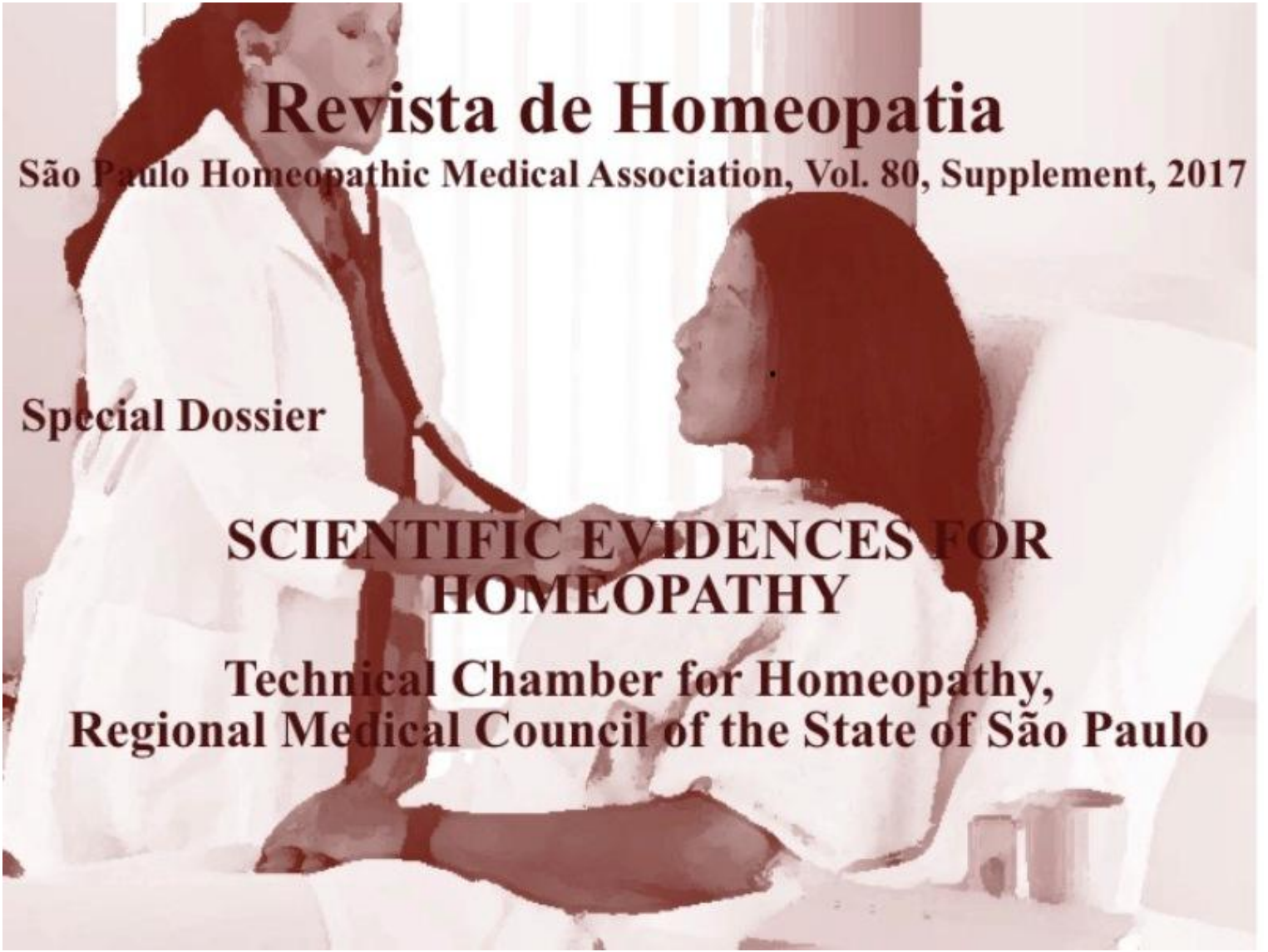

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Special Dossier

SCIENTIFIC EVIDENCES FOR HOMEOPATHY

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Special dossier: scientific evidences for homeopathy

EDITORIAL

To those who demand scientific evidences for homeopathy

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Guest Editor, Special Dossier: Scientific Evidences for Homeopathy

Upon discussing homeopathy in various settings, we often find that people react with mistrust, and raise doubts on its scientific grounds and therapeutic validity. Widely disseminated in the mass media, in an indistinct and reiterated manner, the fallacy – or post-truth – asserting "there are no scientific evidences for homeopathy" is incorporated into the collective subconscious, thus serving as strategy to increase prejudice and radicalize postures against this bicentennial medical approach.

A fruit of disinformation, or of negation of the studies that ground the homeopathic paradigm on many scientific fields, prejudice is once and again fed by unfavorable pieces published in the mass media and social networks, which, in turn, very seldom divulgate studies with results favorable to homeopathy.

To elucidate doctors and society at large in this regard and to demystify culturally rooted dogmatic attitudes, the Technical Chamber for Homeopathy, Regional Medical Council of the State of São Paulo (CREMESP), prepared Special Dossier, "Scientific Evidences for Homeopathy". This project had the support of Brazilian Homeopathic Medical Association (AMHB) and São Paulo Homeopathic Medical Association (APH) via divulgation in its scientific journal, *Revista de Homeopatia*.

In addition to describing the global situation of homeopathy as a medical specialty and its inclusion in the curricula of medical schools, the dossier further includes reviews on research lines that provide grounds to the homeopathic assumptions, to wit: therapeutic similitude, homeopathic pathogenetic trials, serial and agitated dilutions (high dilutions – HDs), and individualization based on the set of characteristic symptoms exhibited by patient/disease. Similarly, the efficacy and safety of homeopathic treatment are demonstrated in randomized, placebo-controlled clinical trials, systematic reviews and meta-analyses.

The dossier begins by a review entitled "Homeopathy: a brief description of this medical specialty", which discusses historical, social and political aspects of the institutionalization of homeopathy in Brazil and its inclusion in health care systems. It further describes the reasons for patients to seek this therapeutic approach.

The review on "Medical education in non-conventional therapeutics in the world (homeopathy an acupuncture)" highlights the relevance of the inclusion of homeopathy and acupuncture in the curriculum of medical schools in many countries around the world. Such inclusion – actualized through various modalities specific for undergraduate and graduate students, medical residents and practicing doctors - is a

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result of the increasing interest of patients, leading to a similar interest among doctors to learn about such medical approaches.

Aiming at providing scientific grounds to the therapeutic similitude principle through systematic study of the rebound effect of modern drugs, the review entitled "Scientific basis of the homeopathic healing principle in modern pharmacology" discusses hundreds of studies published in high-impact scientific journals which demonstrate a conceptual and phenomenological similarity between rebound effect and the vital reaction (or secondary action) homeopathic treatment elicits. To broaden the implications of such similarity, the author describes the use of modern drugs according to the therapeutic similitude principle, leading to the application of the rebound effect (paradoxical reaction of the body) with curative intention.

To account for the plausibility of the homeopathic use of HDs, the present dossier includes three reviews that describe the advances made in fundamental research along the past decades: "The soundness of homeopathic fundamental research", "Effects of homeopathic high dilutions on *in vitro* models: literature review", and "Effects of homeopathic high dilutions on plants: literature review". These reviews discuss hundreds of experiments and dozens of lines of research that together demonstrate the effects of HDs in physical-chemical and biological models (*in vitro*, plants and animals).

Showing that the positive effects of homeopathic treatment are not mere placebo effect, as it is widely advertised, review "Clinical research in homeopathy: systematic reviews and randomized clinical trials" describes positive results found in dozens of homeopathic placebo-controlled clinical trials targeting variable clinical conditions, as well as systematic reviews and meta-analyses. These results are particularly illustrated by 2 clinical trials conducted at prestigious Brazilian research institutions: "Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: a 24-week, randomized, double-blind, placebo-controlled study" and "Randomized, double-blind trial on the efficacy of homeopathic treatment in children with recurrent tonsillitis".

As concerns the safety of homeopathic treatment, the review entitled "Do homeopathic medicines cause drug-dependent adverse effects or aggravation?" demonstrates, through an analysis of placebo-controlled clinical trials, that although mild and transient, homeopathic medicines cause more adverse effects compared to placebo.

The final review, "Do homeopathic medicines induce symptoms in apparently healthy volunteers? The Brazilian contribution to the debate on homeopathic pathogenetic trials" discusses the historical development and state of the art in homeopathic pathogenetic experimentation. These experiments are conducted to establish the curative properties of drugs (pathogenetic effects on health individuals) that ground the application of the therapeutic similitude principle.

Despite the ongoing difficulties and limitations opposing the development of research in homeopathy – partly due to methodological aspects, and partly to lack of institutional and financial support – the experimental and clinical studies described in this dossier, which ground the homeopathic assumptions and confirm the efficacy and safety of this approach to therapeutics – provide unquestionable proof for the "availability of scientific evidences for homeopathy", against the false and prejudiced opinion that is widely divulgated. Nevertheless, further studies are still needed to

improve clinical practice and elucidate some aspects peculiar to the homeopathic paradigm.

With the divulgation of the present dossier, prepared with the support of Technical Chamber for Homeopathy, CREMESP, we hope to dispel doubts and sensitize our colleagues as to the validity and relevance of homeopathy as adjuvant treatment complementary to all other medical specialties according to ethical and safe principles. Our overall goals are to broaden the understanding of human disease, increase the therapeutic resources, contribute to the definition and effectiveness of medicine in chronic diseases, minimize the adverse effects of modern drugs and strengthen the patient-doctor relationship, among other aspects. In this way, we will be able to work together, since "The physician's high and only mission is to restore the sick to health, to cure, as it is termed (Samuel Hahnemann, *Organon of medicine,* § 1).

Homeopathy: a brief description of this medical specialty

Marcelo Pustiglione[1]; Eduardo Goldenstein[2]; Y. Moisés Chencinski[3].

Abstract

Homeopathy is a medical approach with 200 years of history. Along this time it demonstrated its ability to solve problems, with low cost, broad scope and unquestionable social acceptance. According to estimates, approximately 500 million people use homeopathy worldwide, corresponding to about 7% of the world population. However, there are still hindrances to its integration into conventional medicine which need to be put into perspective and removed. The aim of the present article is to contextualize homeopathy as a science and an art in Brazil and worldwide. We analyzed some relevant aspects, such as the profile of users, their reasons to choose homeopathy, and historical and social contexts for the inclusion of homeopathy into health care and educational systems. We conclude that homeopathy is an ethical medical system that provides systemic and safe treatment to patients with optimal cost-benefit ratio. Homeopathy should be included in universities, schools of medicine and at all levels of the healthcare system, thus ensuring its historical nature as a medical specialty.

Keywords

Homeopathy; Medicine; Clinical medicine; Health care

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Introduction

For many decades now the World Health Organization (WHO) has supported the inclusion of so-called "alternative therapeutic practices" to health systems. Such practices are designated as "traditional and complementary medicine" (T&CM). Relative to T&CM, WHO - the mission of which is to "help save lives and improve health" - seeks to facilitate their inclusion in health services, prepares guidelines, stimulates "clinical research on safety and efficacy" and acts as "coordination center to facilitate the exchange of information" [1].

In her lecture at International Conference on T&CM (Delhi, India, February 2013), Dr. Margaret Chan, then WHO Director-General, explained why such approaches are considered a relevant component of health systems. According to her, users of health services worldwide exhibit increasing interest in T&CM, for which reason the latter came to play a relevant role in the economic development of some countries by reducing the expenses with health. In addition, much advance was made in research in this field. These facts led WHO to infer the need of "more thorough integration" of T&CM with health services, for which purpose regulatory agencies and health system users ought to discuss how it might be achieved [1].

As concerns the integration of T&CM into mainstream medicine, Chan stated, "The two systems of traditional and Western medicine need not clash. Within the context of primary health care, they can blend together in a beneficial harmony, using the best features of each system, and compensating for some weaknesses in each. This is not something that will happen all by itself. Deliberate policy decisions have to be made. But it can be done successfully" [1].

Homeopathy is traditionally included within T&CM, while characterized as the one closest to Western clinical practice, whence its considerable social and institutional relevance. Homeopathy is a bicentennial medical approach formulated and developed by the German doctor Samuel Hahnemann (Meissen, 10 April 1755 – Paris, 2 July 1843). It stands out for its effectiveness, low cost, broad scope and indisputable social acceptance [2-10].

From 1796, when it began to be practiced in Saxony, to this day, i.e., along 220 years, the resulting accumulated experience shows that homeopathy has potential to improve the health of people, not only with lower cost compared to mainstream medicine, but also, and more especially, without adverse side effects [5].

We believe that delving into the theoretical and practical foundations of homeopathy will show that it might be characterized as an ethical medicine system that provides systemic and safe care to the sick with optimal cost-benefit ratio. Upon prescribing the best treatment for each individual case and particular moment of the progression of disease (individualized treatment), homeopathic doctors fully comply with bioethical principles beneficence and nonmaleficence. By providing patients and their relatives/guardians information about all the aspects related to treatment (power sharing), they also comply with the principle of autonomy. Finally, inclusion of homeopathic care in all primary care services will comply with the principles of universality and justice [11].

Adequate implantation of homeopathy in national health systems will provide the sick access to this therapeutic option. On a case-by-case basis, it might represent the single treatment or be used in an integrated and complementary manner to other modalities of treatment.

Experience shows that integration between homeopathy and mainstream medicine is extremely useful for the promotion of health, as well as for the treatment of patients with chronic diseases [12]. In addition, it might contribute to the treatment of acute diseases [12]. Nevertheless, one cannot deny there are still problems in the harmonization of these two therapeutic approaches, which need to be duly put into perspective and solved.

All difficulties and adverse propaganda notwithstanding, about 500 million people are estimated to currently use homeopathy as therapeutic option worldwide [12]. This corresponds to about 7% of the world population (about 7.3 billion people in July 2016) [13].

Increase in the demand for homeopathic care in many countries [12] led to the need to expand education in this field. Homeopathy is partially regulated for the countries included in the European Union; in 6 of them it is already integrated into the health system; in 9 countries medical students are given introductory courses; and in 18 countries graduate studies on homeopathy are officially acknowledged. India is still the leader in educational infrastructure. About 260 universities offer undergraduate courses in homeopathy, and there are about 70 graduate courses [12].

The aim of the present study was to perform a descriptive review of publications reporting on the profile of the individuals who seek homeopathy as therapeutic modality and the reasons for such decision. In addition, we provide a brief description of the inclusion of homeopathy in Brazilian health and educational systems and society at large from its initial arrival to the present time, with emphasis on the State of São Paulo.

Methods

On February 2017 we conducted a literature search for articles rated genuine from the scientific point of view, according to their origin and authorship. The main references we used were *Scientific Framework of Homeopathy - Evidence Based Homeopathy* (2014), by Liga Medicorum Homoeophatica Internationalis (LMHI) [12] and *Homoeopathy: science of gentle healing,* a dossier prepared by a committee appointed by Ministry of AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy), Government of India (2015) [14].

We should observe that in 2014, in partnership with the European Committee for Homeopathy (ECH) and the Central Council for Research in Homeopathy (CCRH, India), and based on previous publications and research presented at its 69th Congress (Paris, July 2014), LMHI prepared a summary of the state of the art in homeopathy. The overall goal of this publication was to demonstrate the scientific grounds of homeopathy and its place in the current global context to improve its global visibility, and more particularly facing the medical community [12]. In 2015, the Government of

India – in which country homeopathy is included in the health, educational and research systems – appointed a committee to prepare a dossier aiming at providing an up-to-date and broad panorama of homeopathy "starting from a brief introduction to the science, to its network, infrastructure and status in various parts of the world, with special emphasis to India" [14]. It should be noticed that the dossier was subjected to peer-review, including Indian and international reviewers from France, United Kingdom, USA, Hungary and Brazil – which was represented by Flávio Dantas and Silvia Waisse.

In addition, we also looked for articles in databases Bireme and SciELO using keywords "homeopathy", "clinical medicine" and "health care delivery" in Portuguese, English and Spanish. Information about institutions (São Paulo Homeopathic Medical Association – APH; Brazilian Homeopathic Medical Association – AMHB; department of Publications, Hahnemannian Institute of Brazil – Dpub-IHB) and other sources were procured at the corresponding official websites. Historical data were gathered from the websites of Oswaldo Cruz Foundation (Fiocruz), University of São Paulo and newspaper *O Globo*. The Brazilian government *Diário Oficial* was accessed online.

The information thus collected was analyzed as per the study aims. Some of the data are described in chronological tables or according to subject as per need.

Results

Our survey located about 150 records, from which we excluded the ones without reliable authorship and repetitions. Therefore 43 publications were selected to serve as sources from the present study. On these grounds we analyzed the profile of homeopathy users and the reasons that led them to seek this approach to treatment. We further provide of a short summary of the status of homeopathy in Brazil, with emphasis on the State of São Paulo.

Profile of homeopathy users

Based on studies published in Europe, India and Brazil [15-27] LMHI's *Scientific Framework of Homeopathy* draws a profile of current homeopathy users. Users are individuals with high educational level, within age range 33 to 55 years old, healthy lifestyle and positive attitude toward homeopathy [12]. In other words, the available data indicate that current homeopathy users are individuals fit to make soundly grounded choices. Indeed, a situation desirable in the choice of any treatment.

Factors that lead ill individuals to seek homeopathic care

The summary prepared by LMHI also reports on the factors related to the choice of homeopathy. Studies mainly conducted in Europe [15,16,18,19,21,23,24,26,28] point to the following determinants: a) concern with the side effects of other therapeutic methods: b) poor outcomes of conventional treatments or desire to avoid long-term use

of such treatments; c) positive experience; d) personal preference or family tradition; e) lower cost; f) overall well-being; g) traditional beliefs on immateriality or holism; h) awareness of the ineffectiveness of antibiotics for viral diseases; and i) mistrust of conventional medicine [12].

Therefore, one might infer that the choice of homeopathy is due, on the one hand, to an increasing perception among users of its virtues as systemic therapeutic approach, in addition to being free from adverse effects and having favorable cost-effectiveness ratio. On the other hand, such choice is also associated to increasing mistrust of conventional medicine [12].

In this regard, CCRH's dossier *Homoeopathy: science of gentle healing* observes, "Tact, sympathy, and understanding are expected from the physician, for the patient is no mere collection of symptoms, signs, disordered functions, damaged organs and disturbed emotions", but the patient "is human, fearful, and hopeful seeking relief, help and reassurance" [14]. These requirements are fully met in homeopathic practice, since its goal "is not only to tackle individual diseases in a person, but to understand the person as a whole and relieve him/her of his/her complaints" [14].

Reinforcing this trend regarding homeopathy as therapeutic choice, CCRH's dossier states that, although the thousands of observations and reports require "pragmatic and randomized control trials (…) Over the years, homeopathic medicines have been used successfully for treatment of various conditions, such as acid peptic diseases, anxiety, atopic dermatitis, autism, behavioral disorders, bone fracture healing, conjunctivitis, chickenpox, depression, dysmenorrhea, headaches, herpes zoster, influenza (…) phobias, renal calculi (…) colic or dentition complaints in children, etc." [14]. The latter report is based on the care provided to about 1.1 million individuals who sought primary care at homeopathic services in Delhi [14]. The authors further assert that homeopathy is used for cancer, HIV/AIDS and terminal conditions to provide palliative care for symptoms and improve the quality of life of patients [14]. As promising news, the authors state that "Studies have generated evidence in favor of homeopathy, even through randomized control trials and meta-analyses in conditions such as diarrhea in children, respiratory tract infections in children 9…) hay fever, menopausal complaints, musculoskeletal diseases, osteoarthritis (…) rhinopharyngitis, rheumatoid arthritis (…)" [14].

