombosis can promote thrombotic complications as secondary or rebound effect of the organism. In the use of psychiatric drugs such as *anxiolytics* (barbiturates, benzodiazepines, carbamates, etc.), *sedative-hypnotics* (barbiturates, benzodiazepines, morphine, promethazine, zopiclone, etc.), *stimulants of the central nervous system* (amphetamines, caffeine, cocaine, mazindol, methylfenidate, etc.), *antidepressant* (tricyclic, MAO inhibitors, inhibitors of serotonin uptake, etc.) or *antipsychotic* (clozapine, phenothiazines, haloperidol, pimozide, etc.) it can be observed a paradoxical reaction of the organism, seeking to keep organic homeostasis, promoting the appearance of symptoms contrary to the ones expected from their primary therapeutic use, consequently worsening the initial clinical picture. Drugs with *anti-inflammatory* primary action (corticoids, ibuprofen, indomethacin, paracetamol, salicylates, etc.) might trigger secondary responses by the organism that increase inflammation together with the serum concentration of its mediators. Drugs with *analgesic* primary action (caffeine, calcium channels blockers, clonidine, ergotamine, methysergide, opiates, salicylates, etc.) can exhibit significant hyperalgesia as rebound effect. *Diuretics* (furosemide, torasemide, triamterene, etc.) enantiopathically used to diminish the volume of plasma (edema, arterial hypertension, congestive heart failure, etc.) may cause rebound retention of sodium and potassium thus increasing the basal volume of plasma. Drugs primarily used as *anti-dyspeptic* (antacids, H₂ antagonists, misoprostol, sucralfate, proton-pump inhibitors, etc.) in the treatment of gastritis and gastro-duodenal ulcers might promote, after the primary decrease of acidity, rebound increase of the production of hydrochloric acid by the stomach, eventually causing perforation of chronic gastro-duodenal ulcers. *Bronchodilators* (adrenergic drugs, sodium chromoglycate, epinephrine, ipratropium, nedocromil, salmeterol, formoterol, etc.) used in the treatment of bronchial asthma can worsen bronchial constriction as secondary response by the organism to the interruption or discontinuation of treatment; etc. [10,11].

Rebound effect is an idiosyncratic property of individuals and thus, any particular paradoxical reaction only appears in a small fraction of individuals. However, effects can be devastating causing severe and fatal iatrogenic events as shown by the current available scientific evidence [12], thus justifying the need for individualized therapeutic approaches, such as homeopathy. For instance, COX-2 selective and non selective inhibiting anti-inflammatory drugs cause fatal thrombosis (acute myocardial infarction, stroke) secondary to their anticoagulant primary effect [13]; long-acting bronchodilators (β -agonists) cause irreversible and fatal bronchial spasm after their primary bronchodilating action [14]; serotonin uptake inhibiting antidepressants exacerbate suicidal ideas after an initial improvement of this symptom [15]; statins cause fatal vascular events (acute myocardial infarction, stroke) after an initial increase of their pleiotropic and vasculoprotecting effects [16]; proton-pump inhibitors cause rebound acid hypersecretion (hypergastrinemia, exacerbation of gastritis and ulcers, gastric cancer) after an initial improvement of gastric acidity [17]; etc.

Analogously to classic homeopathic medicines, the rebound effect of modern drugs with action contrary to the symptoms troublesome to patients (“enantiopathic” medicines, namely “anti-”) can be used according to homeopathic criteria, thus stimulating favorable organic reactions, e.g.: contraceptives promoting rebound ovulation and conception in women with functional sterility; immunosuppressants awakening paradoxical immunostimulation in immunosuppressed individuals, etc. This is to say, the principle of therapeutic similitude can be applied with any natural or synthetic substance, whose effects with either mass- or infinitesimal doses are known, becoming thus an alternative to the principle of therapeutic contraries used by conventional medicine [18-20].