Advantages of homeopathy

Following description and rigorous analysis of a wealth of up-to-date sources including fundamental research, clinical trials and literature reviews, CCRH's dossier concludes that the advantages of homeopathic treatment are due to the fact that: (a) it is "safe, effective and based upon natural substances"; (b) since it uses "simple substances in micro-doses, medicines are not associated with any toxicological effect and can be safely used for pregnant women and lactating mothers, infants and children and in the geriatric population"; (c) in infections, "instead of having a direct action on the microorganisms, [medicines] act on the human system (self-protective) to fight [the] disease process. As such, no microbial resistance is known to develop against homeopathic drugs"; (d) "The mode of administration of medicines is easy. There are no invasive methods and medicines are highly palatable, thereby enhancing their acceptability"; (e) "Lack of diagnosis is not a hindrance for initiating treatment with

homeopathic medicines"; (f) "Individualized approach of treatment is in consonance with increasing need for customized treatment, which is being realized in the modern era"; (g) "Homeopathic remedies are not addictive – once relief occurs, the patient can easily stop taking them"; and (h) "Treatment is comparatively more cost-effective than other therapeutic systems" [14].

Inclusion of homeopathy in the Brazilian health and educational systems and society at large with emphasis on the State of São Paulo

"The history of homeopathy in Brazil (…) extends over more than 150 years, when one considers the valuable contributions of Benoit Jules Mure or Émile Germon's activity, both of whom were French" [29]. Current evidences indicate that such history actually extends over 180 years, based on records describing the homeopathic activity of the Swiss doctor Frederico Jahn, who "as early as 1836 defended a thesis entitled 'Exposition on homeopathic doctrine' at School of Medicine of Rio de Janeiro" [30]. The relevance of this fact cannot be stressed enough, when one considers that Jahn defended his thesis only 4 years after the schools of medicine of Rio de Janeiro and Bahia were granted the right to deliver doctoral degrees. In addition, Jahn influenced Dr. Domingos de Azeredo Coutinho de Duque Estrada (1812-1900), who stated that "his first contact with homeopathy was precisely intermediated by Jahn, who provided him the first books to learn about it". Later on, when fighting an epidemic of scarlet fever, Duque Estrada "assumed he was the single homeopath in Rio de Janeiro (…) since Drs. Mure and Lisboa did not yet practice the new doctrine here" [30].

Before entering the history of homeopathy in Brazil, Émile Germon had developed activities in the country as researcher, having been recruited in the early 1820s by José Bonifácio de Andrade e Silva (1763-1838), known as the "father" of Brazilian independence, in addition to naturalist, statesman and poet. Germon returned to Brazil in 1837, now as practicing homeopath [30]. "Germon wrote the first book of homeopathy published in Brazil (*Manual Homeopático*, 1843) based on his personal contact with Hahnemann in Paris, and on his practical experience starting from his return to Brazil in 1837" [29]. These evidences notwithstanding, "the literature unanimously names Benoit Jules Mure (1809-1858) as the introducer of homeopathy in Brazil" [30]. Known in Brazil as Bento Mure, he arrived to Rio de Janeiro in 21 November 1840; this date was selected to celebrate the National Homeopathy Day. Despite the discussions on who truly was the introducer of homeopathy in Brazil, Mure's role in the divulgation of homeopathy and in the creation of clinics for the poor and slaves stand out, to the point he became known as the "people's doctor". In this regard, his partner was the Portuguese-Brazilian surgeon João Vicente Martins (1808-1854). The first Brazilian homeopathic pharmacy, *Botica Homeopática Central*, was established in Rio de Janeiro in 1843 [29-31].

Homeopathy is considered a medical practice in Brazil since the end of the 19th century, being mentioned in the Imperial Decree no. 9,554, from 3 February 1886, which supported the official recognition of homeopathic pharmacies [32].

By that time, physicians were congregated in the Medicine and Surgery Society, created in 1829, which was a partner of the government in the establishment of health legislation and in the fight against disease [33]. The Society represented both specialties: 'medicine', which comprised the allopathic practitioners (who used

cupping, bleeding, cathartics, emetics, expectorants, exfoliative and exutory agents, among others), and 'surgery', which included surgeons and midwives. Eleven years later homeopathy emerged as a 'third approach', and thus might be considered as one of the oldest medical specialties in Brazil. According to Alencastro: "Two out of the five doctors who practiced in Campinas in 1857 were homeopaths" [29]. In 1886, Pedro Ernesto Albuquerque de Oliveira published the first printed medical book in São Paulo, to wit, *Da Febre Typhoide e Enfermidades Sobrevientes no Brasil e seu Tratamento Homeopático* (On typhoid fever and surviving diseases in Brazil and their homeopathic treatment) [29].

Ever since that time, through regional associations, homeopathic doctors have actively participated in the training of medical specialists, as well as of the earliest homeopathic pharmacists, dentists and veterinary doctors.

The newly arrived homeopathy had almost immediate impact on the Brazilian society in the second half of the 19th century. This fact is evidenced in the Brazilian literature. In chapter 13 ("Four in a meeting") of his novel *A Moreninha* (The little dark-skin girl), published in 1844 (the same year its author graduated in medicine, a profession he never practiced), Joaquim Manuel de Macedo (1820-1882) describes a discussion among 4 medicine students as to which approach, allopathy or homeopathy, ought to be used to treat a housemaid who had drank more than she should have [34]. Similar examples might be also found at the beginning of the 20th century. For instance, the one of José Bento Monteiro Lobato (1882-1948), the main Brazilian author of children books, being *O Sítio do Pica-pau Amarelo* (The yellow woodpecker's farm, 1920-47) his most famous work. A lawyer and social critic, Monteiro Lobato approached the issue of the cost-benefit ratio in a letter written in 1912 to a friend, Moura Rangel, in which he describes the difference in the cost of conventional and homeopathic medicines for the treatment of his child, who had atrophic rhinitis. "He [was] cured of everything (…) of rhinitis (…) of the ear [problem} (…)" after taking a few doses of *Mercurius*, followed by one dose of *Sulphur*, (…) cost of the cure: one thousand reales [in present day values, about USD 15] (…) As concerns allopathy, in exchange for no cure: trips to São Paulo, inflating drugs, inflating device and hopelessness" [35].

In São Paulo, "(…) Drs. Alberto Seabra, Murtinho Nobre, Afonso Azevedo, Militão Pacheco and Leopoldo Ramos established (…) the São Paulo Homeopathic Dispensary (…) devoted to free homeopathic care" in 1909" [36].

In 1912, the Hahnemannian School was established at Hahnemannian Institute of Brazil (IHB), including a "medical course according to the contemporary standards, which trains doctors fit to practice both systems (allopathy and homeopathy" [37]. A Hahnemannian Hospital was established in 1916.

On 25 September 1918, Legislative Decree no. 3,540 granted IHB the right to "certificate homeopathic physicians" [29]. Therefore, recognition of homeopathy as medical practice and the training of specialists will commemorate 100 years in 2018.

Presided by the homeopathic physician and university professor, José E. Galhardo, the First Brazilian Homeopathic Congress was held in Rio de Janeiro in 1926. The 36th edition of this national event – biannual since the 1970s - will take place in Curitiba in 2018, thus completing 98 years of history [38].

Table 1. A brief summary of the 90 years of history of the Brazilian Homeopathic Congress (CBH) [38]

CBH	Year	City	President
I	1926	Rio de Janeiro-RJ	Dr. José Emygdio Rodrigues Galhardo
II	1950	Rio de Janeiro-RJ	Dr. Amaro Azevedo
III	1952[1]	São Paulo-SP	Dr. Alfredo Di Vernieri
IV	1952[1]	Porto Alegre-RS	Dr. David Castro
V	1954	Rio de Janeiro-RJ	Dr. Amaro Azevedo
VI	1957	Salvador-BA	Dr. Murillo Soares da Cunha
VII	1958	Rio de Janeiro-RJ	Dr. Alberto Soares de Meirelles
VII	1959	Porto Alegre-RS	Informação indisponível na literatura
VIII	1961	Curitiba-PR	Dr. Waldomiro Pereira
IX	1962	Rio de Janeiro-RJ	Dr. José Carneiro
X	1965	Rio de Janeiro-RJ	Dr. Jaime Treiger
XI	1966	Rio de Janeiro-RJ	Dr. Mario Magalhães Pecego
XII	1972	São Paulo-SP	Dr. Abrahão Brickmann
XIII	1977[3]	Rio de Janeiro-RJ	Dr. Mario Magalhães Pecego
XIV	1978	São Paulo-SP	Dr. Alfredo Castro
XV	1980[4]	Petrópolis-RJ	Dr. Roberto Andrade da Costa
XVI	1982	Curitiba-PR	Informação indisponível na literatura
XVII	1984	Salvador-BA	Dra. Maria Amélia Soares da Cunha
XVIII	1986	São Paulo-SP	Dr. Waltencir Linhares
XIX	1988	Gramado-RS	Dra. Ângela Augusta Lanner Vieira
XX	1990[4]	Vitória-ES	Dr. Ediron Pinho Carpes
XXI	1992	Belo Horizonte-MG	Dr. José de Schembri
XXII	1994	Curitiba-PR	Dr. Marco Antônio Bessa
XXIII	1996	Campo Grande-MS	Dr. José Roberto Campos de Souza
XXIV	1998	Gramado-RS	Dr. Érico Dorneles
XXV	2000	Rio de Janeiro-RJ	Dr. Francisco Vargas de Oliveira Villela
XXVI	2002	Natal-RN	Dra. Maria Adelaide Guedes Bezerra
XXVII	2004	Brasília-DF	Dr. Divaldo Dias Mançano
XXVIII	2006	Florianópolis-SC	Dra. Paloma Arias
XXIX	2008	São Paulo-SP	Dr. Ariovaldo Ribeiro Filho
XXX	2010	Recife-PE	Dra. Odimariles de Melo Souza Dantas
XXXI	2012	Belo Horizonte-MG	Dr. Mario Cabral
XXXII	2014	São Paulo-SP	Dr. Ariovaldo Ribeiro Filho
XXXIII	2016	Campo Grande-MS	Dr. Luiz Darcy G. Siqueira

[1] According to the available records, 2 CBH (III and IV) were held in one and same year. [2] First National Meeting of Students Interested in Homeopathy (ENEIH). [3] Homeopathy is acknowledged as medical specialty. [4] First exam for board certification in homeopathy (Federal Medical Council/Brazilian Medical Association/Brazilian Homeopathic Medical Association

Six years after the creation of the São Paulo Medical Association (APM), the São Paulo Homeopathic Medical Association (APH) was established on 5 June 1936 with the goal to "divulgate the Hahnemannian doctrine". Thus it is one of the oldest among the associations of medical specialties. In 1970 APH moved to a building of its own [39].

On 8 July 1952, Law no. 1,552, published in 13 July 1952, made the teaching of homeopathic pharmaceutics compelling in all Brazilian schools of pharmacy [40]. In this way the ethical scope of each profession was firmly demarcated: homeopathic clinical-therapeutic practice is an exclusive attribution of physicians, while homeopathic pharmaceutics is exclusive attribution of pharmacists.

In 1976, Decree no. 78,841 approved the "General Part" of the Brazilian Homeopathic Pharmacopoeia [41]. On 4 June 1980, The Federal Medical Council (CFM) Resolution no. 1,000 defined homeopathy as a "**single, indivisible**" medical specialty, and as such "**ought to be practiced by duly qualified physicians**", thus reaffirming the stipulations in Legislative Decree no. 3.540/1918 (emphasis is ours).

CFM Resolution no. 1,000/1980 was ratified by Resolutions no. 1,295/1989 and 1,634/2002 [43} modified by Resolution no. 1,659/2003 [44]. Appendix II was rewritten in CFM Resolution no. 1,763/2005 [45]; the new text was approved by Resolution no. 1,785/2006 [46] being partially modified by Resolution no. 1,970/2011 [47].

Together with the national restructuring of the Brazilian Homeopathic Medical Association (AMHB), and through an agreement with CFM and the Brazilian Medical Association (AMB), AMHB is responsible since 1988 for the evaluation of candidates to board certification in homeopathy. In compliance with the stipulations in CFM Resolution no. 1,000/1980, later ratified, board certification requires 2-year training in courses recognized by the AMHB Council of Teaching Institutions (CEF) under supervision of AMHB Scientific Committee and for Assessment of Courses. Completion of such courses is mandatory for taking the exam required for board certification.

According to *Demografia Médica* jointly published in 2015 by School of Medicine, University of São Paulo, CFM and the Regional Medical Council of the State of São Paulo (CREMESP) [48], homeopathy ranked 26th in number of specialists among 53 listed medical specialties. In 2013, CFM registered 2,458 board certified homeopaths, 455 of whom were pediatricians, being the third most frequent specialty among the latter, following allergy and occupational medicine [43]. About 20% of board certified specialists in family and community medicine are also board certified homeopaths [49].

In 1977, Dr. Anna Kossak was approved in public examination as Senior Lecturer in Homeopathic Clinical Practice, Federal University of the State of Rio de Janeiro (UNIRIO). In 1988 she was appointed head professor.

AMHB, affiliated to AMB, was established in 1979 to represent and support the interests of homeopathic physicians in scientific, ethical, social, economic and legal matters [50]. The Association remains in activity up to the present time, having Dr. Ariovaldo Ribeiro Filho, from São Paulo, as its president for the last two terms.

Systematic research in homeopathy began in Brazil in the 1980s. In this regard, François Lamasson Homeopathic Institute - "under the responsibility of Dr. Izao Carneiro Soares and Dr. Gilberto Pozzeti, then professor at School of Pharmacy of Araraquara, State University of São Paulo (UNESP" [51] – stands out. Also remarkable was the work of "homeopathic investigators who performed academic research on the effectiveness and efficacy of homeopathic treatments along the same period, such as Drs. Marcelo Pustiglione (Civil Servant Hospital of São Paulo) and Mário Sposati (Experimental Health Center of Barra Funda, São Paulo), who had resource to homeopathy programs at public health services as [experimental] field"[51]. In this line, we should also mention "the studies by Matheus Marin, from Campinas, on the nature and efficacy of homeopathic medicines based on physical hypotheses and in contact with investigators from State University of Campinas (UNICAMP" [51].

In 1986, National Institute of Medical Care and Social Security (INAMPS) Resolution no. 112, from 21 January, implemented a "Homeopathy Program". In October that same year, the Regional Health Bureau (ERSA) of Marília, São Paulo, made the first public call for homeopathic doctors to be incorporated into the health care network. Inclusion of homeopathy in public health services across the country made its availability universal to the overall population, independently from factors such as educational level and lifestyle.

In addition to CBH and regional scientific meetings, one further contribution to the development of homeopathy as science and art in Brazil was represented by the National Symposium (and International Meeting) of Institution-based Research in Homeopathy (SINAPIH). Along 20 years (1987-2008), SINAPIH was doubtlessly the most prestigious meeting point for homeopathic investigators in Brazil [52]. Since its inception, the goals of SINAPIH were "to promote the advance of scientific knowledge on homeopathy, identify the field currently covered by homeopathic research, detect and discuss theoretical-methodological issues relevant to research in this field and promote exchange of information among investigators" [52]. Starting from 2nd SINAPIH, 6 main areas were defined, which then characterized the following meetings: (1) socio-historical research, (2) clinical research, (3) laboratory research, (4) pharmacological and pathogenetic research, (5) assessment of health services and (6) training of human resources. Also starting from 2nd SINAPIH onward, foreign researchers participated in meetings, most of them sponsored by their institutions of origin, which is indicative of the relevance of SINAPIH (Table 2).

Table 2. International participants in SINAPIH [52]

Investigators	Field of activity	Institution	Country
Bernard Poitevin	Laboratory research	Institut National de la Santé et de la Recherche Médicale - INSERM	France
Jacques Benveniste*	Immunology and homeopathy		
Madeleine Bastide		Université Montpellier I	
Jacques Imberechts	Clinical research	Homoeopathia Europea	Belgium
Harris Coulter	Socio-historical research	Columbia University	USA
Peter Fisher**	Clinical research	Royal Homoeopathic Hospital of London	United Kingdom
Thomas Genneper	Socio-historical research	Institut für Geschichte der Medizin, Robert Bosch Stiftung	Germany
Francisco Xavier Eizayaga Jr.	Pathogenetic research	School of Medicine, Universidad Maimónides	Argentina

*Author of famous studies, including the article on the so-called "memory of water" [53]; **Physician to the British royal family.

In 1988, Inter-Ministry Committee for Planning and Coordination (CIPLAN) passed Resolution no. 4, which introduced homeopathy in public health services [54]. In 1989, Resolutions CIS/SP 81/89 [55} and SS-90 [56] approved and established general guidelines for homeopathic care delivery at federal and state public health services, including "the integrated health actions" or Unified Health System (SUS). Based on CIPLAN Resolution no. 04/88, ERSA-4, São Paulo, made a public call to hire homeopathic doctors [57].

In 1991, APM Scientific Department of Homeopathy was established, following a survey of the opinions of Paulista doctors, most of whom approved this initiative. The Department continues in operation to this day; its current director is Dr. Sérgio E. Furuta, who also is president of APH. That same year, several doctors were named professors of Homeopathic Clinical Practice, UNIRIO, "the one single school that includes homeopathy in the undergraduate medical curriculum, due to the Hahnemannian origin of the School of Medicine and Surgery" [29]. Such doctors were Flávio Dantas and Helio Teixeira (Minas Gerais), Helio Bergo (Espírito Santo), Ana Tereza Dreux Mariani, Cláudio Araújo, Francisco Caixeta and Antonio Carlos Silva Oliveira (Rio de Janeiro) and Marcelo Pustiglione (São Paulo).

A medical residency program in homeopathy was established in 2004 at Gaffrée & Guinle University Hospital (HUGG), UNIRIO. In 2016, Federal University of Mato Grosso do Sul made a call to start its own residency program. Also other initiatives in the academic milieu are deserving of mention, such as the one developed by Dr. Rubens Dolce Filho at Medical School, Federal University of São Paulo (UNIFESP) and Dr. Marcus Zulian Teixeira, PhD, at School of Medicine, University of São Paulo (FMUSP). Several homeopathic doctors participate in international research groups in Europe and South America, among them Flávio J. Dantas de Oliveira and Silvia Waisse. The Directory of Research Groups, National Council of Scientific and Technological Development (CNPq) lists 24 homeopathic research groups [58].

On 3 May 2006, Health Ministry Ruling no. 971 included homeopathy in SUS National Policy of Integrative and Complementary Practices (PNPIC), upon considering that "(…) homeopathy is a complex medical system with integrative and dynamic approach to the health-disease process and actions for prevention of diseases and promotion and recovery of health" [59].

According to an article published in journal *O Estado de São Paulo*, on 3 May 2008, "The Health Ministry reports increasing demand for this therapeutic [system] since the beginning of this decade, representing more than 20% increase compared to the population growth". In addition, "in the past year, this specialty accounted for more than 300,000 consultations within the Unified Health System", corresponding to about 10% of primary care visits along that period [60].

The relevance of homeopathy, a reflection of the global increase in the use of homeopathic medicines for care of ill people and the expansion of the global market, is also evidenced by the concern of health authorities, pharmaceutical industry and consumers with the safety and quality of homeopathic medicines. To ensure that the desired quality is achieved, WHO prepared a document on safety issues that stresses good manufacturing practice (GMP) and provides guidelines for the manufacture of homeopathic medicines [61].

Conclusions

Based on the information described here, we might assert that in addition to advantages related to effectiveness (broad scope, absence of adverse side effects and low cost), as a function of the optimal patient-doctor relationship homeopathy fully complies with the bioethical principles – beneficence/nonmaleficence, autonomy and universality/justice

[11]. Increasingly more evidences emerge as to the outcomes of homeopathic treatment of diseases of any kind, acute, epidemic or chronic, besides its usefulness for palliative care.

Therefore we might conclude that as a function of its uniqueness as therapeutic approach and its bicentennial trajectory, acknowledged by most doctors and society at large, it is both desirable and necessary for homeopathy to be included in universities, medical schools and health care systems at all levels of complexity, to thus ensure its historical characterization as medical specialty.

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Medical education in non-conventional therapeutics in the world (homeopathy and acupuncture)

Marcus Zulian Teixeira·

Abstract

Background: Used as complementary to, alternating or integrated with mainstream medicine, the population's demand for non-conventional therapies has substantially increased in the past decades, requiring from doctors knowledge on the basic notions of such therapeutics to orient their patients regarding treatments different to the ones they usually prescribe. Among them, homeopathy and acupuncture are considered medical specialties in Brazil for various decades. Aim: To describe the current state of medical education in non-conventional therapies (homeopathy and acupuncture) around the world. Methods: We updated data resulting from studies and reviews published until 2013 through a review of more recent studies included in database PubMed. Results: In all countries the teaching of non-conventional therapies is considered a relevant topic for the training of doctors as a function of the increasing interest of the population in their use, with a broad range of approaches targeting undergraduate and graduate students, medical residents and doctors from other medical specialties. Conclusions: The Brazilian medical schools must provide undergraduate and graduate students and medical residents accurate knowledge on the theoretical assumptions and clinical-therapeutic approaches proper to homeopathy and acupuncture, among other non-conventional therapies.

Keywords

Medical education; Complementary and alternative medicine; Homeopathy; Acupuncture; Attitude; Curriculum

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Introduction

Use of non-conventional therapies for treatment of several diseases and health disorders has substantially increased in the past decades. Such therapies are used alternating, complementary to or integrated with mainstream medicine in all countries and population strata. This situation demands from doctors mastery of the fundamental notions underlying such therapies to be able to orient patients wanting to perform treatments different from the ones they are used to prescribe.

As in the United States millions of individuals (30% of adults and 12% of children) employ some form of non-conventional treatment, the National Institutes of Health (NHI) include an agency specifically devoted to research, divulgation and control of such practices (National Center for Complementary and Integrative Health - NCCIH) [1]. These practices are categorized as "complementary health approaches" when concern non-conventional practices or products, and as "integrative health" when they consist of complementary resources added to conventional health care.

In Brazil, after the Health Ministry launched the National Policy of Integrative and Complementary Practices (PNPIC) in 2006, expression "integrative and complementary practices" (PICs) began to be used in the national literature. However, since term "complementary and alternative medicine" (CAM) is still widely used in studies on this field, we also used in the present review to designate non-conventional health practices, approaches and treatments.

Although the Brazilian Medical Association (AMB) and Federal Council of Medicine (CFM) acknowledge homeopathy and acupuncture as medical specialties since 1980 and 1995, respectively, they are poorly available at public and private health services vis-à-vis the actual demand. Paradoxically, a survey conducted by the Regional Medical Council of the State of São Paulo (CREMESP) and CFM in 2013 (*Medical Demography in Brazil*) [2] evidenced that acupuncture and homeopathy ranked 22nd and 28th in number of professionals, respectively, among 53 analyzed medical specialties. A similar survey performed in 2015 [3] showed they ranked 27th and 31st, respectively.

Since these approaches are not included in the standard curriculum of medical schools, doctors are not prepared to discuss the various CAM with patients, resulting in a gap in therapeutics and/or in the doctor-patient relationship. This fact alone ought to serve as trigger for medical schools to teach undergraduate and graduate students and medical residents the basic foundations, scientific evidences and clinical-therapeutic approaches of non-conventional medicine. In addition, effective incorporation of PICs into health services as adjuvant to conventional treatment will increase the efficiency, efficacy and effectiveness of medical interventions in the various specialties and fields of action.

To contribute to the debate on the need to accept and incorporate CAM into the curriculum of medical schools that we promote since 2004 [4-9], we performed the present up-to-date review on the validity of teaching homeopathy and acupuncture to undergraduate and graduate students (medical residents), the attitudes of users and doctors in this regard, corresponding medical educational initiatives in several countries, and the benefits of these efforts for society at large and for the training of doctors.

Materials and methods

The primary sources for the evidences gathered in the present studies were studies and reviews we published until 2013 [4-9] to which new studies published from 2013 to 2017 were added. Such studies were located in database PubMed using keywords "medical education", "attitude", "curriculum", "CAM", "homeopathy" and "acupuncture". We described the Brazilian initiatives for medical education in Brazil comparatively to other countries.

Relevance of CAM teaching to undergraduate medical students

Interest in and use of CAM by the world population

In the first survey (1990) on the prevalence, cost and use of CAM in USA, Eisenberg et al. [10] estimated that 34% of the country adult population used this type of treatments, corresponding to 427 million visits/year with non-medically qualified practitioners. This study was repeated in 1997 [11] when it detected increase in the search for CAM (42% of the population, 629 million visits/year), representing an additional cost of USD 27 billions to the US population, as such treatments were not available at public health services and were not reimbursed by health insurance. A survey performed later, in 2002 [12] found that the prevalence of use of CAM remained constant, 2 or more forms being used by 72 millions of US adults. A study conducted in Europe [13] evidenced similar results; 46% of German and 49% of French citizens reported use of CAM.

In a survey conducted in Florida, USA, in 1998 [14] 62% of the adult residents reported having used 1 or more CAM among 11 modalities included in a list, with greater predominance of home remedies (31%), diets (24%), relaxation (20%) and herbal medicine (18%). In 2002 [12] the therapeutic practices most often used were herbal medicine (18.6%; 38 million users) and chiropraxy (7.4%; 15 million users). A broad-scope survey on use of CAM in USA (National Health Interview Survey, 2007) [1,15] showed that the 10 modalities most used by adults were: natural products (17.7%), deep breathing (12.7%), meditation (9.4%), chiropraxy and osteopathy (8.6%), massage (8.3%), yoga (6.1%), diets (3.6%), deep relaxation (2.9%), guided imagery (2.2%) and homeopathy (1.8%).

The heterogeinity among studies notwithstanding, a systematic review estimated the prevalence of use of CAM in the United Kingdom [16] comprising 89 studies (2000-2011) and 97,222 participants. Varying according to the quality of studies, the average prevalence use of CAM was 41% per year and 52% along life. The modality most often used was herbal medicine, followed by homeopathy, aromatherapy, massage and reflexology. Concluding that a large part of the population used CAM, the authors stressed that healthcare providers need to have knowledge sufficient to provide responsible advise to patients.

Studies on the reasons that lead the USA population to seek non-conventional treatments showed that dissatisfaction with mainstream medicine was the main one [17,18]. A second reason was to attain a holistic understanding of illness (body-mind-spirit interrelation) [19]. Analogously, studies conducted in Brazil [20,21] showed that patients seek homeopathy due to the following reasons: dissatisfaction with

conventional medicine, avoidance of the side effects of conventional drugs, improvement of the doctor-patient relationship, and treatment that considers the individual as a whole (body-mind-spirit). Among cancer patients, improvement of the immune system is also mentioned [22,23].

Recent studies conducted in several countries once again showed that CAM is used by a significant part of the population (more than 50%) in a complementary or integrative manner for countless disorders and diseases: Germany (cancer) [22-24], Korea (neuropsychiatry) [25], Germany (epilepsy) [26], Canada (pediatric neurology) [27], Saudi Arabia (dermatology) [28], Serbia (cancer) [29], Australia (cancer) [30] and Taiwan (brain trauma) [31], among others.

Relevance of CAM teaching for doctors

The second survey conducted in USA [11] showed that more than 60% of CAM users did not report this fact to their doctors. Research performed with breast cancer patients revealed they avoid discussing concomitant CAM use with their doctors for expecting reprove, due to the mistrust and lack of knowledge of professionals in this regard [32,33]. Lack of interest of doctors in complementary CAM use might mean risk to patients due to possible drug interactions or adverse effects [34,35].

The vast majority of doctors are not prepared to answer questions or orient their patients as concerns the mechanisms of action, therapeutic indications and adverse effects of CAM or on drug interactions [35,36]. Additional factors, such as insufficient dialog between conventional and non-conventional doctors, doubts on the professionals' skills and risk of unreal expectations of cure, place patients in a position of uncertainty vis-à-vis CAM. Systematic inclusion of information on CAM in the curriculum of medical schools, in addition to reducing ongoing prejudice would afford future doctors the knowledge needed for their patients to properly benefit from CAM [6,37-43].

Moreover, inclusion of CAM topics in the medical school curriculum would add humanizing and health-centered components to health care [7,44] by disclosing the broad scoped, complex and uncertain nature of medical practice, with development of additional skills for clinical decision-making and promotion of new grounds for future research [45-47].

Systematic adjuvant use of CAM in severe [22-27] and hard to treat [48-51] diseases might improve the therapeutic response and quality of life of patients. In several initiatives [52-54] integration of conventional and non-conventional practices improved the quality of care delivery and the cost-effectiveness ratio.

Doctors and students' attitudes toward CAM

Doctors' attitudes

Ignorance of the fundamentals of CAM by doctors leads to frustration among the patients who use them concomitantly to conventional treatment. The reason is that they are deprived of safe guidance as to the main indications and possible risks of CAM [55-57].

Parallel to the increasing interest of patients in CAM, a need rose among doctor to meet such demand, which in USA is channeled to non-medically qualified practitioners. Together with the disgust of patients for the conventional health system, the dissatisfaction of doctors with that same approach increased the latter's interest in CAM [58,59].

Meta-analysis of 12 surveys of conventional doctors' attitudes toward CAM showed they rated them moderately effective [60]. A study on the attitude of general practitioners in Victoria, Australia [61] toward CAM showed that acupuncture, hypnosis and meditation had good acceptance, being mentioned by 80% of their patients and used by 50% of them. The surveyed doctors reported to have training in several modalities: meditation (34%), acupuncture (23%), vitamin-mineral therapy (23%), hypnosis (20%), herbal medicine (12%), chiropraxy (8%), naturopathy (6%), homeopathy (5%), spiritual healing (5%), osteopathy (4%), aromatherapy (4%) and reflexology (2%). About 30% of the interviewees expressed interest in learning chiropraxy, herbal medicine, naturopathy and vitamin-mineral therapy.

In a survey of doctors in Denver, CO, USA [62] on their personal and their patients' experience with CAM, 76% of the interviewees reported to have patients who used CAM, 59% were questioned about particular modalities, 48% had recommended CAM to patients and 24% had used it themselves. Few doctors reported to feel comfortable upon discussing CAM with their patients, and most of them (84%) believed they needed to learn more so as to dispel their patients' doubts in an adequate manner.

A study of the attitudes, knowledge and interest of pediatricians of Michigan, USA, in regard to CAM [63] showed that more than 50% of them had interest in taking training courses, would use it in themselves and recommend it to patients. The modalities preferred were: biofeedback (23.6%), self-help groups (23.3%), relaxation (14.9%), hypnosis (13.8%) and acupuncture or acupressure (10.9%). Other surveys conducted in other locations with doctors from various specialties (surgeons, oncologists, etc.) evidenced a similar interest in the use of and training in CAM [64-69].

Recent surveys of doctors with various specialties and from different countries, including China [70], Hungary [71], México [72], Germany [73,74], Iran [75], USA [76,77], Australia [78] and United Kingdom [79], among others, found similar results. Doctors expressed interest in learning about CAM, and the results evidenced the need for doctors to have knowledge on the fundamentals, scientific evidences and clinical-therapeutic approaches of the various modalities of CAM.

Medical students and residents' attitudes

A survey conducted with medical students at Düsseldorf University (Germany) [80] evidenced that the interviewees had knowledge of CAM, personal experience as users and interest in learning 1 or more modalities. The preferred modalities were: acupuncture (55.7%), homeopathy (42.1%), autogenic training (24.9%) and reflexology (11.4%), because they believed these were the most efficacious ones. A study performed with 800 medical students at 2 schools in Melbourne (Australia) [81] found positive attitudes toward CAM and interest in learning about, while few students had actual knowledge of this subject. A survey conducted with medical students in Singapore [82] detected positive attitudes toward CAM: 92% of the interviewees believed that the notions and methods of CAM might benefit conventional medicine, 85% had interest in learning about and 91% asserted CAM might play a significant role in their future medical practice.

Analogously, a study performed with 1st and 2nd year students at the medical school of Georgetown University, Washington DC, USA [83] found that most interviewees (91%) agreed on that CAM includes notions and methods that might benefit medicine, 85% asserted that knowledge on CAM is relevant for future health care providers, and more than 75% that CAM ought to be included in the curriculum. The preferred level of information was the one that enables giving advice to patients, and the preferred modalities acupuncture, chiropraxy, herbal medicine and food supplements. Also other surveys evidenced similar results [84-87].

A survey of the attitudes of medical students at School of Medicine, University of São Paulo [5] toward homeopathy and acupuncture found that more than 85% of the interviewees believed they should be included in the undergraduate curriculum; 65% expressed considerable interest in learning about them. Although most had no or little knowledge about the subject (76%), 67% of the participants reported to believe that CAM has some level of efficacy, having chronic diseases as their main indication, exclusively (37%) or together with acute conditions (29%). About 35% of the interviewees were favorable to outpatient clinics for both modalities in public health services; 34% considered they ought to be also available at hospitals; 60% believed in their integration with conventional medicine.

To assess a 4-year medical residency program in integrative family medicine carried out at Washington University (USA), in which CAM is added to the conventional curriculum, a study performed with 39 3rd and 4th year residents found that 80% of the interviewees considered the program ought to provide training in CAM. Most of them had already recommended some CAM modality to patients in the past year [88]. A survey conducted with 153 medical residents from a family health program in Arkansas (USA) [89] found that most had minimal knowledge about CAM, did not ask their patients about CAM use and felt uncomfortable upon discussing potential risks and benefits with patients. Nevertheless, most interviewees expressed interest in learning about CAM.

The Association of American Medical Colleges (USA) stated that medical students ought to have sufficient knowledge on CAM to be able to give advice to their patients on the possible benefits and risks of each modality [90].

Recent studies stress the lack of knowledge on CAM of medical students and residents along their training years, as well as their considerable interest in learning about it, thus reinforcing the relevance of systematic inclusion of CAM in the standard curriculum [91-94].

Medical education in CAM around the world

In response to the increasing interest in CAM, medical schools and graduate and residency programs began to include it in the curriculum, after having noticed that thus they broaden the scope of action of medicine and improve the doctor-patient relationship [95].

In the United Kingdom, legislation considers graduate education for doctors. In 1993, the British Medical Association [96] recommended medical schools to offer introductory courses on CAM to all undergraduate students. Three years later [97] 23% of medical schools had included disciplines for teaching basic concepts of CAM. In 1999, 40% of the medical schools in the European Union included courses on CAM [98]. In 1997, the French Order of Physicians acknowledged that homeopathy ought be prescribed by doctors with graduate university training.

In some USA states (Arizona, Nevada and Connecticut, among others) there are agencies to certificate homeopathic practitioners. The American Institute of Homeopathy grants diplomate (advanced specialty) status (DHt) to doctors, and the Council of Homeopathic Certification grants certificates in classical homeopathy. Some states grant licenses to doctors specialized in acupuncture. Reflecting the changes demanded by the country population, the latest edition of the Ethics Manual of the American College of Physicians includes a specific section on “alternative therapies” and recommends doctors to respect their patients’ choice of non-conventional treatments [99].

A large number of medical schools in USA offer lectures on holistic medicine or CAM [100]. A survey conducted in 1995 by the Society of Teachers of Family Medicine in 97 medical schools found that 39.2% of them provided some form of training in CAM to medical residents, mostly as optional courses (72.2%). Among non-university-based residency programs for family doctors, 28.1% offered teaching on CAM [101].

A study performed in 1997/98 with 117 medical schools in USA showed that 64% of them included lectures on CAM [102]. A survey conducted in 1998 with medical schools in Canada found that 81% included CAM topics in the curriculum, being acupuncture and homeopathy the modalities most widely taught [103]. In 1998/99, a study with 80 medical schools in Japan found that 20% taught CAM, being acupuncture the predominant modality [104].

In one study on education in CAM in USA [105] respondents were 73 course directors (from 53 medical schools). The topics most frequently taught were acupuncture (76.7%), herbs and botanicals (69.9%), meditation/relaxation (65.8%), spiritualism/faith/praying (64.4%), chiropraxy (60.3%), homeopathy (57.5%) and nutrition/diets (50.7%). While the amount of time devoted to individual topics varied widely, most received about 2 contact hours. The ‘typical’ CAM course was sponsored

by a clinical department (64.9%) as an elective (75.3%) taught in the first or fourth year of medical school, and had fewer than 20 contact hours of instruction (52.1%). Most of the courses were taught by individuals identified as CAM practitioners or prescribers. Most courses sought to teach general notions of CAM (61.6%) while very few emphasized the scientific evidences for and effectiveness of CAM or offered practical training in specific techniques (17.8%).

Although homeopathy and acupuncture are acknowledged as medical specialties in Brazil since 1980 and 1995, respectively, they were incorporated into the curriculum by very few medical schools, mostly as electives [4,6,8].

Proposals for medical education in CAM

Undergraduate courses

A project was developed in Germany to integrate natural healing procedures into teaching and research at Ludwig-Maximilian University, Munich [106]. This elective for medical students includes teaching on the fundamentals of and research in acupuncture, manual therapy, nutrition, homeopathy, hydrotherapy and herbal medicine. Scientific evidences for the effects and efficacy, indications and contraindications of each modality are addressed, and practical training is offered.

Proposals to integrate Western and Eastern (Chinese) medicine were developed in Taiwan [107] and Japan [108] starting from fundamental medical teaching. The rationale underlying these proposals is the belief that a unified medical care system will reduce the overall expenses with health.

University of Arizona [109], the pioneer in medical education in CAM in USA since 1983, offers 4th year undergraduates a 4-month elective in integrative medicine since 1997. The overall goal is to delve deeper into subjects superficially discussed along the first years of the course and to provide clinical experience. Similar initiatives were established at other medical schools [110,111].

According to the National Center for Complementary and Alternative Medicine (NCCAM-NIH) CAM teaching for medical undergraduate students ought to be oriented by the fundamentals of each modality, with emphasis on scientific evidences [112]. Several levels of CAM competencies are acknowledged in USA: a) low, doctors just have knowledge enough to indicate CAM and refer patients to more qualified practitioners; b) medium, doctors have practical skills sufficient to treat specific conditions; and c) high, doctors are fit to treat various diseases.

In the past decade, NCCAM-NIH funded CAM Education Program aiming at integrating CAM into the curriculum of medical schools so as to train professionals to meet the population demands. Such initiative resulted in various benefits: increase of academic activities related to CAM, development of new programs and increase of intra- and inter-university collaboration. Common challenges included the need for qualified professors, reformulation of curriculum, lack of definition of CAM and future sustainability of programs [113,114].

A similar initiative was developed in Canada to establish programs to integrate CAM into undergraduate medical courses. Activities included development of specific skills, reviews of relevant topics, repository of teaching and learning resources and a guide for the development, implantation and sustainability of the CAM curriculum [115].

A consortium of dozens of medical schools in USA, Canada and Mexico which develop active programs for teaching of CAM and integrative medicine congregates efforts to include these approaches into the curriculum of undergraduate courses and medical residency programs. The Consortium of Academic Health Centers for Integrative Medicine (CAHCIM) [116] influenced the National Board of Medical Examiners (USA) to include questions on CAM and integrative medicine in exams.

A survey conducted at 41 medical schools in Korea (2007-2010) [117] found that CAM was officially taught at 35 of them (85.4%). The most common courses were introduction to CAM or integrative medicine (88.65), traditional Korean medicine (57.1%), homeopathy/naturopathy (31.4%) and acupuncture (28.6%). Educational formats included lectures by professors and demonstrations by practitioners. The value order of core competencies was attitude (40/41), knowledge (32/41) and skill (6/41).

In Brazil, homeopathy and acupuncture at taught as electives [118,119] in just a few medical schools. Inclusion in the curriculum depends on the will of course directors and teaching is usually performed by specialists on a voluntary basis [4,6,8,120].

Just as in Brazil along several decades, also in other countries the idea of including homeopathy and acupuncture into the medical school curriculum as electives is increasing. With this, prejudice is combated and positive attitudes towards these approaches develop in the future doctors [6,121-123].

Medical residency and graduate education

In USA, the Society of Teachers of Family Medicine Group on Alternative Medicine developed consensual recommendations on attitudes, knowledge and skills in CAM to include it in family medicine residency programs [124]: cultural influence on convictions and choices relating to health; theoretical and philosophical grounds of CAM modalities; indications and potential adverse effects of each modality; scientific evidences for the efficacy and cost-benefit of each modality.

In 1996, University of Arizona developed a new approach to medical education denominated 'integrative medicine' defined as medicine that emphasizes the doctor-patient relationship and integrates the best of CAM with the best of conventional medicine. Thus it includes humanistic, preventive and curative aspects of the various therapeutic approaches. The goal of integrative medicine is to develop a way for conventional and non-conventional doctors to work together comfortably for the sake of the improvement of their patients.