Also basic research shows the action of high dilutions in the induction of a homeostatic therapeutic response by testing the protective or healing effects of homeopathic preparations of several toxics (arsenic, mercury, copper, lead, etc.) in laboratory models (animal, vegetal, cell-lines, etc.) subjected to experimental intoxication with the corresponding substance [21]. Other fields of science employing the term “hormesis” have also shown the toxic action of countless agents be reversed by the therapeutic use of these same agents in infinitesimal doses given with the aim of awakening the phenomenon of organic or homeostatic compensation [22].

- **Homeopathic pathogenetic trials**

To learn the pathogenetic properties of substances essential to apply the principle of therapeutic similitude, homeopathy resorts to so-called homeopathic pathogenetic trials (HPTs) as its model of clinical-pharmacological studies (similar to modern phase 1 preclinical trials). HPTs take into account all kinds of signs and symptoms (mental, general and physical) elicited by the tested substance, taken in mass- or infinitesimal doses, corresponding to the therapeutic, adverse and side-effects of drugs of modern pharmacology:

“The whole pathogenetic effect of the several medicines must be known; that is to say, all the morbid symptoms and alterations in the health that each of them is specially capable of developing in the healthy individual must first have been observed as far as possible, before we can hope to be able to find among them, and to select, suitable homoeopathic remedies for most of the natural diseases.” (*Organon of medicine*, §106) [9]

Following the premises stipulated by Hahnemann (*Organon of medicine*, §105-145) [9], countless substances were tested under different HPT protocols [23,24] aiming at acquiring the “knowledge of the tools destined for the cure of natural diseases” through the inquiry of “the pathogenetic power of medicines, so that, when needing to heal, one can choose among them one whose symptomatic manifestations might compose an artificial disease as similar as possible to the totality of the main symptoms of the natural disease to be healed”.

All symptoms thus observed in HPTs are compiled in the homeopathic materia medica (HMM) following an anatomical-functional system (mind, head, eyes, ears, nose, face, mouth, throat, stomach, abdomen, etc.). In clinical practice, homeopaths also employ repertories of homeopathic symptoms (RHS) where all homeopathic medicines that elicited one same symptom in HPTs are grouped together under the same heading (“rubric”) thus facilitating the choice of a homeopathic remedy encompassing the totality of characteristic symptoms of the patient.

- **High dilutions or dynamized medicines**

Opposite to the dose-dependent biochemical model of modern pharmacology, it cannot fail to astonish a scientific thought restricted to the molecular paradigm the fact that high diluted (“potentized” or “dynamized” in homeopathic jargon) substances can awaken some responses in biological systems or living beings. This is the major target of criticism against the homeopathic model despite it is not its chief assumption.

Since Hahnemann’s time to this day, both HPTs and the principle of therapeutic similitude (which is the core homeopathic assumption) have been applied in both mass- and infinitesimal doses.

It is worth to highlight that nanoscience and studies on electromagnetic fields are increasingly playing a major role in modern scientific research and countless applications are being developed for medicine. A simple search in PubMed database using search-terms “nanoparticle” + “medicine” results in thousands of scientific studies addressing the use of such infinitesimal particles in biomedical science; the same happens when search-terms are “electromagnetic fields” + “medicine”. This indicates a current awareness of the relationship between the subatomic (non-molecular) world and human health, as well as its possible therapeutic use.

Coming back to homeopathy, it is worth to understand how infinitesimal doses first emerged in its therapeutic horizon. Initially aiming at avoiding the “intoxication” and “aggravation” that medicinal substances applied according to the principle of similitude could cause in patients, Hahnemann proposed a pharmacotechnical method to prepare homeopathic medicines (“dynamization”), whereupon substances were serially diluted and agitated. In this way, it was sought to “diminish their primary pathogenetic effect”. A

posteriori it was observed that such infinitesimal and “imponderable” preparations were able to mobilize the biological and psychological activity of the several spheres of human individuals.

“The homoeopathic system of medicine develops for its special use, to a hitherto unheard-of degree, the inner medicinal powers of the crude substances by means of a process peculiar to it and which has hitherto never been tried, whereby only they all become immeasurably and penetratingly efficacious and remedial, *even those that in the crude state give no evidence of the slightest medicinal power on the human body*. This remarkable change in the qualities of natural bodies develops the latent, hitherto unperceived, as if slumbering hidden, dynamic powers which influence the life principle, change the well-being of animal life. This is effected by mechanical action upon their smallest particles by means of rubbing and shaking and *through the addition of an indifferent substance, dry of fluid, are separated from each other*. This process is called *dynamizing, potentizing* (development of medicinal power) and the products are dynamizations or potencies in different degrees.” (*Organon of medicine*, §269) [9]

Shortly, the pharmacotechnical method of dynamization (Hahnemann’s centesimal method, cH) consists in serial centesimal (1:100) dilutions of the source-substance together with agitation – 100 vigorous beatings (“succussion”) at each step, as follows:

- ✓ 1 part of source-substance (plant, animal or mineral) + 99 parts of water \Rightarrow 100 succussions \Rightarrow 1cH (10^{-2} mols);
- ✓ 1 part of 1cH + 99 parts de water \Rightarrow 100 succussions \Rightarrow 2cH (10^{-4} mols);
- ✓ 1 part of 2cH + 99 parts of water \Rightarrow 100 succussions \Rightarrow 3cH (10^{-6} mols);
- ✓ 1 part of 3cH + 99 parts of water \Rightarrow 100 succussions \Rightarrow 4cH (10^{-8} mols); etc.
- ✓ 12cH \Rightarrow 10^{-24} mole of source matter (Avogadro’s number: $6.02 \cdot 10^{23} = 1\text{mol}$) \Rightarrow lack of matter (“imponderable”).

The ability of the “medicinal information” contained in the infinitesimal doses of high diluted substances - analogously to mass-doses (independently of their application according to the principle of therapeutic similitude) - to promote alterations in biological systems has been researched and confirmed by several scientific studies in both physical-chemical and biological models.

- ***Physical-chemical research models***

Some hypotheses grounded on physical-chemical experimental models seek a scientific explanation for the transmission of the *information about the primary effects of substances* through infinitesimal doses. Among them, it can be mentioned researches focusing on the electromagnetic alterations of water according to “quantum electrodynamics” where matter is not seen as an inert agglomeration of molecules but as a dynamic environment able to choose and catalyze molecular reactions according to the different electromagnetic fields occurring within them.

Through mathematical and experimental models it is suggested that the electromagnetic field of any solute can generate some “stable coherence dominions” in the solvent (with specific structures and vibrations) producing agglomerates or “clusters” of water molecules (with their own size and geometry) as a kind of “electromagnetic signature of the substance in the water” (so-called “memory of water”). Being so, the organization of water would be a coherent, reproducible process associated with far-reaching and extremely low electromagnetic interactions, repeatedly conveying the electromagnetic information of the solute diluted and agitated through the process of homeopathic dynamization [26-29].

Quoting from scientific studies in this field, low-temperature thermoluminescence has been employed in the attempt to understand the special structure of high dilutions. After freezing liquid nitrogen (77°K), ultradilutions of different substances activated by γ -rays irradiated the same thermoluminescence spectrum than the source-substances in mass-doses [30-33].

Focusing on research conducted in Brazil, studies carried out at the Chemistry Institute of State University of Campinas (UNICAMP) [34] and the Physics Institute of University of São Paulo (USP) [35] among others were able to evidence such “memory of water” in several physical-chemical models and with different applications.

Recent studies using ultra-sensitive methods (transmission electronic microscopy, electron diffraction and atomic emission spectroscopy) showed the presence of nanoparticles in homeopathic high dilutions, suggesting that such infinitesimal particles can be associated with the activity of homeopathic preparations [36].

- ***Biological research models***

In 1988, a research team chaired by immunologist Jacques Benveniste published in journal *Nature* the results of an *in vitro* study showing the effect of high dilutions of anti-IgE antibodies on the degranulation of basophils [37]. This study was harshly criticized by a *Nature's* team that visited Benveniste's laboratory on the grounds of its theoretical foundations, difficulty to reproduce its results and insufficient methodology [38]. At a later stage, Benveniste's team [39,40] repeated the study using perfected methods and statistical analysis and again concluded for the effect of high dilutions. However, two later studies sought to reproduce the first one but failed to obtain the same results; the authors concluded that the model was difficult to reproduce [41,42].