Program in Integrative Medicine includes a 2-year residential fellowship that educates 4 fellows with 6 years of previous clinical experience, on average, each year. The first year is divided into 3 didactic sections: philosophical foundations, lifestyle practices (health promotion and prevention) and therapeutic systems and modalities (botanical

medicine, manual medicine, Chinese medicine, homeopathy, energy medicine and allopathic medicine). The second year is devoted to 4 process sections, to wit: clinical integration (application of theoretical knowledge to clinical practice), personal development and reflection, research education and leadership. Residents must select 1 CAM modality for additional training during the second year, being encouraged to test the modalities they recommend to patients on themselves. In this adaptation of integrative medicine to the conventional medical residency curriculum, each resident devotes 8-10 hours/week to the study of CAM, to a total of 1,000 hours along the 2 years in the program.

The Bruce Rappaport Faculty of Medicine at Technion (Haifa, Israel) [125] established an elective introductory course in CAM for residents and specialists in the department of family medicine. Four modules in CAM (herbal medicine, traditional Chinese medicine, homeopathy and nutritional medicine) are taught during a 16-session course. This initiative induced a positive change in the students toward CAM based on evidences. As a result, the students began to use CAM on themselves and their relatives and to recommend it to patients.

Based on the various initiatives developed in the past decades, investigators discussed what ought to be taught in CAM courses and how aiming at formulating guidelines for programs to improve and attain their goals [126-131].

In Brazil, residency programs in homeopathy and acupuncture were approved by the National Committee of Medical Residency (CNRM) in 2002 (CFM Resolution no. 1,634/2002). Access is direct (no previous residency program is required) and programs last 2 years. Residency programs in homeopathy are offered at only 3 Brazilian institutions (Federal University of the State of Rio de Janeiro - UNIRIO, Federal University of Mato Grosso do Sul and Regional Public Hospital of Betim) [132]. In turn, acupuncture is offered at 8 institutions [133]: FMUSP; School of Medicine of São José do Rio Preto (São Paulo); Francisco Morato State Civil Servant Hospital (São Paulo); Homero de Miranda Gomes Regional Hospital (São José, Santa Catarina); Prof. Polidoro Ernani de São Thiago University Hospital, Federal University of Santa Catarina; Federal University of São Paulo; Clinical Hospital, Federal University of Pernambuco; and Base Hospital, Federal District.

Overall, in Brazil homeopathy and acupuncture are taught to doctors as specialization courses or non-degree graduate courses offered by training institutions [134,135] with about 1,200 credit-hours. Completion of courses enables doctors to take board certification exams applied by official specialty institutions in agreement with AMB [136,137].

Discussion

CAM such as homeopathy and acupuncture represent therapeutic options for a broad scope of human diseases. These non-conventional practices have been increasingly sought after by the world population. Homeopathy and acupuncture have wide clinical application for centuries, and even millennia (in the case of the latter), are acknowledged as medical specialties, are available in the Brazilian national health service, reimbursed by health insurance, and their assumptions are scientifically

grounded on fundamental and clinical research [118,119,138-141]. Nevertheless, ignorance of their basic aspects by doctors results in prejudice and groundless criticism, perpetuated as a function of their non-inclusion in the standard curriculum of medical schools.

To overcome such impasse, homeopathy and acupuncture ought to be included in the curriculum of all Brazilian schools of medicine as elective and mandatory disciplines. Considering the complexity and diversity of both, theoretical disciplines ought to comprise at least 30 credit hours (2 credits) for students to acquire knowledge sufficient to provide advice to patients. The same disciplines might be also taught at graduate and medical residency programs. Outpatient clinics ought to be made available parallel to the theoretical disciples to afford clinical and therapeutic experience to students. Availability ought to be extended in the form of specific non-degree graduate and medical residency programs. In all such instances, the scientific evidences that ground these therapeutic approaches ought to play a foremost role, as they translate concepts different to the ones usually taught into the academic language, thus facilitating the learning of beginners.

In parallel to the need of a considerable number of doctors specialized in homeopathy and acupuncture in the public and private health care networks to meet the repressed demand, specialized professors and investigators should be hired by medical schools to enable an effective formulation of teaching, research and care initiatives. Congregation of such professionals in specific departments would promote the exchange of experiences and actual implementation of such initiatives.

An example of this type of organization is provided by School of Medicine and Surgery, UNIRIO. A pioneer in university teaching of homeopathy, it includes a Department of Homeopathy and Complementary Therapeutics composed of certified professors (homeopathic doctors) responsible for the activities at a teaching outpatient clinic and disciplines Homeopathic Materia Medica (elective, 30 credit hours, 2 credits) and Homeopathic Therapeutics (elective, 30 credit hours, 2 credits) [142]. Thanks to this infrastructure, starting 2004, UNIRIO offers a medical residency program in homeopathy.

Since acupuncture and homeopathy are used in a complementary and adjuvant manner for treatment of countless contemporary diseases, it is difficult to understand why the corresponding specialists are not included in the medical staff of public and private health services. Practically all outpatient clinics and hospital words ought to be able to apply these CAM modalities to minimize the suffering of patients, improve clinical effectiveness in the cure of diseases and reduce the cost and side effects of conventional treatments. Unfortunately, these aspects are not considered by course directors, hospital managers and health policy makers.

Explanations for this paradox were suggested in an analysis of the factors that facilitate or hinder the implantation of public policies for homeopathic conducted among municipal public health managers in São Paulo [143]. Facilitating aspects included: availability of homeopathic doctors in the health care network, user's demand, managers' acceptance of homeopathy, and availability of reference services where homeopathic care might be delivered. Hindrances mentioned were: need to hire homeopathic doctors (the main problem by far), influence of upper management levels opposed to homeopathy, priorities to be met before new projects might be developed,

purchase and delivery of medicines, duration of homeopathic consultations and ignorance of homeopathy rationale.

In 2006 the Health Ministry launched the National Policy of Integrative and Complementary Practices (PNPIC, MS ruling no. 971/2006) [144,145] which ensures the population partial access to CAM. Under PNPIC, patients are provided traditional Chinese medicine/acupuncture, homeopathy, botanicals and herbal medicine care gratis, among others at Health Basic Units (HBU) and Family Health Support Units (NASF), in addition to hospitals.

Tepid, vis-à-vis the huge interest in CAM, the effects of PNPIC illustrate the relevance medical education in non-conventional medicine ought to be attributed. The number of acupuncture procedures in 2007, i.e. the year PNPIC was implemented, was 97,240 to rise to 216,616 (122% increase) the following year. In regard to homeopathy, 312,533 consultations were performed in 2007 [146]. At that time, homeopathy was available at public health services in just 2% of the Brazilian municipalities.

Conclusions

Through this brief description of the situation of medical education in CAM, we hope to stimulate discussions on the relevance of Brazilian medical schools adjusting the curriculum to the actual demand. The reason is that homeopathy and acupuncture teaching, research and care are likely to meet the demands of the interested population, and doctors should be able to give proper orientation as to their mechanisms of action, therapeutic indications, drug interactions and possible adverse effects so that they might be employed in a safe and efficacious manner.

The evidences provided here should also ground and promote greater support among medical institutions (AMB, CFM, State Regional Medical Councils, among others) to the implantation and availability of homeopathy and acupuncture as medical specialties at the various health care sectors and services, considering their current poor availability and the increasing interest of the population.

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Scientific basis of the homeopathic healing principle in modern pharmacology

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Abstract

Background: Homeopathy employs the so-called 'principle of similars' as therapeutic method - which consists in administering medicines that cause certain symptoms in healthy individuals to treat similar symptoms in sick individuals (*similia similibus curantur*) - to induce a secondary and healing reaction by the body against its own disorders. This secondary (vital, homeostatic or paradoxical) reaction of the body is based on the 'rebound effect' of modern drugs, a type of adverse event that occurs following discontinuation of several classes of drugs prescribed according to the 'principle of contraries' *(contraria contrariis curantur)*. Aim: The present review sought to scientifically substantiate the homeopathic healing principle vis-à-vis experimental and clinical pharmacology through a systematic study of the rebound effect of modern drugs or paradoxical reaction of the body. Methods: Employing as reference studies and revisions on the subject published since 1998, we updated the data adding recent studies included in database PubMed. Results: The rebound effect occurs after discontinuation of several classes of drugs with action contrary to the symptoms of diseases, exacerbating them to levels above the ones before treatment. Regardless of disease, drug, dose and duration of treatment, the rebound phenomenon manifests in a small proportion of susceptible individuals. Following the homeopathic premises, modern drugs might also be used according to the principle of therapeutic similitude, thus employing the rebound effect (paradoxical reaction) with curative intent. Conclusions: Evidenced by hundreds of studies that attest to the similarity of concepts and manifestations, the rebound effect of modern drugs scientifically substantiates the principle of homeopathic cure. Although the rebound phenomenon is an adverse event studied by modern pharmacology, it is not known by health care professionals, thus depriving doctors of knowledge indispensable for safe management of drugs.

Keywords

Homeopathy; Pharmacology; Physiological effects of drugs; Law of similars; Pharmacodynamic action of homeopathic remedies; Secondary action; Rebound effect

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Introduction

As early is in ancient Greece, Hippocrates, the 'Father of Medicine', taught that diseases could be treated according to the principle of contraries *(contraria contrariis curantur*) or of similars (*similia similibus curantur*). These recommendations were followed by later medical schools [1-3].

Currently, the principle of contraries is massively employed in conventional therapeutics. Medicines are used whose primary action is contrary ('anti') the signs or symptoms of diseases to neutralize or palliate their manifestations. In turn, the principle of similars is applied in homeopathic therapeutics. Medicines are used whose primary action is similar (*homeo*) to the signs and symptoms of diseases to trigger a reaction in the body against such manifestations, i.e., disease.

The homeopathic method of treatment is based on four pillars: 1) principle of therapeutic similitude, 2) testing of medicines on healthy individuals (homeopathic pathogenetic trials – HPT), 3) prescription of individualized medicines, and 4) use of serially diluted and agitated (potentized) medicines (high dilutions - HD). Although much relevance is attributed to HDs - introduced later into the homeopathic model initially to minimize possible worsening ('aggravation') of symptoms resulting from the application of the similitude principle - the first 2 pillars represent the proper foundation of the homeopathic epistemological model (hard core, in Lakatos' terms) [4]. In turn, medicines ought to be individualized (selected according to the all the characteristic signs and symptoms exhibited by patients) as indispensable condition for triggering a therapeutic response.

Given the epistemological relevance of therapeutic similitude vis-à-vis the remainder of homeopathic assumptions, in 1998 this author started a project aiming at providing scientific grounds for this principle through systematic study of the 'rebound effect' of modern drugs ('paradoxical reaction' of the body) [7-23]. The rebound effect consists in the appearance of a secondary reaction opposed to and after the end of the primary action of countless categories of conventional palliative drugs. This phenomenon is analogous to the one described in homeopathy, as is shown below.

Along the past decade, pharmacologists suggested a therapeutic strategy named 'paradoxical pharmacology'. Similar to the one applied in homeopathy for more than 2 centuries, it advocates the use of conventional drugs that cause a short-term exacerbation of disease to treat the very same disease in the long run [24-36]. Analogously, since the beginning of the research [7-9] we have been advocating the use of modern drugs according to the therapeutic similitude principle. In other words, using drugs which cause adverse events similar to the manifestations of disease to treat them homeopathically. This means employing the rebound effect (paradoxical reaction) with curative intention [37-46]; results are promising and indications countless. An example is provided by the use of potentized estrogen for treatment of endometriosis-related pelvic pain [44-46].

The present review of the rebound effect of modern drugs aims at providing scientific grounds to the homeopathic healing principle (therapeutic similitude) vis-à-vis clinical and experimental pharmacology by demonstrating the properties, particularities and similarities between both phenomena.

Materials and methods

Reference sources were studies and reviews on the rebound effect we published since 1998 [7-20,37-46]. The data were updated through a search of recent studies included in database PubMed using keywords 'rebound', 'withdrawal', 'paradoxical', 'acetylsalicylic acid', 'anti-inflammatory', 'bronchodilator', 'antidepressant', 'statin', 'proton pump inhibitor', 'bisphosphonate', 'biological therapy' and 'immunomodulatory drug'. We also describe suggestions for use of modern drugs according to the therapeutic similitude principle [24-36,37-46]. This is, by applying the rebound effect (paradoxical reaction) with curative intention; examples from present-day clinical practice are provided.

The similitude principle according to homeopathy

In the development of the homeopathic approach to treatment, Samuel Hahnemann (1755-1843) had resource to the phenomenological method of qualitative research to describe the effects of contemporary drugs on the human physiology and ground the therapeutic similitude principle. Hahnemann first noticed that medicines cause signs and symptoms in healthy individuals similar to the ones exhibited by patients cured with the same medicines. He then sought to confirm this empirical observation through analogy and enumeration. He surveyed the literature and found hundreds of clinical reports by doctors from all times and places, involving many different categories of drugs (strong argument) which confirmed his finding ["Examples of homeopathic cures performed unintentionally by physicians of the old school of medicine", 47]. With these evidences in hands and through the application of Aristotelian inductive reasoning (*modus ponens*), Hahnemann outlined the homeopathic healing principle: **for any medicine to cure symptoms in the sick, it must induce similar symptoms in the healthy**:

> And whence could arise that curative power which it [arsenic] exhibits in certain species of intermittent fevers (a virtue attested by so many thousands of examples, but in the practical application of which, sufficient precaution has not yet been observed, and which virtue was asserted centuries ago by Nicholas Myrepsus, and subsequently placed beyond a doubt by the testimony of Slevogt, Molitor, Jacobi, J.C. Bernhardt, Jüngken, Fauve, Brera, Darwin, May, Jackson and Fwler) if it did not proceed from **its peculiar faculty of exciting fever,** as almost every observer of the evils resulting from this substance has remarked, particularly Amatus Lusitanus, Degner, Buchholz, Heun and Knape. We may confidently believe E. Alexander, when he tells us that **arsenic** is a sovereign remedy in some cases of angina pectoris, since Tachenius, Guilbert, Preussius, Thilenius, and Pyl, gave seen it give rise to a strong **oppression of the chest**; Gresselius, to a **dyspnea approaching even to suffocation**; and Majault, in particular, saw it produce **sudden attacks of asthma excited by walking, attended with great prostration of the vital powers** (original emphasis) [47, p. 81-2].

It is traditionally asserted that homeopathy began with Hahnemann's publication of *Essay on a new principle to ascertaining the curative powers of drugs* [48], in 1796. In

this essay Hahnemann described the pharmacological effects of dozens of contemporary medicines, distinguishing between their 'primary actions' and the consequent and opposed 'secondary indirect actions' of the body, thus evidencing the new healing principle. Continuing with the example of arsenic:

> *Arsenic (Arsenicum album).*
>
> - *Direct primary action:* Tendency to excite spasm in the blood vessels and chills, with daily paroxysms; with continuous use in large doses, it gradually causes an almost constant feverish state; reduction of the muscle fiber tonus and of the nerve sensitivity (paralysis); it promotes cough (asthma); it causes some chronic skin diseases (desquamating).
> - *Secondary indirect action (healing principle):* Treatment for intermittent fever, with daily recurrence; useful for hectic and remittent fever; some kinds of paralysis; cough (asthma); similar skin diseases.

In § 63 to 65 of *Organon of medicine* [49], Hahnemann attempted a physiological explanation for such 'natural healing law'. He grounded the similitude principle on the primary action of drugs and the consequent and opposite secondary action, or vital reaction of the body:

> 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. Although a product of the medicinal and vital powers conjointly, it is principally due to the former power. 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) [49].

As an example, Hahnemann described the primary actions of drugs in the various physiological systems and consequent secondary actions (reaction) of the body, characterized by effects opposite to the primary physiological changes. The latter lead the body back to the state previous to intervention (life-preserving power, i.e., modern homeostasis):

> [...] 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), diarrhea 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) [49].

Pointing to the unpleasant results of indiscriminate use of medicines with action contrary to the signs and symptoms of disease (*Organon of medicine,* § 59-61) [49], Hahnemann called the attention to the fact that the secondary action (vital reaction) of the body might cause undesirable effects ("a relapse – indeed, a palpable aggravation of the malady"). Therefore, upon denying the efficacy of palliative or antipathic treatment (principle of contraries) for treatment of chronic diseases, Hahnemann sought to validate homeopathic treatment (similitude principle) through resource to Aristotelian inductive reasoning (*modus tollens*, affirmation through negation, indirect demonstration, i.e., the null hypothesis of modern biostatistics):

> Important symptoms of persistent diseases have never yet been treated with such palliative, antagonistic remedies, without the opposite state, a relapse - indeed, a palpable aggravation of the malady - occurring a few hours afterwards. For a persistent tendency to sleepiness during the day the physician prescribed coffee, whose primary action is to enliven; and when it had exhausted its action the day - somnolence increased; - for frequent waking at night he gave in the evening, without heeding the other symptoms of the disease, opium, which by virtue of its primary action produced the same night (stupefied, dull) sleep, but the subsequent nights were still more sleepless than before; - to chronic diarrheas he opposed, without regarding the other morbid signs, the same opium, whose primary action is to constipate the bowels, and after a transient stoppage of the diarrhea it subsequently became all the worse; - violent and frequently recurring pains of all kinds he could suppress with opium for but a short time; they then always returned in greater, often intolerable severity, or some much worse affection came in their stead. […] weakness of the bladder, with consequent retention of urine, was sought to be conquered by the antipathic work of cantharides to stimulate the urinary passages whereby evacuation of the urine was certainly at first effected but thereafter the bladder becomes less capable of stimulation and less able to contract, and paralysis of the bladder is imminent; - with large doses of purgative drugs and laxative salts, which excite the bowels to frequent evacuation, it was sought to remove a chronic tendency to constipation, but in the secondary action the bowels became still more confined; […] severely burnt parts feel instantaneous alleviation from the application of cold water, but the burning pain afterwards increases to an incredible degree, and the inflammation spreads and rises to a still greater height […] How often, in one word, the disease is aggravated, or something even worse is effected by the secondary action of such antagonistic (antipathic) remedies, the old school with its false theories does not perceive, but experience teaches it in a terrible manner (*Organon of medicine,* § 59) [49].

Since the secondary reaction of the body (opposed to the primary action of the drug) could occur with any category of drugs independently from the dose (ponderable or highly diluted), Hahnemann raised the similitude principle to the status of "natural phenomenon" (*Organon of medicine,* § 58, 61, 110-112) [49].

Through administration to the sick of the very medicines that induce similar symptoms in the healthy on HPT (similar to our phase I clinical trials) [50,51], the aim of therapeutic similitude is to trigger a curative homeostatic reaction by making the body react against its own disorders. It should be noticed that terms 'secondary action/reaction', 'vital reaction' and 'homeostatic reaction' designate one and the same phenomenon, i.e., the ability of living beings to maintain the internal environment constant (homeostasis) through automatic self-adjustment of the physiological processes, ranging from simple cell mechanisms to complex mental functions.

Similitude principle in modern pharmacology

In modern scientific terms, Hahnemann's 'primary action' corresponds to the 'therapeutic, adverse and side effects' of conventional drugs. In turn, the homeopathic 'secondary action' or 'vital reaction' corresponds to the 'rebound effect' or 'paradoxical reaction' of the body that follows discontinuation of countless categories of drugs that work in a manner opposed (palliative, antagonistic or enantiopathic) to the signs and symptoms of disease.

By definition, 'rebound effect' consists in the production of increased negative symptoms when the effect of a drug has passed or the patient no longer responds to the drug; if a drug produces a rebound effect, the condition it was used to treat may come back even stronger when the drug is discontinued or loses effectiveness [52]. Analogously, 'paradoxical reaction' is a response opposed to the foreseen effect of a drug. Briefly, we might understand rebound effect as an automatic and instinctive manifestation of the homeostatic mechanisms aiming at reestablishing the original state, altered by the primary action of drugs, resulting in an effect opposed and contrary to the expected one.