Following the steps of earlier research [43-54], recent multicentric studies led by orthodox researchers found results similar to Benveniste's, namely that high dilutions of histamine significantly inhibited IgE-induced degranulation of basophils [46-50].

Reproducing Endler's et al. model [51,52] showing the action of high dilutions of thyroxin on the delay of metamorphosis and growth in tadpoles in a series of 4 studies, Guedes et al. [54] performed a similar study at the Department of Pathology of the Medical School of USP confirming the initial results.

Tens of similar studies, described in recent reviews [54-60] were performed in the same vein with different research subjects (cell-lines, plants, animals) showing that high dilutions exhibit the same primary effect (*information*) than the source-substance in the crude state.

- ***Individualized treatment***

According to Hahnemann, a doctor self-defining as a “genuine artist of healing” must be able to recognize what must be healed in each individual case, understand the healing properties of medicines and adjust them qualitatively and quantitatively to the needs of the patient according to the principle of therapeutic similitude.

Approaching the process of becoming ill as a weakening of the normal physiological processes of adjustment and compensation, Hahnemann correlated any internal imbalance to the various individual symptomatic manifestations, using such “totality of symptoms” as the chief criterion to diagnose the “affection of the vital force” (individual predisposition, morbid susceptibility or homeostatic imbalance) and to prescribe the homeopathic medicine more similar to the ill individual:

“[...] the totality of these its symptoms, of this outwardly reflected picture of the internal essence of the disease, that is, of the affection of the vital force, must be the principal, or the sole means, whereby the disease can make known what remedy it requires - the only thing that can determine the choice of the most appropriate remedy - and thus, in a word, the totality of the symptoms must be the principal, indeed the only thing the physician has to take note of in every case of disease and to remove by means of his art, in order that it shall be cured and transformed into health.” (*Organon of medicine* §7) [9]

From the set of patent signs and symptoms, homeopathic semiology emphasizes the “more striking, singular, uncommon and peculiar (characteristic)” of each case (idiosyncratic), while dismissing common, generic and indefinite symptoms as lacking inherent individualizing power:

“In this search for a homoeopathic specific remedy, that is to say, in this comparison of the collective symptoms of the natural disease with the list of symptoms of known medicines, in order to find among these an artificial morbific agent corresponding by similarity to the disease to be cured, the more *striking, singular, uncommon and peculiar* (characteristic) signs and symptoms of the case of disease are chiefly and most solely to be kept in view; for it is more particularly these that *very similar ones in the list of symptoms of the selected medicine must correspond to*, in order to constitute it the most suitable for effecting the cure. The more general and undefined symptoms: loss of appetite, headache, debility, restless sleep, discomfort, and so forth, demand but little attention when of that vague and indefinite character, if they cannot be more accurately described, as symptoms of such a general nature are observed in almost every disease and from almost every drug.” (*Organon of medicine*, §153) [9]

According to Hahnemann, the totality of characteristic and peculiar symptoms could never be as complete as to point to the most indicated remedy without also including mental and psychological features, according to the importance and complexity of individualization required for the success of homeopathic treatment in any kind of disease:

“We shall, therefore, never be able to cure conformably to nature - that is to say, homoeopathically - if we do not, in every case of disease, even in such as are acute, observe, along with the other symptoms, those relating to the changes in the state of the mind and disposition, and if we do not select, for the patient's relief, from among the medicines a disease-force which, in addition to the similarity of its other symptoms to those of the disease, is also capable of producing a similar state of the disposition and mind.” (*Organon of medicine*, §213) [9]

Associating individualization of medicines with the prescription of “*one single, simple* medicinal substance at one time”, Hahnemann proved to be adamantly against the simultaneous use of more than one homeopathic medicine (a premise dismissed by many homeopaths) on the grounds that HPTs had been carried out with single and simple substances thus criticizing the use of compound means (mixtures of medicines or so-called homeopathic complexes) without first subjecting them to HPT:

“In no case under treatment it is *necessary and therefore not permissible* to administer to a patient more than *one single, simple* medicinal substance at one time. It is inconceivable how the slightest doubt could exist as to whether it was more consistent with nature and more rational to prescribe a *single, simple* medicine at one time in a disease or a mixture of several differently acting drugs. It is absolutely not allowed in homoeopathy, the one true, simple and natural art of healing, to give the patient *at one time* two different medicinal substances.” (*Organon of medicine*, §273) [9]

“As the true physician finds in simple medicines, administered singly and uncombined, all that he can possibly desire [...] he will, mindful of the wise maxim that *it is wrong to attempt to employ complex means when simple means suffice*, never think of giving as a remedy any but a single, simple medicinal substance;

for these reasons also, because even though the simple medicines were thoroughly proved with respect to their pure peculiar effects on the unimpaired healthy state of man, it is yet impossible to foresee how two and more medicinal substances might, when compounded, hinder and alter each other's actions on the human body [...]" (*Organon of medicine* §274) [9]

In this way, the efficacy and effectiveness of a single and individualized homeopathic medicine for a given clinical condition are directly related to their concomitant power of action on the psycho-emotional and organic disorders of each ill individual as well as on other general features not directly related to the specific disturb.

To summarize, a proper homeopathic treatment prioritizes the individualization of a single medicine according to the most peculiar and characteristic signs and symptoms of patients encompassing different semiologic fields (mental, general and physical). In this way, for a same disease, different individuals may be prescribed different single medicines at different times as a function of their singular pattern of susceptibilities (physical, psychical, emotional, dietary, climatic, etc.).

It must be highlighted that this *process of individualization of medicines requires a variable period of regular follow-up* when the responses to different medicinal hypotheses (individualized single medicines) are successively assessed and medicines, doses, and dilutions are progressively adjusted to the idiosyncratic aspects of the patient. Until reaching the ideal medicine ("*simillimum*"), discontinuation of allo-enantiopathic medicines currently used by the patient – whenever indispensable for the equilibrium of organic vital functions – must be ruled by ethical and safety criteria in order to avoid iatrogenic effects due to the possible lack of homeopathic therapeutic action [61].

Clinical Research in Homeopathy

- *General overview*

As a function of the singular features of the homeopathic epistemological model, which makes it an *individualizing therapeutic approach par excellence*, it is easy to anticipate the difficulties met when attempting to design clinical trials on the grounds of the current scientific methods.

In a first meta-analysis, published in the *British Medical Journal*, Kleijnen et al. [62] reviewed the methodological quality of 107 homeopathic randomized controlled trial (RCTs) and concluded that only 22 (20%) of them had satisfactory methodological quality (minimum score 55/100). From these 22 studies, 15 (68%) showed significant efficacy of homeopathic treatment versus placebo. This allowed the authors to conclude that evidence was positive, albeit insufficient to draw definitive conclusions.

Analogously, in a meta-analysis published in *The Lancet* in 1997, Linde et al. [63] reviewed systematically 89 homeopathic RCTs and concluded that the results observed were not placebo-effect (results with homeopathy were 2.45 times better than placebo). However, since the number of RCTs for a same clinical condition was too small, the authors grouped together different kinds of studies and this was the ground for later criticism.

As mentioned above, some essential requirements must be fulfilled for homeopathic treatment to accomplish its desirable results. In particular, *individualization of medicines according to the totality of characteristic symptoms of patients* is a *sine qua non* condition and must mandatorily be included in the design of epistemologically valid studies. Again, this means that for a same disease, each patient might be prescribed a different medicine, since by principle there are no "specific medicines for specific clinical conditions" [64,65].

Several RCTs that *did not fulfill this requirement* but prescribed the same medicine to all patients complaining from a same disease failed to show significant outcomes. An exemplary instance is a study using

Arnica montana indiscriminately in inflammatory processes [6]. Conversely, a meta-analysis seeking to assess the efficacy of 32 RCTs studies, of variable methodological quality that prioritized individualization as the gold-standard of *homeopathic clinical epidemiology*, indicated that individualized homeopathy is significantly more effective than placebo [67].