According to reviews on this subject [53-55], the rebound effect appears following interruption or discontinuation of drugs, causing manifestations with stronger intensity and/or more frequent than the ones originally suppressed (which distinguish it from relapse of the original disease following the end of the primary action of drugs). These manifestations appear at variable intervals and also have variable duration. As a feature intrinsic to the phenomenon, one should consider a minimum interval of time to have a sound notion of the true magnitude of the phenomenon; this minimum interval corresponds to the full metabolism of drugs or absence of therapeutic effect (biological half-life). While discontinuation is a requisite for the rebound effect to manifest – since the primary action continues as long as receptors are bounded to the drug – some studies showed that it might also occur along the course of treatment, in cases of therapeutic failure or development of tolerance, tachyphylaxis or receptor desensitization. In turn, drug tapering avoids abrupt discontinuation, and thus minimizes the occurrence of the rebound effect.

The following examples with various categories of drugs illustrate the universal nature of the rebound effect [7-23].

Drugs classically used for treatment of **angina pectoris** (β-blockers, calcium channel blockers, nitrates, and others) with beneficial effects through their primary action might trigger a paradoxical increase of the frequency and intensity of chest pain after discontinuation. Drugs used for **arterial hypertension** (α-2 agonists, β-blockers, ACE inhibitors, MAO inhibitors, nitrates, sodium nitroprusside, hydralazine, and others) might produce rebound arterial hypertension once the primary biological effect ends. **Antiarrhythmic** drugs (adenosine, amiodarone, β-blockers, calcium channel blockers, disopyramide, flecainide, lidocaine, mexiletine, moricizine and procainamide, among others) may trigger rebound exacerbation of basal ventricular arrhythmias. **Antithrombotic** drugs (argatroban, bezafibrate, heparin, salicylates, warfarin, clopidogrel, and others), might promote thrombotic complications as result of the rebound effect. Drugs with primary **pleiotropic or vasoprotective** effect (statins) might cause rebound endothelial dysfunction, resulting in predisposition to paradoxical vascular accidents.

Analogously, discontinuation of **anxiolytics** (barbiturates, benzodiazepines, carbamates, and others), **sedative-hypnotics** (barbiturates, benzodiazepines, morphine, promethazine, zopiclone, and others), **stimulants of the central nervous system** (amphetamines, caffeine, cocaine, mazindol, methylphenidate, and others), **antidepressants** (tricyclic, MAO inhibitors, selective serotonin reuptake inhibitors, and others) or **antipsychotics** (clozapine, phenothiazines, haloperidol, pimozide, and others) might cause rebound aggravation of the original condition after the end of their primary therapeutic effect.

Anti-inflammatory agents (steroids, ibuprofen, indomethacin, paracetamol, salicylates, and others) might trigger paradoxical increase of inflammation and rebound thrombosis (ibuprofen, indomethacin, diclofenac, salicylates, rofecoxib, and celecoxib, among others) as a function of their primary platelet anti-aggregation action.

Analgesics (caffeine, calcium channels blockers, clonidine, ergotamine, methysergide, opiates, salicylates, and others) might trigger rebound hyperalgesia. **Diuretics** (furosemide, torasemide, triamterene, and others) might cause rebound sodium and potassium retention, with consequent increase of the plasma volume and the blood pressure. **Bronchodilators** (short- and long-acting ß-adrenergic agonists, sodium cromoglycate, epinephrine, ipratropium and nedocromil, among others) might promote rebound bronchoconstriction as paradoxical reaction to discontinuation.

Anti-dyspeptic (antacids, H_2 antagonists, misoprostol, sucralfate, protons pump inhibitors, and others) might trigger rebound increase of hydrochloric acid and gastrin production, with worsening of the original condition. **Antiresorptive** drugs used for treatment of osteoporosis (bisphosphonates, denosumab, odanacatib and others) might cause paradoxical atypical fractures due to rebound osteoclast activity increase.

Discontinuation of drugs for treatment of **multiple sclerosis** (glucocorticoids, interferon, glatiramer acetate, natalizumab, fingolimod, and others) might cause rebound increase of inflammation, with attending exacerbation of clinical symptoms and increase of demyelination lesions. **Immunomodulatory** agents (recombinant monoclonal antibodies, tumor necrosis factor inhibitors, among others) indicated for treatment of psoriasis might trigger rebound psoriasis after discontinuation. The list of examples is much longer.

These clinical and experimental pharmacological evidences [7-23] show that the characteristics of the rebound effect are similar to the homeopathic secondary action or reaction (*Organon of medicine,* § 59, 64, 69) [49]: 1) it induces a body reaction opposed to and of greater intensity compared to the primary action of drugs; 2) it takes place after the end of the primary action of the drug, and as automatic manifestation of the body; 3) it does not depend on the type of drug, dose, treatment duration or category of symptoms (disease); 4) its magnitude is proportional to the primary action of the drug; and 5) it appears in susceptible individuals only (idiosyncrasy).

Despite the idiosyncratic nature of the rebound effect – which appears in a small proportion of individuals – scientific evidences point to the occurrence of severe and fatal events as result of the paradoxical reaction of the body following discontinuation of different categories of drugs. This corroborates the magnitude of the phenomenon, the need to be duly known by health care providers and the benefits of its therapeutic application according to the similitude principle.

Rebound effect promotes severe and fatal events [16,17,20,21]

Rebound effect of platelet anti-aggregation drugs [10,11]

Acetylsalicylic acid (ASA)

ASA belongs to non-steroidal anti-inflammatory drugs (NSAID) that are non-selective cyclooxygenase (COX) inhibitors; COX catalyses the conversion of arachidonic acid into prostaglandins (COX-2) and thromboxanes (COX-1). Largely used for prevention of thromboembolic events, ASA is able to avoid thrombus formation through inhibition of COX-1 (mediator of platelet activity by the thromboxane A2 (TXA_2) synthesis) and platelet aggregation.

Experimental studies [56-63] showed that following discontinuation of platelet anti-aggregation drugs for thromboembolism prevention, a rebound or paradoxical reaction might occur, resulting in increase of COX-1 production and platelet activity (TXA_2) to values higher than the ones before treatment. With this the odds for thromboembolic events (unstable angina (UA), acute myocardial infarction (AMI), stroke, and others) increase among susceptible individuals.

In a retrospective study [64] 1,236 patients hospitalized for acute coronary syndrome (ACS) were inquired as to discontinuation of prophylactic ASA. 51 cases of ACS occurred within 1 month after withdrawal, representing 4.1% of all coronary events and 13.3% of cases of relapse. Among the patients who relapsed, the incidence of ACS with ST- elevation was higher among the ones who had discontinued ASA compared to the 332 patients who had not (39% vs. 18%; p= 0.001). The average interval between ASA withdrawal and acute coronary event was 10±1.9 days. These findings support the hypothesis that ASA withdrawal in coronary patients might represent a real risk for occurrence of a new thromboembolic event.

To investigate ASA discontinuation as risk factor for ischemic stroke (IS), Maulaz et al. [65] conducted a case-control study with 309 patients with IS or transient ischemic attack (TIA) subjected to long-term ASA treatment before the index event and 309 controls who had not had IS in the previous 6 months. The authors compared frequency of ASA discontinuation 4 weeks before an ischemic cerebral event among patients and before interview among controls. ASA discontinuance exhibited odds ratio (OR) 3.4 (95% confidence interval – 95%CI: 1.08-10.63; p< 0.005) for IS or TIA, i.e., 3.4 times higher risk for ischemic events among the patients who had discontinued treatment. These findings stress the relevance of adhering to ASA treatment, and provide an estimate of the risk associated with ASA discontinuation among patients at high risk for IS.

A meta-analysis [66] was performed with 50,279 patients (6 studies) at high risk for coronary artery disease (CAD) to assess the risk of discontinuation of or non-adherence to ASA. One study (31,750 patients) assessed adherence to ASA for secondary prevention of CAD, 2 studies (2,594 patients) the influence of ASA discontinuation on acute CAD, 2 studies (13,706 patients) adherence to ASA before or shortly after coronary artery bypass surgery, and 1 study (2,229 patients) ASA discontinuation among patients subjected to drug-eluting stent. Overall, ASA non-adherence/withdrawal was associated with 3-fold higher risk of major adverse cardiac events (OR = 3.14; 95%CI 1.75-5.61; p= 0.0001).

To assess the risk of AMI and death by CAD after discontinuation of aspirin low-dose in patients with history of cardiovascular events, a recent case-control study was conducted in the United Kingdom with 39,513 individuals who received a first prescription for ASA (75-300 mg/day) for secondary prevention of cardiovascular outcomes. The participants were followed up for 3.2 years, on average, to detect cases of non-fatal AMI or death by CAD. There were 876 cases of non-fatal AMI and 346 deaths by CAD. Compared to current users, the patients who had recently discontinued ASA exhibited significantly higher risk of non-fatal AMI or death by CAD combined (relative risk – RR: 1.43; 95%CI: 1.12-1.84) and of non-fatal AMI alone (RR: 1.63; 95%CI: 1.23-2.14). There was no significant association between recent discontinuation of low dose ASA and risk of death by CAD (RR: 1.07; 95%CI: 0.67-1.69). For every 1,000 patients-years there were about 4 more cases of non-fatal AMI among patients who discontinued low dose ASA (recent discontinuers) compared to patients who continued treatment [67,68].

In a recent review, Gerstein et al. [69] called the attention to rebound platelet aggregation associated with ASA discontinuation in the perioperative period, which might trigger significant ischemic events among patients with established cardiovascular disease. In many surgical procedures, the risk of bleeding due to intraoperative ASA is minimal compared to the risk for thromboembolism concomitant to discontinuation [70-73].

Studying the frequency of stroke occurring after antiplatelet drugs (APD) discontinuation, Sibon & Orgogozo [74] found that only 4.49% of strokes were related to recent APD discontinuation, but all cases occurred between 6 and 10 days after withdrawal (p< 0.0001).

Countless evidences confirm rebound platelet aggregation to be a natural and universal (independent from the drug used) phenomenon; all categories of APD (salicylates, heparin,

warfarin, clopidogrel, and others) cause rebound thromboembolism after discontinuation, and might cause severe and fatal cardiovascular accidents [75-79].

Non-steroidal anti-inflammatory drugs (NSAID)

The mechanisms by which NSAID, including COX-2 inhibitors, increase cardiovascular risk are several: reduced prostacyclin production in the vascular endothelium, suppression of nitric oxide synthesis, reduced neovascularization, abolition of adrenomedullin activity, and increased free-radical production, among others. These mechanisms also influence the platelet activity, which plays a crucial role in the development of events.

Just as ASA, also other classes of non-selective COX inhibitor NSAID increase the risk of AMI after discontinuance. One case-control study performed in the United Kingdom [80] with 8,688 cases and 33,923 controls assessed risk for AMI during and after exposure to diclofenac. The results showed that risk for AMI was 1.52 (95%CI 1.33-1.74) times higher among the individuals who had stopped treatment 1 to 29 days prior to the index event compared to non-users. These results suggest that rebound effect might occur several weeks after NSAID discontinuation. Also ibuprofen discontinuation triggers rebound platelet aggregation with increased thrombus formation and cardiovascular events (AMI) [81]. Use of NSAID is independently associated with increased risk for cerebrovascular events in patients with stable atherothrombosis [82].

To assess the cardiovascular risks of selective COX-2 inhibitors, a retrospective cohort study analyzed the medical records of 1.4 million users (1999-2001) [83]. The results showed that 8,199 patients (0.58%) suffered a heart attack during use of rofecoxib. Previous studies had demonstrated that chronic use of rofecoxib in high dose (> 50 mg/day) might increase the risk for severe cardiovascular problems [84-87].

Linking the rebound effect to platelet activity and considering that antiplatelet therapy with ASA is associated with reduced vascular mortality, Serebruany et al. [88] sought to establish the effect of use and withdrawal of NSAID on platelet activity. The authors concluded that drug discontinuation was associated with rebound platelet activation, which might result in higher risk for vascular events. Also *in vitro* experiments demonstrated that same thrombogenic mechanism for rofecoxib [89].

Confirming this hypothesis, observational studies detected high risk for AMI among new rofecoxib users [90,91]. Events occurred soon after discontinuation of rofecoxib in low dose, similar to the rebound effect dynamics. Using data collected in a previous cohort study [92], a case-control study [93] assessed the temporal nature of risk for first AMI associated with use of rofecoxib and celecoxib. The results showed that risk for AMI was higher following use of rofecoxib (RR: 1.67; 95%CI: 1.21-2.30); events occurred 9 (6-13) days after onset of treatment, on average. Treatment duration was not associated with increased risk, which remained high along the first 7 days after rofecoxib discontinuation (RR: 1.23; 95%CI: 1.05-1.44) to return to baseline between days 8 and 30 (RR: 0.82; 95%CI 0.61-1.09), thus characterizing the rebound phenomenon.

In a large systematic review of the effects of NSAID (both selective and non-selective COX-2 inhibitors) on cardiovascular events, 23 observational studies (17 case-control and 6 cohort studies) were analyzed, to a total of 1.6 million patients [94]. Rofecoxib was associated with patent dose-related risk, RR 1.33 (95%CI: 1.00-1.79) with ≤ 25 mg/day and RR 2.19 (95%CI: 1.64-2.91) with > 25 mg/day. Relative to the older, non-selective drugs, diclofenac exhibited RR 1.40 (95% CI: 1.16-1.70; 9 studies), meloxicam RR 1.25 (95%CI: 1.00-1.55; 3 studies) and indomethacin RR 1.30 (95%CI: 1.07-1.60; 6 studies). The data showed that risk was higher at the onset of treatment (first 30 days) consisting of first cardiovascular events.

In a nationwide case-control study conducted in Finland (33,309 cases; 138,949 controls) on risk for hospital admission with AMI under NSAID use [95] the estimated RR was: rofecoxib, 1.36 (95%CI: 1.18-1.58; 12 studies); diclofenac, 1.40 (95%CI: 1.19-1.65; 10 studies); meloxicam, 1.24 (95%CI: 1.06-1.45; 4 studies); and indomethacin, 1.36 (95%CI: 1.15-1.61; 7 studies). In another meta-analysis [96] Kearney et al. assessed the effects of selective and nonselective NSAID on risk for severe vascular events along 4 weeks at least (145,373 participants). The authors reviewed data from 138 randomized trials and obtained RR 1.42 (95%CI: 1.13-1.78) for rofecoxib and 1.63 (95%CI: 1.12-2.37) for diclofenac.

Reinforcing the causal role of the rebound effect, several studies conducted in the past decade reported similar results [97-101] calling the attention to the occurrence of fatal vascular events after NSAID discontinuation. A recent meta-analysis published in the *British Medical Journal* [102] analyzed a cohort of 446,763 individuals, including 61,460 who exhibited AMI during use of all classes of NSAID. The results indicated increased risk for AMI independently from drug class, dose and length of use. Use along 1-7 days was associated with higher risk (OR: 1.24; 95%CI: 0.91-1.82) for celecoxib, (OR: 1.48; 95%CI: 1.00-2.26) for ibuprofen, (OR: 1.50; 95%CI: 1.06-2.04) for diclofenac, (OR: 1.53; 95%CI: 1.07-2.33) for naproxen and (OR: 1.58; 95%CI: 1.07-2.17) for rofecoxib.

Rebound effect of bronchodilators *(ß-adrenergic agonists)* [10,12]

Several studies performed along the past decades confirmed clinical and experimental observations showing that 'rebound bronchoconstriction' might occur after partial or complete discontinuation of bronchodilators, with 'worsening of asthma' and increase of 'bronchial reactivity' [103-108].

As consequence of reports of severe paradoxical bronchospasm associated with use of the long-acting ß2 agonist salmeterol and previous epidemics of asthma-related deaths in patients using other long-acting ß agonists (LABA) the US Food and Drug Administration (FDA) requested GlaxoSmithKline to conduct a randomized trial comparing salmeterol to placebo. The study (Salmeterol Multicenter Asthma Research Trial - SMART) was started in 1996, to be prematurely interrupted in September/2002 after an interim analysis suggested increased risk for asthma-related death among the participants who used the drug compared to the placebo group [12].

In 2005, the FDA Public Health Advisory began warning about the higher risk of severe asthma and death by asthma associated with use of LABA (salmeterol and formoterol), even when combined to steroid fluticasone. On those grounds FDA demanded GlaxoSmithKline to add a warning on labels for doctors and users to be aware of the potentially fatal side effects of these drugs [109].

Following countless complaints from the scientific community [110] aroused by GlaxoSmithKline hiding SMART results, the data corresponding to the overall analysis of the 26,355 randomized participants were finally published in 2006 [111]. Following a review of the interim analysis, exploratory analysis of each outcome in the various subpopulations was performed. The results showed significant increase in respiratory event-related deaths (RR: 2.16; 95%CI: 1.06-4.41), asthma-related deaths (RR: 4.37; 95%CI: 1.25-15.34), and asthma-related deaths and life-threatening experiences combined (RR: 1.71; 95%CI: 1.01-2.89) among the subjects receiving salmeterol versus placebo. Such increase was greater among African Americans compared to whites.

In 2006 Salpeter et al. [112] published a meta-analysis of 19 placebo-controlled trials involving 33,826 participants with asthma corresponding to 16,848 patient-years (mean trial duration 6 months). Only 15% of the participants were African-American. The tested LABA were salmeterol, formoterol and eformoterol. About 53% of the participants from both groups concomitantly used inhaled steroids. The aim of the study was to assess the effects of LABA on severe asthma exacerbations demanding hospital admission, life-threatening asthma attacks, and asthma-related deaths. Subgroup analysis was performed to compare the results for salmeterol and formoterol in children and adults. For group LABA, hospital admission exhibited OR 2.6 (95%CI: 1.6-4.3) and life-threatening exacerbations OR 2.1 (95%CI: 1.5-3.0). Risk for hospital admission was increased for salmeterol (OR: 1.7; 95%CI: 1.1-2.7), formoterol (OR: 3.2; 95%CI: 1.7-6.0), children (OR: 3.9; 95%CI: 1.7-8.8) and adults (OR: 2.0; 95%CI: 1.0-3.9). Fatal asthma attacks associated with LABA had OR 1.8 (95%CI: 1.1-2.9) without significant difference between salmeterol and formoterol or between children and adults. OR of asthma-related deaths was obtained from SMART (OR: 3.5; 95%CI: 1.3-9.3; p= 0.013). Compared to group placebo, the risk of severe exacerbations and asthma-related deaths doubled (from 2 to 4 times). In spite of the well-known protector effect of inhaled steroids, the authors analyzed separately studies in which more than 75% of the participants concomitantly used these drugs; risk of hospital admission had OR 2.1 (95%CI: 1.34-3.4) which reveals the magnitude of the rebound effect [112].

In the physiological explanation of the findings, the authors correlated ß-agonist regular use (combined or not to inhaled steroids) with tolerance to drug effects and poorer disease control [113-116]. Tolerance is due to a negative feedback mechanism in the ß-adrenergic system that represents an adaptive response to receptor stimulation. Stimulation results in receptor uncoupling and internalization (desensitization) followed by decrease of the receptor density and downregulation of receptor gene expression [117]. The maintenance of some degree of bronchodilation notwithstanding, regular use of ß-agonists increases bronchial hyperreactivity. These effects, together with reduction of the response to subsequent ß-agonist rescue, might impair the control of asthma without the warning represented by increase of symptoms [116,118]. As indicated in older studies [103-108],

'bronchial hyperreactivity' is the same as 'rebound hyperreactivity' or 'rebound bronchoconstriction' [119].

A recent retrospective cohort study analyzed risk for severe asthma exacerbation among 940,449 asthma patients. The results evidenced significant association between hospital admission and intubation and use of LABA by comparison to short-acting ß-agonists [120]. Diverging from a previous meta-analysis [121] which found reduction of the risk for death by asthma with combination of salmeterol and inhaled steroids, a later meta-analysis [122] evidenced higher risk of severe adverse events with both formoterol alone or combined with inhaled steroids.

Several other studies [123-125] confirmed the occurrence of severe rebound bronchoconstriction following LABA discontinuation, resulting in severe and fatal events.

Rebound effect of antidepressants *(tricyclic and serotonin reuptake inhibitors)* [10,13]

Just as other classes of palliative drugs, also antidepressants are associated with rebound increase of depression symptoms following discontinuation (or dose reduction among more susceptible individuals) attended by patent changes in the involved receptors and/or mediators. In a review on this subject, Wolfe [54] observed that antidepressants might cause a variety of withdrawal reactions beginning few days after discontinuation and lasting several weeks. Both tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI) cause a similar syndrome, commonly characterized by gastrointestinal or somatic distress, sleep disorders, mood changes and motion problems, among others. Treatment consists in restarting the drug, prevention in tapering.