In a critical review of homeopathic RCTs published in *Annals of Internal Medicine*, Jonas et al. [68] reported that clinical and laboratory studies showed results that challenge current scientific reason. These authors highlighted the three systematic reviews mentioned above [62,63,67] as the ones employing evaluation methods fit for homeopathy and that reported better outcomes with homeopathy versus placebo. Dismissing meta-analyses with questionable methods or that dismissed the intrinsic particularities of the homeopathic model [66,69,70] the authors stressed the scientific evidence for the efficacy of homeopathic treatment in allergy [71,72] and infantile diarrhea [73], whilst they failed to find satisfactory outcomes in RCTs evaluating homeopathy in the prevention of headache [74] and influenza [75]. While discussing the lack of conclusive evidence to judge on the efficacy of homeopathic treatment, they insist on that it deserves an unbiased opportunity to prove its value through evidence-based criteria.

Some isolated RCTs showed the efficacy of individualized homeopathic treatment in migraine [76], fibromyalgia [77], attention deficit hyperactivity disorder [78,79], prevention of infections of the upper airway [80], and so forth.

As an individualized and globalizing therapeutic approach, homeopathy can bring efficacy and safety into conventional medicine, with both healing and prophylactic actions, diminishing thus both the manifestation of symptoms and the predisposition to disease with low costs and minimal side-effects [81-85].

It is worth to highlight that homeopathic semiology seeks to diagnose the several patterns of susceptibility of patients (biological, climatic, dietary, psychological, emotional, etc.) in order to identify the characteristic symptoms that ground the choice of an individualized homeopathic medicine. On the other hand, by stimulating patients to speak about their idiosyncrasies in full detail, it mobilizes unspecific internal processes that by their own can afford relief to many symptoms.

Together with placebo-effect, improvement brought by such *rapport-effect* can make the short-term observation of the specific effect of homeopathic medicines difficult, because they might favor a rise in the number of false-positive results depending on the influentiable characteristics of the sample as also is the case when the duration of treatment is not enough for the homeopathic reaction to attain its plenitude [86,87].

It can be, thus, concluded that the standards to design conventional RCTs meet serious hindrances when applied to the study of homeopathic medicines versus placebo [88,89], which on the other hand demands the inclusion of *epidemiological criteria* agreeing with its epistemological model.

- ***Importance of therapeutic individualization for the clinical efficacy of homeopathy***

The efficacy and effectiveness of homeopathic treatment are directly related to the *degree of similitude* between the totality of the characteristic symptoms of patients and the symptoms elicited by medicines in HPTs.

Since homeopathy employs high diluted simple substances with infinitesimal power of primary action – opposite to the mass-doses with powerful pathogenetic action and significant side-effects of conventional therapeutics – the symptoms of the single properly chosen medicine must show high similarity with the most peculiar and idiosyncratic characteristic of the patient so that the “imponderable” primary effect of the dynamized medicine might awaken the needed vital or homeostatic reaction through the principle of therapeutic similitude.

For this and other motives, Hahnemann and all his followers emphasize the requisite of individualization of medicines and the use of single and simple medicines (*single individualized medicine*) in homeopathic clinical practice and to apply the principle of therapeutic similarity between the totality of characteristic symptoms of patients and the pathogenetic manifestations of the single and simple substances that were tested on human beings, whilst it is criticized the use of compound means (mixtures of medicines or *homeopathic complexes*) not previously subjected to HPT.

With the explicit goal of studying the putative relationship between the clinical effects of homeopathic treatment and placebo-effect, Shang et al. [90] performed a comparative study between homeopathic and conventional RCTs, which was published by *The Lancet* in 2005. Matching 110 homeopathic RCTs and 110 conventional RCTs for the same disease and the same type of effect (specific effects), the authors classified these studies according to the *classical criteria of methodological quality* (number of participants, methods of randomization, use of double-blinding, type of publication, estimation of odds-ratio, etc.), used meta-regression in statistical analysis and assessed how bias or systematic error in the performance and description of studies could interfere the final interpretation of outcomes.