In another review [126], Lader broadened the comprehension of this 'withdrawal syndrome' (rebound effect) of antidepressants through further data and studies:

> The phenomenon has been postulated to be associated with rebound symptoms such as return of depression following abrupt discontinuation. Discontinuation symptoms are now known to be associated with most classes of antidepressants, if medication is stopped without appropriate down-tapering of dose and/or dose frequency. The phenomena associated with stopping almost all antidepressants including the SSRIs are believed to result not from true dependence but from a reduction in intra-synaptic serotonin (5-HT) levels following receptor down-regulation [126].

This syndrome is characterized by 'time-locked emergence of new' or time-point (biological half-life) and is clearly defined by measurable signs and symptoms that appear following reduction or discontinuation of an antidepressant along a few weeks [127]. Typically, patients describe transient symptoms that begin and peak within 1 week since treatment interruption, are mild in severity and run a limited course, usually lasting up to 3 weeks [128]. Although data in the literature indicate that these mild, self-limited rebound symptoms appear in a small proportion of individuals [128,129] some studies show that severe and disabling withdrawal syndrome might occur in up to 5% of patients, thus requiring changes in therapeutic strategy for such idiosyncratic individuals [130]. The

literature indicates that paroxetine is associated with a significantly greater proportion of withdrawal reactions (around 5%) than other SSRI (fluoxetine, for example), with deterioration of various aspects of health and functioning [128,131-134]. The most likely explanation for this difference is the long half-life of the main metabolite of fluoxetine, which thus acts as natural buffer [135].

As with other categories of drugs, rebound or withdrawal reactions are not specific for the clinical conditions (disease) for which a drug is used. The antidepressant discontinuation syndrome is similar (incidence, nature and extent) in depression, panic disorder, generalized anxiety disorder, social anxiety disorder and obsessive-compulsive disorder. Analogously, duration of treatment does not influence withdrawal reactions [136].

In a review of neurobiological mechanisms underlying the antidepressant withdrawal syndrome, Harvey et al. [137] suggested a preliminary molecular perspective and a hypothesis on the neuronal implications of drug discontinuation. They described evidences that support possible association between the rebound effect of antidepressants and abnormalities in the brain glutamate activity, nitric oxide and γ-amino butyric acid.

The symptoms that appear following antidepressant discontinuation (withdrawal syndrome) include dizziness, nausea, gastrointestinal distress, headache, gait instability, lethargy, paresthesia, anxiety, irritability, vivid dreams and depressed mood, among others. While cholinergic overdrive may account for some of the symptoms that appear after withdrawal of tricyclic antidepressants, others suggest increased excitability of serotonergic neurons. Just as chronic antidepressant treatment results in desensitization of post- and presynaptic serotonin ($5\text{-}HT_{1A}$) receptors, abrupt interruption of 5-HT reuptake inhibition causes transient deficit of the intra-synaptic 5-HT availability due to loss of the inhibition of the $5\text{-}HT_{1A}$ receptor-mediated postsynaptic control, resulting in paradoxical increase of the circulating 5-HT [137-139].

Countless studies conducted in recent years call the attention to an increased risk for suicidal ideation, attempts or behaviors (suicidality) associated with use of antidepressants. In the most comprehensive meta-analysis of placebo-controlled studies that sought to analyze the relationship between antidepressants and suicidality among pediatric patients, Hammad et al. [140] included all the studies submitted to FDA. The analyzed data corresponded to 4,582 patients in 24 clinical trials. 16 trials studied patients with major depressive disorder (MDD), 4 obsessive-compulsive disorder (OCD), and 4 non-obsessive-compulsive anxiety disorder (non-OCD anxiety). Only 20 trials were included in the analysis of the relationship with risk of suicidality. The multicenter trial (TADS) [141] was the only individual study that showed statistically significant relative risk (RR: 4.62; 95% CI 1.02-20.92). The overall RR for SSRI in the depression studies was 1.66 (95%CI: 1.02-2.68). For all drugs and all indications, RR was 1.95 (95%CI: 1.28-2.98). The overall risk difference (RD) for all drugs and all indications was 0.02 (95%CI: 0.01-0.03). FDA concluded that these medications were associated with twice higher risk of causing suicidality.

According to the aforementioned considerations, the most plausible hypothesis for this relationship is that antidepressant (partial or full) discontinuation might trigger significant worsening of depression symptoms that are initially suppressed (suicidality, for instance),

as a result of rebound phenomenon [132,142-145]. However, the adverse events assessed in randomized trials (meta-analyses) are only the ones that occur during or immediately after treatment, while drugs with long half-life (as e.g. fluoxetine) are not considered. Such agents require longer follow up so that the rebound effect might manifest, different from antidepressants with short half-life (paroxetine, sertraline, venlafaxine, among others) [146-148]. As mentioned above, not taking the biological half-life of drugs into account is a relevant source of bias in the study of the rebound effect.

Several other studies that assessed risk of suicide among antidepressant users reported similar findings [149-155]. This fact should call the attention of doctors and patients as to the care needed in the discontinuation of these drugs.

Rebound effect of lipid-lowering drugs *(statins)* [14]

Statins are the most widely prescribed cholesterol-lowering drugs, and are considered to be the first choice for prevention of CAD and atherosclerosis (i.e., the main cause of death in developed countries). Statins act by inhibiting 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, namely, the rate-limiting enzyme in endogenous cholesterol biosynthesis. This enzyme catalyzes reduction of HMG-CoA to mevalonic acid. Enzyme inhibition is effective to lower the plasma total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglyceride levels in humans and thus might be useful to treat atherosclerosis and dyslipidemia [14].

The clinical benefits of statins seem to extend beyond their lipid-lowering effects. In addition to reducing the cholesterol biosynthesis, mevalonate inhibition by statins also reduces the synthesis of significant intermediates, such as isoprenoids (farnesyl pyrophosphate, geranylgeranyl pyrophosphate, coenzyme Q10, dolichol, isopentenyladenosine, and others). These intermediates participate in posttranslational prenylation of several proteins (e.g., Ras, Rho, Rac) which modulate a wide variety of cellular processes including cellular signaling, differentiation and proliferation. Given the central role of these isoprenylated proteins in the endothelial function, atherosclerotic plaque stability, platelet activity, coagulation, oxidation and inflammatory and immune responses, the primary effects of these compounds are extremely beneficial for a broad spectrum of disorders (cardiovascular disease, osteoporosis, Alzheimer's disease and related vascular dementia, viral and bacterial infections, among others). These cholesterol-lowering-independent effects of statins are termed 'pleiotropic effects', and involve vasoprotective actions, including improvement of the endothelial function, increased nitric oxide (NO) bioavailability with antioxidant effects, inhibition of inflammatory-thrombogenic responses, immunomodulatory actions, progenitor cell regulation, and atherosclerotic plaque stabilization [156-158].

Independently from rebound increase of cholesterol biosynthesis, scientific evidences suggest that discontinuation of statins leads to rebound impairment of the vascular function (pleiotropic effects) with consequent increase of morbidity and mortality among patients with vascular disease. Statin withdrawal increases the activation of heterotrimeric G-proteins Rho and Rac, which trigger reactive oxygen species (ROS) production and

suppression of NO bioavailability. In humans, statin discontinuation results in a pro-oxidant, proinflammatory and pro-thrombotic state, with deterioration of the endothelium function. Epidemiological studies indicate that statin discontinuation in patients with AMI and ischemic stroke significantly increases the odds of early cardiological and neurological deterioration, attended by poor outcomes. Shortly, statin withdrawal results in rapid return to endothelial dysfunction and amplification of oxidative and inflammatory processes, which may increase the vascular risk [159-162].

Clinical studies found that statin discontinuation, especially after acute vascular events (AMI or stroke), has a harmful effect on cardiovascular parameters and mortality (rebound effect). Patients who discontinued statins exhibited poorer outcomes compared to the ones never prescribed these drugs. Observational studies [163-168] showed that statin withdrawal resulted in increased mortality risk (by fatal vascular events) compared to drug maintenance (2.3 to 7.5-fold) and no treatment (1.25 to 1.69-fold). Interventional studies reported that statin interruption led to significantly increase of the mortality risk compared to treatment maintenance (4.66-fold) [169] in addition to significantly increased risk of fatal vascular events compared to treatment maintenance (2.27 to 8.67-fold) and no treatment (19.01-fold) [169,170]. Statin discontinuation was also considered an independent predictor of all-cause 1-year mortality [171].

In an analysis of data from 2,466 Canadian patients with brain hemorrhage (2003-2008), Dowlatshahi et al. [172] described the relationship of statin use and discontinuation with IS incidence through assessment of event severity and 30-day mortality. Overall, 537 patients (21.7%) used statins and exhibited less propension for severe IS on admission (54.7% vs. 67%) although the rates of unfavorable outcomes (70% vs. 67%) and 30-day mortality (36% vs. 37%) were similar compared to non-users. 158 among those 537 patients had statins interrupted on admission; this group was more prone to exhibit severe IS (65% vs. 27%; $p< 0.01$), unfavorable outcomes (90% vs. 62%; $p<0.01$) and higher 30-day mortality (71% vs. 21%; $p< 0.01$). Following adjustment for IS severity, statin discontinuation remained associated with unfavorable outcomes (adjusted OR: 2.4; 95%CI: 1.13-4.56) and high mortality (adjusted OR: 2.0; 95%CI: 1.30-3.04). The authors concluded that statin discontinuation is a factor for poorer outcome and a marker of poor prognosis, as mentioned above. Upon analyzing the data from 12,689 patients with IS admitted to 17 hospitals in Northern California, USA (2000-2007), Flint et al. [173] found similar results. The patients who discontinued statins on admission exhibited significantly higher risk of death (RR: 2.5; 95%CI: 2.1-2.9; $p< 0.001$).

Contributing to broaden the scope of research, later studies [174-179] reinforced the previous findings that statin discontinuation might induce rebound deterioration of the vascular function and subsequent vascular accidents.

Rebound effect of gastric acid suppressants *(antacids, H_2 antagonists, proton pump inhibitors)* [15]

According to FDA [180], rebound acid hypersecretion is defined as increase in gastric acid secretion (basal and/or stimulated) above pretreatment levels following discontinuation of antisecretory agents. Initially reported in association with use of H_2 antagonists, rebound

acid hypersecretion is related to elevation of the serum gastrin and/or upregulation of the H_2-receptors. Elevated gastrin levels or hypergastrinemia is a secondary effect of chronic inhibition of the gastric acid secretion, with occurs in long-term antisecretory treatment. Increased plasma gastrin stimulates histamine production and release by enterochromaffin-like (ECL) cells, which induces gastric acid production by the parietal cells. In addition, increase of the parietal cell mass might occur together with chronic use of antisecretory agents, this being an additional mechanism that accounts for the increase in acid secretion that occurs after treatment discontinuation. Another possible cause of rebound acid secretion is increased sensitivity to histamine [181].

While neutralization of the gastric acidity by antacids (aluminum/magnesium hydroxide or calcium carbonate) does not have antisecretory effect, it also causes rebound acid hypersecretion following treatment discontinuation. Clinical trials confirmed this hypothesis upon detecting occurrence of rebound effect 1 hour after administration of the standard antacid dose to healthy individuals [182,183].

Analogously, H_2 antagonists (cimetidine, famotidine, nizatidine and ranitidine) cause rebound acid hypersecretion after drug withdrawal. Although the exact mechanism remains unclear, the main hypotheses are that the rebound effect is related to greater responsiveness of the H_2-receptor to stimulation by histamine after chronic competitive inhibition and impairment of the inhibitory branch of gastrin-dependent acid secretion [184]. Studies with patients and healthy individuals showed that rebound acid hypersecretion occurred 2-3 days after 4-week treatment and lasted 10 days [185-190].

Proton pump inhibitors - PPI (esomeprazole, lansoprazole, omeprazole and pantoprazole) block the final step of acid secretion, resulting in intense and persistent reduction of gastric acid, with concomitant increase of gastrin release. This rebound hypergastrinemia results in continuous stimulation of ECL cells and consequent hyperhistaminemia, without increase of the gastric acid secretion, since the proton pump is effectively blocked. In addition, stimulation of ECL cell proliferation increases the ECL cell mass, which persists longer than the effect of PPI when the drug is discontinued. As any rebound effect manifestation, rebound acid hypersecretion is evident at a given time-point after treatment withdrawal, as a function of the half-life of drugs (absence of biological effects). Following sufficient time of treatment with PPI, rebound acid hypersecretion occurs from the second week (half-life of PPI) to the normalization of the ECL cell mass (about 2 months), i.e., 2-3 months after treatment discontinuation. This phenomenon lasts long, at least two months longer than the duration of treatment, being attended by persistent and significantly elevated acid hypersecretion [191-197].

Gastrin has trophic action in many tissues and stimulates the *in vitro* growth of a large number of tumor cell lines, including colon cancer cells. While some authors associate hypergastrinemia to increased risk for colon cancer, 2 population-based case-control studies conducted in the United Kingdom (1987-2002) and Denmark (1989-2005) did not find any evidence of such increase among regular PPI users [198,199]. However, it should be noticed that rebound hypergastrinemia occurs some time after treatment discontinuation (half-life) which fact was not considered in these studies (assessment bias).

Some studies suggest that the increase in the frequency of gastroesophageal reflux disease (GERD) in the past decades might be due to excessive use of PPI for treatment of unspecific symptoms. For this same reason, hypergastrinemia might play a role in the progression of Barrett's esophagus into cancer, considering the noteworthy rise in the incidence of adenocarcinoma of the cardioesophageal junction along the past 2 decades and that acid-suppressive therapy for GERD considerably increased along this same period [200-203].

A population-based cohort study conducted in Denmark (1990-2003) found direct relationship between increased incidence of gastric cancer and increased number of prescriptions or length of treatment with PPI compared with users and non-users of H_2 antagonists. According to the authors, these data suggest that hypergastrinemia might be a risk factor for development of gastric cancer, as consequence of excessive PPI use [204].

Carcinoid tumors have long been acknowledged to be a consequence of hypergastrinemia in Zollinger-Ellison syndrome and atrophic gastritis [205]. Analogously to esophageal cancer, the increase in the incidence of gastric carcinoids along the past 3 decades (400% among men and 900% among women) might also be associated with the widespread selling of PPI [206-208]. According to McCarthy [203] the scientific basis to correlate chronic use of PPI with the rise in carcinoid tumors is quite strong and should be taken into consideration. Hypergastrinemia might also stimulate the development of carcinoid tumors in other sites.

To assess the occurrence and clinical relevance of rebound acid hypersecretion following discontinuation of PPI, Hunfeld et al. [209] performed a systematic review that included 8 studies. 5 studies (including 4 randomized trials) did not find any evidence for rebound acid hypersecretion (RAHS) following PPI withdrawal. From the 3 remaining uncontrolled trials, 2 suggested that RAHS might occur in *H. pylori*-negative patients after 8 weeks of treatment with PPI. The authors concluded that there is no strong evidence for clinically relevant increase of acid production following PPI withdrawal. Fossmark and Waldum [210] criticized the selection of studies for the just mentioned review, since it did not consider a treatment duration sufficient for development of significant hyperplasia of the ECL cells and subsequent RAHS. These authors stressed that it is not possible to assess RAHS after one single dose of PPI or less than 25 days of treatment, even though the studies were randomized trials: "these five studies merely show that PPI must be used more than 1-25 days to induce RAHS ".

Clinical evidences for RAHS after PPI withdrawal were provided by recent interventional studies [211-215]. Upon investigating whether RAHS also occurs in patients without GERD, some studies found worsening of symptoms in about 70% of long-term PPI users following discontinuation of treatment [211,214].

PPI are commonly used, and represent a considerable onus for the health system in many countries for being prescribed for a wide variety of acid-dependent gastrointestinal symptoms [216-220]. In Denmark, use of PPI increased 7 times from 1993 to 2007, in addition to substantial increase from 20 to 33 daily doses per 1,000 individuals from 2003 to 2007. In 2006, about 7% of Danish population was treated with PPI [221-223]. In Australia, use of PPI increased 1,318%, while the one of H_2 antagonists decreased by 72% [224]. In USA, use of PPI continuously increased from 1999 to 2004, while the one of H_2

antagonists decreased. In 2007, esomeprazole, lansoprazole and pantoprazole ranked 4th, 8th and 13th among the most sold drugs in US, corresponding to 26.4, 20.4, and 16.1 million prescriptions, respectively. Comparatively, ranitidine and famotidine ranked 47th and 120th among generic drugs, corresponding to 13 and 3 million prescriptions, respectively [225].

While such liberal use of PPI is recommended recent protocols for dyspepsia [226,227], a large proportion of PPI users do not exhibit acid-dependent symptoms or precise indication for this treatment [219,221,228-231]. Some studies indicate that up to 33% of patients who start PPI refill the prescription with no indication whatsoever for maintenance treatment [219,232]. As a function of the development of RAHS, such empirical behavior might complicate PPI withdrawal, causing relapse of acid-dependent symptoms (heartburn, acid regurgitation and dyspepsia) and consequent resumption of treatment [211,212,233].

Other studies [234-237] stress the relevance of RAHS following PPI discontinuation, calling the attention of doctors to the risks associated with and care required by this treatment.

Rebound effect of bone resorption inhibitors *(bisphosphonates and denosumab)* [18]

Osteoporosis is characterized by bone mass reduction and increased bone fragility. It affects 10 million people in USA and more than 75 million worldwide (20-30% of postmenopausal women). Antiresorptive drugs, such as bisphosphonates (BP), are considered the first-choice to reduce the risk of osteoporotic fractures. By inhibiting bone resorption through osteoclast activity reduction, BP (alendronate, risedronate, ibandronate and zoledronic acid, among others) increase the bone mineral density (BMD), thus reducing the risk of fractures. In USA, more than 150 million prescriptions of BP were filled for outpatients from 2005 to 2009 [238].

BP exhibit specific pharmacological properties that distinguish them from other bone resorption inhibitors, including skeletal retention (bone matrix) and long-term persistence of effects after discontinuation [239]. These characteristics result in a long half-life, which hinders the definition of the duration of the biological activity of BP, and consequent investigation of rebound effect, as is shown next.

In spite of the confirmed usefulness of BP to reduce the frequency of 'typical' fractures among patients with osteoporosis, the number of reports of 'atypical' subtrochanteric or diaphyseal femur fractures in patients using BP after no or low-energy trauma increased in in recent years. In 2010, the American Society for Bone and Mineral Research (ASBMR) published the report by a task force that investigated several issues related with this disorder [240]. Systematic reviews discussed clinical and experimental evidences for the occurrence of this adverse event secondary to use of BP seeking to understand its pathogenesis [241-245].

Atypical femur fractures associated with BP exhibit specific radiological characteristics (transverse or oblique direction, no comminution, cortical thickening, stress fracture or stress reaction on the affected and/or the contralateral side) and exclusive clinical

manifestations (long prodrome with pain, bilaterality, slow consolidation). The fact such fractures occur without previous history of trauma suggests a systemic pathogenesis like the rebound phenomenon, since this type of fracture is commonly associated with significant trauma (traffic accidents, for instance) in which the energy conveyed to the bone results in the propagation of several fracture lines, resulting in comminution. Although their incidence is low, this type of fracture exhibits high morbidity.

A case series [244] and epidemiological studies [246-250] evidenced the relationship between BP use for variable periods (3 months to 9 years) and occurrence of atypical fractures; association with cumulative medication use was ruled out. As mentioned above, such variable interval of time for the phenomenon to manifest is a consequence of the long half-life of BP (up to 5 years after 1-year treatment). This is a peculiar feature of 'deposit drugs', retained for years in the body (in the bones, in this case), which does not allow for immediate manifestation of rebound effect after discontinuation. Tolerance, tachyphylaxis and receptor desensitization account for the occurrence of rebound effect also during long-term treatment with BP.