After a first and general analysis of all studies thus surveyed – most having low methodological quality – the authors observed that both homeopathy and conventional medicine were effective when compared to placebo, analogously to the results of the meta-analysis published by *The Lancet* in 1997 [63]. However, when systematic error was prioritized and only studies with *high methodological quality* were selected for analysis *according to the number of participants* (“8 homeopathic clinical studies” versus “six conventional clinical studies”) outcomes showed weak evidence for the specific effect of homeopathic medicines (OR 0.88; IC 95% 0.65-1.19) and strong evidence for the specific effects of conventional intervention (OR 0.58; IC 95% 0.39-0.85). Starting from the prejudiced assumption that the specific effects of homeopathic high dilutions are “implausible” – due to the difficulty to explain them according to the criteria of dose-dependent pharmacology – the authors concluded that the clinical effects of homeopathy are placebo-effects.

In studies seeking to compare the efficacy of different medical approaches, as is the case of homeopathy and conventional medicine, clinical epidemiology rules that the criteria of methodological quality specific to each one must be included as basic premises in their design and performance in order for research to reproduce clinical reality (*effectiveness or external validity*). In this way, homeopathic clinical trials ought to prioritize as *high methodological quality criteria* the following premises: individualization in the choice of medicines, doses and dilutions; duration of study sufficient to adjust treatment to the complex individuality of each patient; evaluation of the global and dynamic response to treatment through specific instruments (quali-quantitative analysis) and so forth.

However, in Shang et al.’s [90] meta-analysis, these *homeopathic criteria of high methodological quality were dismissed*, since only 16% of the homeopathic studies initially selected and none of the 8 studies with higher methodological quality selected for the second phase of analysis *complied with the requirement of individualization in the choice of the medicine*, namely the chief premise of the homeopathic model. This represents a too high level of bias or systematic error regarding the epistemological assumptions of homeopathy. Most homeopathic RCTs selected showed designs unfit to an approach grounded on individualization but employed the same remedy (44%) or mixture of medicines (32%) for a clinical complaint common to all patients.

Due to the limitations shown [91], it is patent that such study as well as the editorial (“The end of homeopathy”) and two further critical papers all published in the same issue of *The Lancet* had the explicit purpose of discrediting homeopathy [92]. Despite Shang et al.’s biased study was severely criticized by researchers and epidemiologists [93-95] and disregarded the epistemological model of homeopathy, it has been quoted as an example of the inefficacy of homeopathy.

However, this example illustrates the utmost care that must be devoted to the design of homeopathic clinical trials so that they comply with the scientific rationale of its model and the true possibilities and limitations of its application to the treatment of different human diseases can be assessed.

In order to improve the design of homeopathic RCTs, in 2009 this author suggested a model of homeopathic mixed clinical trial (RCT followed by long-term open trial, with quali-quantitative evaluations in all phases of the study) [96]. In this way, it was sought a conciliation between clinical epidemiology and the particular premises of homeopathy in order to offer an alternative to dogmatic crystallization, stimulate creativity and approximate the horizons of homeopathy and conventional medicine.

Conclusion

Since it is grounded on assumptions differing from the traditional scientific ones, the homeopathic model is a victim of atrocious criticism by people ignorant of its rationale. Through the media or coming from colleagues, homeopathic practitioners are used to hear expressions such as “the assumptions of homeopathy are pseudoscientific”, “there is no reliable scientific evidence proving the efficacy of homeopathic treatment of diseases”, “people using homeopathic remedies will never carry out scientific studies”, etc.

In order to inform doctors unacquainted with the particularities of the homeopathic model, this article elaborates on its assumptions and clinical applications and draws parallels with contemporary science so that by speaking the same language, homeopathy and conventional medicine might be approximated.

To attain a desirable level of evidence, with an increase in the scientific production of homeopathy, new laboratory and clinical studies are needed. At the same time, it is required from the scientific and academic milieus an impartial and unbiased attitude allowing for homeopathic researchers duly permeated by scientific spirit to have an opportunity to carry out their projects.