The earliest hypothesis to explain the occurrence of atypical fractures suggest that the long duration of the action of BP, suppressing bone remodeling, might result in hypermineralization and micro-damage accumulation, with resulting impairment of the bone integrity. However, histomorphometric analysis of samples of biopsy of affected bones showed no hypermineralization or abnormalities in hydroxyapatite crystals. These findings are indicative of greater bone mineral maturity with no change whatsoever in the crystallization indices after treatment [244,251-254].

As in the case of other categories of drugs, experimental studies demonstrated rebound (paradoxical) increase of osteoclast activity following BP discontinuation [245,251,255]. Such 'biphasic anti-osteolytic effect' was evidenced by rebound increase of bone remodeling markers (collagen type 1 C-telopeptide), eroded surfaces (3 times higher than at baseline) and of the number of active osteoclasts (6 times higher than at baseline) after initial decrease caused by the direct action of BP. The magnitude of the rebound phenomenon accounts for the occurrence of complete fractures, in the absence of trauma, affecting one of the stronger areas of the femur, as well as their slow consolidation. These aspects reinforce the hypothesis that rebound effect is the main systemic pathogenic mechanism of atypical femur fractures. Other studies reported rebound bone resorption following discontinuation of other antiresorptive agents (hormone replacement therapy and monoclonal antibodies) [245].

While the incidence of hip fractures decreased since the introduction of BP in USA, subtrochanteric or femoral diaphyseal fractures increased along the same period. Although they represent a small subset (5-10%) of all femur and hip fractures, the subtrochanteric ones have considerable influence on morbidity and mortality, the results being similar to the ones of hip fractures [256,257]. In a prospective 2-year study of 87 patients with subtrochanteric fractures the mortality rate was 8% after 4 months, 14% after 12 months and 25% after 24 months. Revision surgery was required in 8% of the cases. By the end of the follow-up period, only 46% of the patients regained their walking ability and 71% had living conditions similar to those before the fracture [258].

Rebound bone resorption attended by increase of bone remodeling markers, osteoclast activity and propension for atypical fractures was described also after discontinuation of other categories of antiresorptive agents, such as hormone replacement therapy, human monoclonal antibodies (denosumab) and selective cathepsin K inhibitors (odanacatib), among others [245,259-262].

Other recent studies corroborate the occurrence of atypical femur fractures during treatment with BP and denosumab [263-266], therefore supporting the increasing calls warning doctors and patients about this serious adverse event.

Rebound effect of immunomodulating agents for treatment of multiple sclerosis (*natalizumab and fingolimod*) [19]

According to current hypotheses, the main event in the pathogenesis of multiple sclerosis (MS) is activation of peripheral autoreactive T lymphocytes. Following proliferation and crossing through the blood-brain barrier, these cells trigger a cascade of inflammatory events, which culminates in demyelination and axonal damage. Lymphocyte migration through the blood-brain barrier requires interaction of adhesion molecules expressed on the cell surface, such as selectins and integrins via their endothelial receptors [19].

Natalizumab (NTZ), a humanized monoclonal antibody, is a selective inhibitor of the aforementioned adhesion molecules, thus it hinders lymphocyte migration to the central nervous system (CNS), consequently reducing the frequency of acute exacerbations, number of brain lesions and progression of disease [19]. Fingolimod (FGD) is a modulator (functional antagonist) of the sphingosine-1-phosphate receptor on lymphocytes, able to reduce the ability of these cells to migrate from lymph nodes to CNS, thus minimizing neuronal inflammation and consequent demyelination [19].

The beneficial primary effect of treatment notwithstanding, observational studies [267-275] evidenced worsening of disease activity following NTZ discontinuation (rebound effect or immune reconstitution inflammatory syndrome - IRIS - without progressive multifocal leukoencephalopathy) [276-278]. This condition is attended by intense exacerbation of symptoms, increase of the number and/or size of demyelination lesions and disease progression.

In addition to NTZ, also other immunomodulating drugs or biological response modifiers, such as FGD [279] and tumor necrosis factor alpha antagonists - anti-TNFα (infliximab, adalimumab, etanercept) [280] might cause rebound demyelination disorders.

Recent studies [281-286] corroborate the occurrence of severe rebound demyelination (IRIS) following discontinuation of immunomodulating drugs (NTZ and FGD) used for treatment of MS, attended by cognitive disorders, neurodegeneration and fatal outcomes.

Rebound effect of immunomodulating agents for treatment of psoriasis (*efalizumab and anti-TNFα*) [23]

Psoriasis is an autoimmune inflammatory disease modulated by Th1 lymphocytes. Following contact with an unknown antigen, a subset of T lymphocytes converts into CD4+ and CD8+ memory T cells. The latter proliferate and migrate from lymph nodes to the skin, where they trigger an inflammatory reaction, with production of proinflammatory mediators (the number of T cells infiltrating the skin is correlated with disease activity). Advances in the understanding of the pathophysiology of psoriasis along the past decades, including the role of T cells and cytokines, were crucial for the development of biological therapy with immunomodulating drugs [23].

Term 'biological' alludes to the use of agents synthesized from living body products, which modulate the immune system through stimulating or inhibitory actions on specific sites. In the case of psoriasis, biologic drugs selectively inhibit the activation and maturation of antigen-presenting cells, thus blocking cytokine secretion and inhibiting the activation and proliferation of T cells, their migration to the skin, effector function and reactivation. While the safety profile of these drugs is considered more favorable compared to the conventional systemic immunosuppressant agents, since they do not cause generalized immunosuppression, the initial enthusiasm was soon replaced by a cautious attitude resulting from the accumulated experience and occurrence of severe adverse effects. Biological drugs for psoriasis fall into 2 main categories: T cell modulators (efalizumab and alefacept) and anti-TNFα (infliximab, adalimumab and etanercept) [23].

Efalizumab, the main agent for treatment of psoriasis, is a human monoclonal IgG1 antibody, which binds to leukocyte function-associated antigen (LFA)-1 alpha-chain, blocking the interaction between LFA-1 and intercellular adhesion molecule (ICAM)-1. The results are reduced T cell activation, inhibition of the migration and recruitment of T cells to the dermis/epidermis and reduced cell T reactivation in various steps of the pathophysiology of psoriasis [23].

In spite of the beneficial primary effects of this palliative (enantiopathic, contrary) treatment, some studies reported worsening of disease activity following discontinuation of the aforementioned immunomodulating agents (rebound psoriasis) [287-290]. This condition is attended by exacerbation of signs and symptoms (increase of the size or greater severity of skin lesions, worsening of arthritis, etc.).

Randomized placebo-controlled trials [287,291-297] evidenced occurrence of rebound psoriasis following discontinuation of efalizumab (≥125% worse compared to baseline, Psoriasis Area and Severity Index – PASI) in about 15% of patients. Observational studies [298-308] reported even greater estimates, of up to 30% of patients.

In some cases, rebound effect might result in fatal disease progression (IRIS) [276,309-312], just as in the case of NTZ for treatment of MS. This adverse event led the European Medicines Agency (EMA) to recommend withdrawing the marketing authorization for efalizumab on February 2009 [312].

Analogously, several studies showed that discontinuation of other immunomodulating drugs used for treatment of psoriasis trigger rebound effect: alefacept [313,314], etanercept [298,306,315] and infliximab [316,317]. Many authors do not characterize worsening of psoriasis 'during' treatment with anti-TNFα as rebound psoriasis (since according to the classic definition, rebound effect occurs after discontinuation of drugs). Yet several studies [318-322] found exacerbation of psoriasis with shift in its morphology (toward the pustular, erythrodermic or guttate forms) during treatment with anti-TNFα (etanercept, adalimumab and infliximab, among others), which might be considered as probable rebound effect (development of tolerance) as mentioned above.

Epidemiology of the rebound effect of modern drugs

Rebound effect appears after a variable interval (hours to weeks) following the end of the biological effect (half-life) of drugs; also its duration is variable. The interval between drug discontinuation and appearance of rebound effect is similar for drugs with short half-life: 10 days for salicylates, 14 days for diclofenac and 9 days for rofecoxib [10,11], 7 days for statins [14], 7-14 days for SSRI antidepressants [10,13] and PPI [15], on average. In the case of deposit drugs (bisphosphonates) [18] this time is longer. The duration of the rebound effect remains for 30 days for rofecoxib [10,11], 22 days for SSRI [10,13] and 30 days for IBP [15]. There is no relationship between treatment duration and manifestation of rebound effect.

In randomized placebo-controlled studies, the average risk of thrombotic events was 3.4 times higher following discontinuation of salicylates, 1.52 higher after NSAID, 1.67 higher after rofecoxib [10,11] and 1.69 higher after statin [14] withdrawal. Analogously, the risk of suicidality was 6 times higher after SSRI discontinuation [13] and the one of rebound bronchospasm 4 times higher following LABA withdrawal [10,12].

Illustrating the frequency and magnitude of the rebound effect, which might cause severe and fatal adverse events, epidemiological studies evidenced that LABA cause about 1 rebound episode of bronchospasm followed by death per 1,000 patient-years; this corresponded to 4,000-5,000 deaths in USA in 2004 (and 40,000-50,000 deaths worldwide) [10,12]. SSRI cause 5 rebound suicidal behaviors per 1,000 adolescent-years, which corresponded to 16,500 events in USA in 2007 [10,13]. Salicylates cause about 4 episodes of rebound AMI per 1,000 patient-years [10,11]. Some studies reported that the incidence of gastric carcinoid tumors increased in the past decades (100% among men and 900% among women) in association with increasing use of PPI, in relation to rebound hypergastrinemia [15]. Bisphosphonates cause 1-3 paradoxical severe atypical fractures per 1,000 patient-years (0.1-0.3%) [18]. Natalizumab causes rebound exacerbation of MS in about 10% of patients, attended by severe demyelination (IRIS) in some cases [19]. Efalizumab causes rebound psoriasis in 15-30% of patients, and might also induce IRIS [23].

Paradoxical pharmacology [24-36]

A therapeutic approach developed by Richard A. Bond in 2001 [24], 'paradoxical pharmacology' suggests employing the paradoxical effects of drugs (secondary reaction of the body opposed to the primary effects of drugs) with curative intention. Universal in nature, according to Bond, such paradoxical, bidirectional or compensatory effects are proper to various categories of drugs, independently from the dose used, and appear in a variable proportion of susceptible individuals. Although not fully elucidated, the paradoxical effect manifests at various levels of the autoregulation biological systems, making the functioning of the full body extremely complex, from the subcellular level (channels, enzymes, receptors, transporters, organelles, etc.) to cells, tissues and organs [25-29].

Affecting all physiological systems, these paradoxical and bidirectional effects have variable mechanisms: different actions in one same receptor due to time-related effects (e.g., ß-blockers with intrinsic sympathomimetic activity); stereochemical effects (e.g., salbutamol); multiple receptor targets with or without associated time-related effects (e.g., procainamide); antibody-mediated reactions (e.g., heparin-induced thromboembolism); pharmacokinetic effects of competing compartments (e.g., bicarbonate); interruption of and non-linear effects in systems (e.g., dopaminergic agents); systemic overcompensation (e.g., antiretroviral therapy and IRIS); other higher-level feedback mechanisms (e.g., acne fulminans associated with isotretinoin), among others [29].

Just as this author found in his systematic study of the rebound effect, also pharmacologists describe several examples of paradoxical and bidirectional effects of drugs affecting various systems and involving different categories of drugs: immunomodulators (systemic glucocorticoids and anti-TNFα), anticancer drugs (chemotherapy, radiotherapy and arsenic), antiarrhythmic agents (procainamide and isoproterenol), antihypertensive drugs (methyldopa, clonidine, guanabenz, moxonidine and thiazides), vasodilators (nitrates), drugs for treatment of heart failure (ß-blockers, ACE inhibitors, angiotensin II receptor blockers and hydralazine), lipid modifying drugs (fibrates and ezetimibe), inotropes and chronotropic drugs (isoprenaline, epinephrine, β-blockers and calcium channel blockers), vasoconstrictors (ergot alkaloids, vasopressin), anesthetics (sevoflurane, ketamine, propofol), antiepileptic drugs (e.g., benzodiazepines, barbiturates, hydantoin), hypnosedatives (anticholinergics, antihistamines, antispasmodics, barbiturates, benzodiazepines, bromides, chloral hydrate, ethanol, opioids), psychotropic drugs (antidepressants, antipsychotics), drugs with action on the peripheral nervous system (acetylcholinesterase inhibitors, capsaicin), antidyskinetics (dopaminergic agents), acid-base agents (sodium lactate, bicarbonate), agents active on the bone metabolism (e.g., parathyroid hormone, bisphosphonates), electrolytes (hypertonic saline, magnesium hydroxide), glycemic agents (insulin, hypoglycemic agents), steroids (dexamethasone), thyroid agents (iodine, lithium), antihyperuricemic agents (xanthine oxidase and urate oxidase inhibitors), gastrointestinal drugs (opioids, cholecystokinin and ceruletide), agents active in the blood (erythropoietin, vitamin K antagonists, platelet adenosine diphosphate receptor antagonists), bronchodilators (e.g., short- and long-acting β_2-agonists), dermatological drugs (high-intensity long-wave ultraviolet light, 8-methoxypsoralen and histamine-receptor antagonists), among others [29].

According to Bond, a possible hypothesis to account for the working of paradoxical pharmacology is the difference between the acute and chronic effects of drugs [24]. Stressing that the acute and chronic responses to drugs might be substantially different, and often of opposite nature, that author suggests that "exacerbating a disease makes use of the body's compensatory and redundant mechanisms to achieve a beneficial long-term response". This phenomenon is particularly evident in receptor-mediated events; acute exposure to agonists might activate receptors and increase signaling, while chronic exposure might desensitize receptors, with consequent signaling decrease. The same applies to receptor antagonists.

Analogously to homeopathic treatment, which employs minimal doses (HD) to avoid possible initial worsening of disease, the advocates of paradoxical pharmacology suggest, as general rule, beginning treatment with very small doses to then increase them gradually over weeks [24].

As examples of the therapeutic use of paradoxical reactions, some authors list clinical conditions that might be thus treated. Congestive heart failure (CHF) is related to deficient cardiac contractility; acute use of ß-adrenergic agonists increases the heart contractility, improves hemodynamics and reduces the related symptoms. In turn, chronic use of such drugs results in higher mortality. Short-term use of ß-adrenergic antagonists (ß-blockers: carvedilol, metoprolol and bisoprolol, among others) reduces contractility and exacerbates CHF, with worsening of disease. In turn, long-term use of these drugs results in increased cardiac contractility and lower mortality [24,28,29,30]. The same occurs with calcium channel blockers [31].

Analogously, ß-adrenergic agonists are the most powerful bronchodilators and play a considerable role in all the stages of the management of asthma. However, as was mentioned above, chronic use of these drugs is associated with paradoxical irreversible and fatal bronchospasm. In turn, short-term use of ß-adrenergic antagonists causes bronchoconstriction and worsening of asthma, while long-term use causes bronchodilation and improvement of asthma management [24,28,32,33].

Additional examples are use of methylphenidate (CNS stimulant) for treatment of attention-deficit hyperactivity disorder (ADHD) and of 5-HT_{1A} receptor agonists (hyperalgesia mediators) to achieve analgesia [28]. It is long known that thiazides afford paradoxical antidiuretic benefits in the treatment of diabetes insipidus, with reduction of polyuria and elevation of the urine osmolality [34].

Arsenic trioxide (As_2O_3), a carcinogen, has been used in homeopathy for more than 2 centuries as adjuvant for treatment of various types of cancer. As a function of its biphasic effects, it is considered by paradoxical pharmacology as a promising anticancer agent [35,36,323-325]; its clinical efficacy was demonstrated for acute promyelocytic leukemia [326-329], small-cell lung cancer [330,331] and liver cancer [332,333], among other uses [29].

New homeopathic drugs: use of modern drugs according to the therapeutic similitude principle [37-46]

Once again, the basic assumption underlying the homeopathic healing principle is the use of drugs that cause pathogenetic manifestations (signs, symptoms, physiological or pathological effects, etc.) similar to the disorders to be cured. A similar use might be made of any type of drug (natural or synthetic) and in any dose (ponderable or infinitesimal) provided the therapeutic similitude principle is observed. Thus being, modern drugs might be used according to the homeopathic assumptions, provided they induce primary effects (therapeutic, adverse or side effects) similar to the full set of characteristic signs and symptoms exhibited by patients.

Since 2003 [37-46] this author advocates the use of the rebound effect of modern drugs with curative intent. For this purpose patients are given drugs, in HD, which caused a similar set of adverse events in phase I-IV pharmacological clinical trials aiming at stimulating the homeostatic reaction of the body against its own disorders.

To make this idea feasible, a *Homeopathic Materia Medica of Modern Drugs* [39] was prepared, in which all the primary or pathogenetic effects (therapeutic, adverse and side effects) of 1,250 modern drugs described in *The United States Pharmacopeia Dispensing Information (USPDI)* [334] are organized according to an anatomical-functional distribution following the format of the traditional homeopathic materia medica [335]. To facilitate the choice of the individualized medicine to be prescribed, according to the full set of similar symptoms (i.e., the *sine qua non* requirement for the success of homeopathic treatment) next a *Homeopathic Repertory of Modern Drugs* [39] was prepared. Here pathogenetic effects and the corresponding drugs are organized according to the format of the traditional homeopathic repertories, following the aforementioned anatomical-functional distribution [336].

The full project, entitled *New Homeopathic Medicines: use of modern drugs according to the therapeutic similitude principle*, is available as 3 digital volumes (*Scientific Basis of the Principle of Similitude in Modern Pharmacology*, *Homeopathic Materia Medica of Modern Drugs,* and *Homeopathic Repertory of Modern Drugs*) online, open-access (http://www.newhomeopathicmedicines.com) to all interested readers.

As example of off label use of countless categories of modern drugs according to the therapeutic similitude principle, dozens of drugs that increase the blood pressure as primary effect (adalimumab, cyclosporine, dopamine and anti-inflammatory agents, among others) might be homeopathically used for treatment of hypertension, **provided other primary or pathogenetic effects are similar to the full set of signs and symptoms exhibited by the patient**. When one complies with such **therapeutic individualization**, drugs that increase the blood sugar (amprenavir, corticotropin, diazoxide and estrogen, among others) might be homeopathically used for treatment of diabetes. Drugs that cause inflammation of the gastric mucosa (abacavir, anti-inflammatory agents, carbidopa and cilostazol, among others) might be homeopathically used for treatment of gastritis and gastric ulcer. Drugs that cause immunosuppression (cyclosporine, steroids and immunosuppressant agents, among others) might be used to stimulate the immune system of immunosuppressed patients, and so forth [39-43,46].

As a concrete application, we recently developed a clinical research protocol for use of potentized estrogen (17-ß estradiol) for treatment of endometriosis-associated pelvic pain, since estrogen causes endometrial hyperplasia or proliferation as adverse event [44]. Reporting significant improvement versus placebo in relation to pain, depression and quality of life [45], this study can be accessed in the present special dossier.

Conclusions

Upon describing the undesirable effects of indiscriminate use of drugs according to the contrary principle, Hahnemann called the attention to the risks derived from their secondary action (rebound effect or paradoxical reaction) resulting in "more serious disease or frequently even danger to life and death itself". In turn, he validated the therapeutic similitude principle through the Aristotelian *modus tollens*:

> If these ill-effects are produced, as may very naturally be expected from the antipathic employment of medicines, the ordinary physician imagines he can get over the difficulty by giving, at each renewed aggravation, a stronger dose of the remedy, whereby an equally transient suppression is effected; and as there then is a still greater necessity for giving ever - increasing quantities of the palliative there ensues either another more serious disease or frequently even danger to life and death itself, but never a cure of a disease of considerable or of long standing (*Organon of medicine*, § 60) [49].

Bridging between the therapeutic similarity principle and modern scientific reason, hundreds of studies in the medical literature describe the occurrence of secondary reactions following and opposed to the primary actions of many categories drugs, thus corroborating the homeopathic assumption. Such secondary action or reaction, which occurs automatically and instinctively to maintain the system homeostasis, is described by contemporary pharmacology and physiology as rebound effect of drugs or paradoxical reaction of the body, respectively. Analogously, the primary action of drugs represents the therapeutic, adverse and side effects of modern drugs.