On the other hand, it is the task of the homeopath, namely the one acquainted with this important therapeutic treasure, to divest him or herself from any trace of contra-cultural mentality and participate more actively in the diffusion and expansion of homeopathy, through projects in the field of health-care, learning and research in order for information to dissolve the centuries-old barrier separating professional brethren devoted to afford relief to the suffering of the same patients.

In the case of projects in basic research, many tests must be carried out with a given substance (high dilution) in order to adjust the design of studies, since homeopathic “information” must be adjusted to the patterns of sensibility individualizing the species under study (animal, plant, cell-lines, etc.) according to multiple criteria (individualization of the dilution of the medicine, of the duration of treatment and response, and so forth).

Regarding clinical trials, they must include both the assumptions of modern clinical epidemiology and the epistemological particularities of the homeopathic model (individualization in the choice of the medicine, duration of treatment sufficient to adjust it to each individual complexity, etc).

In this way, we will be able to minimize prejudiced attitudes currently making dialog and understanding difficult between both medical approaches that conversely, ought to work together for the sake of the treatment of the countless human diseases.

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Evidência científica do modelo epistemológico homeopático

RESUMO

A Homeopatia é baseada em princípios e em um sistema de conhecimentos diferentes daqueles que suportam o modelo biomédico convencional. Este conflito epistemológico é a principal justificativa para a dificuldade em aceitá-la, com base no raciocínio científico predominante. Para legitimar a Homeopatia de acordo com tais padrões, devemos realizar pesquisas que validem seus conceitos básicos: o princípio da similitude terapêutica, experimentação de medicamentos em indivíduos sadios, prescrições individualizadas e o uso de altas diluições. Da mesma forma, a pesquisa básica deve fornecer dados experimentais e modelos teóricos capazes de lidar com os princípios homeopáticos, enquanto a experimentação clínica deve confirmar a eficácia e efetividade da Homeopatia no tratamento das doenças. Este artigo discute o modelo epistemológico da Homeopatia, justificando seus princípios básicos com dados experimentais extraídos de diferentes áreas de pesquisa e referendando seu uso terapêutico em resultados de ensaios clínicos. Neste contexto, o princípio da individualização do tratamento é uma condição *sine qua non* para operacionalizar a similitude terapêutica e, conseqüentemente, para o tratamento homeopático exibir eficácia e efetividade clínica.

Palavras-chave: Fundamentos da homeopatia; Ensino médico; Leis de similitude; Ação farmacodinâmica de medicamentos homeopáticos; Pesquisa biomédica.

Evidencia científica del modelo epistemológico homeopático

RESUMEN

La Homeopatía esta basada en principios y en un sistema de conocimientos diferentes de aquellos que soporta el modelo biomédico convencional. Este conflicto epistemológico es la principal justificativa para la dificultad en aceptarla, con base en el raciocinio científico predominante. Para legitimar la Homeopatía de acuerdo con tales padrones, debemos realizar investigaciones que validen sus conceptos básicos: el principio de la similitud terapéutica, la experimentación de medicamentos en individuos sanos, prescripciones individualizadas y el uso de altas diluciones. De la misma forma, la investigación básica debe fornecer datos experimentales y modelos teóricos capaces de contemplar los principios homeopáticos, entre tanto la experimentación clinica debe confirmar la eficacia y efectividad de la homeopatía en el tratamiento de las enfermedades. Este artículo discute el modelo epistemológico de la homeopatía, justificando sus principios básicos con datos experimentales extraidos de diferentes areas de investigación y respaldando su uso terapéutico con base en resultados de ensayos clinicos. En este contexto el principio de la individualización del tratamiento es una condición *sine qua non* para operacionalizar la similitud terapéutica y conseqüentemente para el tratamiento homeopático exibir eficacia y efectividad clinicas.

Palabras-llave: Fundamentos de la homeopatía; Enseñanza médica; Leyes de similitud; Acción farmacodinámica de medicamentos homeopáticos; Investigación biomédica.



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