By definition, the intensity and/or frequency of the rebound effect are higher compared to the original symptoms, suppressed by the primary action of the drug. This characteristic distinguishes the rebound effect from the natural return of chronic symptoms after the end of treatment. While drug discontinuation is a requisite for occurrence of rebound effect, it might also appear during treatment, as a function of the development of tolerance or therapeutic failure.

In conventional therapeutics, a large number of iatrogenic events might be avoided were health care providers to pay attention to the possible occurrence of rebound effect [21]; worsening of diseases is minimized by tapering. While not conventionally described or included among the adverse effects of classical pharmacology, the effects of discontinuation are a part of the pharmacology of any drug [55] therefore they ought to be considered in the teaching of modern pharmacology.

By employing the rebound effect of conventional drugs with curative intent we might broaden the scope of therapeutic similitude through the addition of hundreds of 'new homeopathic drugs'. Such new drugs cover signs and symptoms absent in the classical homeopathic pathogenetic trials and will allow treating countless modern disorders, diseases and syndromes with homeopathy.

Just as homeopathic practitioners assert along more than 2 centuries [38,43] the advocates of paradoxical pharmacology [28] call investigators to approach the paradoxical phenomenon (rebound effect, therapeutic similitude) with no prejudice whatsoever, and to challenge the current dogmatic therapeutic paradigms through new approaches no matter how difficult is for our peers to accept new ideas.

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The soundness of homeopathic fundamental research

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Abstract

Fundamental research in homeopathy has much advanced in the past 20 years. From exploratory studies with animals and plants to the characterization of the systemic effects of homeopathic medicines and *in vitro* studies with isolated cell systems to assess changes in the mechanisms of cell adaptation and intracellular signaling facing variable homeopathic treatments. The amount of articles published over time enabled several systematic reviews. Recently, demonstration that homeopathic medicines might modify cell functions through epigenetic mechanisms (DNA methylation and demethylation) paved the road for a fully new field of research. In parallel, the discovery of nanoparticles and specific physical properties of homeopathic dilutions brought light to a previously poorly known field, as it was believed that homeopathic dilutions consist in nothing but water. Thus being, challenges for the future concern the demonstration, or not, of the interrelationship between both phenomena.

Keywords

Fundamental research; Homeopathy; Experimental models; Nanoparticles; Epigenetics

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The story begins by a question we have being hearing for decades: "Is homeopathy synonym of placebo?" This old controversy was elucidated in the past years, as the scientific literature included in database PubMed shows, especially as concerns meta-analyses of clinical trials [1-11]. Yet not only clinical trials provide scientific grounds to homeopathy. Along the past 10 years, considerable advance was made in fundamental research, most such studies having been performed in Brazil, Italy and India, seeking to elucidate the mechanisms of action of homeopathy.

Among recent systematic reviews [12-15] the ones assessing the reproducibility of studies conducted with dilutions above Avogadro's number stand out, including many different biochemical, immunological, botanical, cell biology and animal experimental models.

An analysis of studies performed in 2010 considered the (internal, independent or multicenter) reproducibility of studies [14]. A total of 107 studies were located, from which 53 exhibited comparable effects (35 internal, 8 multicenter and 10 independent repetitions); 8 studies exhibited consistent effects, however, not exactly the same as the ones in their predecessors; and 17 studies did not report any reproducible result.

A new survey was performed in 2015 of studies published from 1994 to 2015 [15]. A total of 126 experiments were located, 98 of which subjected to replication. Among the latter, 69 studies reported comparable effects, 20 no effects and 9 opposite effects. Statistical analysis led to reject the null hypothesis. About 82.9% of the studies exhibited internal reproducibility, 75% multicenter and 48.3% external or independent reproducibility.

Also plant models afforded relevant data on the reproducibility of results and on the pathophysiological mechanisms involved in the response to stressors following treatment with homeopathic drugs. A review from 2011 [16] which surveyed studies performed from 1920 to 2010 retrieved 34 articles fit for analysis according to the Manuscript Information Score (MIS). The articles were published from 1965 to 2010. A total of 37 experiments were described; 22 described data subjected to statistical treatment. Reproducible effects were found for decimal and centesimal dilutions, including potencies above Avogadro's number. Only one study with independent replication reported opposite results between the participating laboratories.

From 2000 onward, a considerable number of studies conducted with *in vivo* and *in vitro* experimental models were published, resulting in sufficient articles included in database PubMed for systematic review starting 2010. A systematic review performed by us in 2010 on animal experimentation [12] showed that the methods used until then were sufficiently adequate to obtain reliable data. Most such data exhibited convergence with the information in the homeopathic materia medica, i.e., the main tool used in clinical practice. The experimental models employed medicines prepared according to the isopathy and similitude (homeopathy) principles. In both cases it was possible to understand the complexity of the systemic actions of medicines, especially as concerns the modulation of the host-parasite relationship and the recovery of the body stability in the face of aggressive stimuli, which could be also corroborated through mathematical models.

The follow up of the aforementioned study was published in 2015. This new study reviewed articles on animal experimentation with homeopathy from 2010 to 2015 [13]. A total of 53 studies were located, relative to 12 different animal species; 29 studies used dilutions above Avogadro's number. Only 2 studies reported negative results, 1 with fish and 1 with bees; both employed commercial combinations of homeopathic medicines. The studies published after 2010 exhibited greater technical refinement, including association to results obtained also *in vitro* and 3 or more replications. A summary of the main findings of the reviews is described in Table 1.

Table 1. Summary of the main findings of 2 systematic reviews of animal models for homeopathic research published from 2010 to 2015 [12,13]

Parameters	**Articles published in 2010 [12]**
Total number of experiments	10 on isopathy 23 on similitude
Percentage of randomized samples	100%
Blind protocol	23 yes 10 no
Correlation between blind protocol and positive/negative outcomes	No (p= 0.6456, Fisher's test)
Convergence of experimental results and materia medica	87% for the studies on similitude
Parameters	**Articles published in 2015 [13]**
Total number of articles	53; 29 with dilutions above, and 10 with dilutions below Avogadro's number
Number of investigated species	12
Positive outcomes	100% for studies above Avogadro's number 80% for studies below Avogadro's number
Percentage of randomized samples	82%
Blind protocol	43%
Internal reproducibility	11%

In the past years, a patent trend to prioritize studies *in vitro* or with methods alternative to the use of animals developed, being encouraged by the main journals for complementary medicine, including *Homeopathy* [17]. The need to prioritize *in vitro* studies corroborating clinical results or obtained in animal models resulted in an interesting characteristic of the homeopathic phenomenon, already mentioned in previous reviews [13] but not taken into account until that point, to wit, translationality. This aspect allows for results obtained *in vitro* or in animal and plant models to generate information with immediate clinical applicability.

In 2017 we published 2 articles in journal *Cytokine* which clearly demonstrate this aspect. In the first article [18] we reported that macrophage-*Leishmania amazonensis* co-culture treated with *Antimonium crudum* 30cH *in vitro* exhibited significant reduction of lysosome activity, demonstrated through morphological analysis of the cells on fluorescence microscopy. We also found that treatment of infected cells

significantly reduced the peak of release of a chemokine crucial for monocyte recruitment in the inflammation site, to wit, MCP-1 (or CCL2) which only occurs in infected cells. However, we did not find any indication that treatment increased digestion of parasites. Considering the translational nature of the homeopathic phenomenon, these findings mean that in a hypothetical clinical situation, treatment of patients with *Antimonium crudum* 30cH might result in improvement of inflammatory lesions, but not in the elimination of infection.

Curiously, we had reached the very same conclusion in a previous, *in vivo* study, based on histopathological assessment [19]. Such result led us to ponder whether use of *Antimonium crudum* 30cH might be interesting, from the epidemiological point of view, to potentiate the parasiticide efficacy of the chemotherapy agents traditionally used for treatment of leishmaniasis. The reason is that by interrupting monocyte migration to the primary lesion, treatment might arrest the parasite cycle and proliferation in the definitive host, in this case the patient. The result might be greater parasite vulnerability to parasiticide agents and reduction of the duration of chemotherapy treatment, and thus of the its toxicity. It is superfluous to observe that reproducible, randomized, double-blind clinical trials are needed to validate this hypothesis. However, an *in vivo* study with a malaria model suggests this idea might be plausible [20].

Our second study [21] shows that treatment of mice with uropathogenic *E. coli*-induced experimental cystitis treated with *Cantharis vesicatoria* 6cH induced changes in the distribution of the various leukocyte subtypes along the urinary tract mucosa. The bladder mucosa exhibited predominance of B cells compared to all other cell subtypes, while the pelvic mucosa exhibited greater concentration of T lymphocytes and macrophages. High concentration of B lymphocytes in the bladder implies greater local IgA production which facilitates the control of infection in the lower urinary tract. This phenomenon would impair the propagation of infection to the kidney, i.e., so-called "ascending infection", which is usually attributed poor prognosis. Also in this case the experimental data awakened interest in the performance of randomized clinical trials to corroborate the clinical application of these findings.

The crux of the matter is that in none of those studies we found an 'antibiotic' effect, but facilitation of the host's adjustment to pathogens. Studies on parasitology conducted with laboratory animals treated with homeopathic and isopathic medicines corroborate this inference [22-27]. These data taken together with all other recent fundamental research studies reveal phenomenological particularities of homeopathic treatment that are not comparable to the phenomena observed in classic pharmacological studies, therefore, such particularities need to be taken into account in the design of clinical protocols. Among such particularities, non-linearity, coordinated systemic effects and probable epigenetic regulation are the most relevant, as shown by the series of studies conducted by the group chaired by Paolo Bellavite, from University of Verona, Italy [28-34].

Bellavite's group investigated 2 medicines, *Gelsemium sempervirens* and *Arnica montana*. The studies with *Gelsemium* found a non-linear anxiolytic-like effect in mice [29], i.e., without direct dilution-effect relationship. The behavioral changes observed were compatible with the ones described in the homeopathic materia medica. Two years later, these authors published an *in vitro* study conducted with SH-SY5Y cells in which treatment with *Gelsemium* in dilutions 2c to 30c modulated several genes involved in neuronal functions [31].

A clinical trial [32] exhibited considerable effectiveness of *Arnica montana* versus placebo, including improvement of post-traumatic pain, swelling and ecchymosis. In parallel, *in vitro* studies with human M2–polarized THP-1 macrophages through sensitization with PMA and interleukin (IL)-4 showed that treatment with *Arnica* modulated the expression of various genes involved in the regulation of chronic inflammation, such as a CXCL1, CXCL2, IL8 and BMP2, which encode vasoactive chemokines and cytokines [33]. In another experiment, dilutions 2c to 15c upregulated genes HSPG2, FBN2 and FN1, involved in the modulation of the extracellular matrix with participation in wound healing. The results also evidenced downregulation of some genes related to the aerobic metabolism, which suggests regulation of oxidative activity and consequently probably of *in vivo* tissue damage. In addition, *Arnica montana* 2c increased cell migration [34]. These findings corroborate the ones of previous *in vivo* studies, in which the action of *Arnica montana* 6c on vascular dynamics in acute inflammation proved to depend on individual variations [35].

Recently, the group chaired by Professor Anisur Khuda-Bukhsh, in India, showed, in cultures of various tumor cell lines, that the regulatory activity of several homeopathic medicines on gene expression occurred through epigenetic mechanisms, such as methylation/demethylation, triggering of pro-apoptotic mechanisms and regulation of telomerase activity [36,37].

In addition to the intracellular environment, also physical-chemical properties of the solvent used for preparation of highly diluted medicines are the focus of recent studies. Starting 2010, when presence of myriads of nanoparticles of variable nature suspended in homeopathic high dilutions was first reported [38], the idea quickly arose that the mechanism of action of homeopathic medicines might be related to nanopharmacology. This finding was repeatedly detected in the past years, particularly in experiments conducted in India [39-41].

In parallel, Demangeat, in France, identified nanobubbles in solutions subjected to agitation [42] which might also act as intracellular nanovectors.

Recently, studies conducted by Steven Cartwright [43,44] found that agitated solutions are associated with changes in the dipole activity of the water used as vehicle. This finding corroborates the hypothesis of electric resonance between medicine and intracellular water. Possibly nanoparticles also participate in this process.

However, it is still not known which of the aforementioned factors are truly determinant for modulation of cell functions to occur in such a refined manner. It is neither known how the information contained in medicines is 'decoded' by living systems at the systemic and epigenetic levels.

To summarize, the homeopathic phenomenon exhibits well-defined peculiar characteristics in which the rationale underlying classical pharmacology (dose-dependence) does not apply. Thus being, a new theoretical basis was suggested by Bastide and Lagache in the 1980s and 1990s, based on fundamental concepts of biosemiotics [45]. Application of the recent experimental findings to this conceptual basis represents a possible path for understanding how the similitude principle works in living beings in a highly specific manner [46]. Yet, this is a long path that we still need to tread.

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Effects of homeopathic high dilutions on *in vitro* models: literature review

Silvia Waisse·

Abstract

Background: the effects of homeopathic high dilutions (HDs) are controversial because they exceed Avogadro's number. Aim: to perform a literature review on the effects of HDs on *in vitro* models. Methods: a systematic search was performed in database PubMed for studies assessing simple HDs on *in vitro* models published from 2007 onward. Results: 28 publications met the inclusion/exclusion criteria; 26 studies demonstrated patent effects of simple HDs on *in vitro* models; most such studies were conducted in countries where homeopathy attained a high level of institutionalization. Conclusions: *in vitro* models patently evidence biological activity of HDs above Avogadro's number and account for effects found in clinical practice. Most studies were conducted in countries where homeopathy is officially recognized, which facilitates access to resources for the development of research.

Keywords

Homeopathy; High dilutions; *In vitro* models; Review

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Introduction

As is known, the action of homeopathic medicines is considered implausible by a part of the scientific community, because they are diluted above Avogadro's number (6 x 10^{-23}). Therefore, the odds of detecting one single molecule in dilutions are practically zero, for which reason homeopathic high dilutions (HDs) cannot have any physical-chemical activity whatsoever [1].

However, countless experimental models sought to explain the effects of HDs in clinical practice and laboratory research. One of such attempts is the so-called "weak quantum theory": based on original research by Atmanspacher et al. [2], several studies suggest that the effects of HDs do not involve local interactions (causal) but a kind of interconnection modeled on the entanglement exhibited by subatomic particles with a common origin [3-7].

According to other authors, the actions of HDs should be understood based on the interaction of starting material and solvent. The information contained in the former is somehow transferred to the latter, which then carries it to the biological target. Indeed, several studies demonstrated measurable physical changes in HDs, including thermoluminescence [8], luminescence delay [9], dielectric dispersion [10,11], fluorescence [12], ultraviolet light transmission [13,14], magnetic properties [15], impedance and other electrical properties [16-18], analogy to spin supercurrents in superfluids [19] and aqueous nanodomain formation [20]. It is worth to call the attention to the studies on proton NMR relaxation started in 1985 [21] and the more than 20 years of research on electromagnetism [7]. A more recent study gathered evidences of the presence of stable water nanostructures in homeopathic HDs through Fourier-transform infrared spectroscopy, visible ultraviolet spectroscopy, fluorescence microscopy and atomic-force microscopy [22].

These studies notwithstanding, the questions on the biological action of HDs remain unanswered. In this regard, a systematic literature review of *in vitro* studies was published in 2007 [23]. *In vitro* studies are free from the complexity and confounding factors inherent to *in vivo* models and clinical trials. In addition, *in vitro* models provide the grounds for the latter and might explain their underlying mechanisms, as well as effects observed in clinical practice. However, the aim of Witt et al.'s review [23] was mainly to assess the methodological quality of studies, rather than their results. The aim of the present study was to perform a descriptive review of publications reporting on *in vitro* effects of simple HDs from 2007 to the present time.

Materials and methods

A search was conducted in February 2017 for articles included in database PubMed published from 2007 onward in any language, using keywords "homeopathy" AND "in vitro". Term "homeopathy" was used because there is no consensus in the literature on how to designate homeopathic HDs (e.g., dynamizations, potencies, serial agitated dilutions, infinitesimal dilutions, etc.). The time frame was established considering that a similar review was published in 2007.

Inclusion criteria: articles describing original research on the effects of simple (not combined) HDs on *in vitro* models. Studies published "ahead of print" in journals included in PubMed were considered.

This search strategy was selected to facilitate direct assessment of the included articles by interested readers, as well as to ensure the methodological quality of the studies (inclusion in database PubMed). For this reason other sources of information were not considered, such as other databases, manual search of references, direct contact with authors, etc.

The analyzed parameters were: 1) country of origin; 2) study aims; 3) tested medicine(s); 4) HD level; 5) experimental model; and 6) effects of HDs compared to controls (positive/negative).

Results

A total of 61 records were located, which were subjected to title and abstract analysis. As a result, 33 records were excluded, because they did not meet the inclusion criteria. After addition of "ahead of print" published articles, 28 studies were included in the present review. The summary of findings is described in Table 1.

Table 1. Summary of findings in *in vitro* studies conducted with homeopathic high dilutions

Author, year	Country	Aims	Medicines	Dilutions	Experimental model	Effects
Santana et al., 2017 [24]	Brazil	Mechanism of anti-inflammatory action	Antimonium crudum	30cH, 200cH	Macrophage-Leishmania amazonensis co-culture	POSITIVE Reduction followed by increase of macrophage spreading; increased percent parasite internalization; potentiation of parasite-induced reduction of cytokine production
Lima et al., 2016a [25]	Brazil	FSH in HD vs. FSH in ponderable dose	FSH	6cH	Ovine preantral follicle development	POSITIVE Increase of follicle diameter; increased survival rate; greater follicle activation rate on day 1
Lima et al., 2016b [26]	Brazil	FSH in HD vs. FSH in ponderable dose vs. 0.2% alcohol	FSH	6cH	Development, hormone production and gene expression in isolated bovine preantral follicles with or without culture medium addition	POSITIVE On cell proliferation, the effect of 0.2% alcohol was greater vs. FSH 6cH, in turn greater to FSH in ponderable dose; estradiol production increased with all treatments; FSH 6cH induced greater connexin 43 production than FSH in ponderable dose

Wani et al., 2016 [27]	India	Anticancer activity	Terminalia chebula	MT, 6x, 6c, 30c	MDAMB-231 and MCF-7 breast cancer cells, and HEK-293 non-cancer cells; nanoparticles	POSITIVE HDs reduced the viability of cancer cells only; all tested HDs reduced the growth kinetics of cancer cells; nanoparticle structure of HD 6cH differed from MT, with particles of 20 nm of diameter
Mondal et al., 2016 [28]	India	Anticancer activity	Psorinum	6x	A549 human lung epithelial adenocarcino-ma cells	POSITIVE Inhibition of cell proliferation; cell cycle arrest in sub-G; ROS production; mitochondrial membrane depolarization; DNA damage; promotion of apoptosis through caspase-dependent, mitochondria-mediated pathway
Lee et al., 2016 [29]	South Korea	Inflammation modulation	Rhus toxicodendron	4d, 30x, 30c, 200c	Mc3t3-E 1 murine pre-osteoblastic cells	POSITIVE Increased COX-2 mRNA and protein expression; increase of PgE2; reduced NO production
Pasetti et al., 2016 [30]	Brazil	Bacterial resistance	Belladonna, nosode	6c, 30c	MRSA	POSITIVE Inhibition of MRSA growth with reduction of DNAse production; increased susceptibility to oxacillin
Guedes et al., 2016 [31]	Brazil	Amphibian metamorphosis	T3	10cH	Rana (Lithobates) catesbeianus tail explants	POSITIVE T3 10cH influenced T3-induced caspase 3 and 7 mRNA expression, with delay of tadpole metamorphosis
Tupe et al., 2015 [32]	India	Protein glycation	Syzygium jambolanum, Cephalandra indica	MT, 30c, 200c	Human red blood cells	POSITIVE Reduction of glycation markers (fructosamine, protein carbonyls and protein-attached sugar); protection against free thiol and amino groups. Phenols and flavonoids were detected in all samples
Samadder et al., 2015 [33]	India	Anticancer activity	Lycopodium clavatum	5c, 15c	HeLa cervical cancer cells and PBMC	POSITIVE Reduced proliferation and viability of cancer cells, without cytotoxicity on normal PBMC; considerable apoptosis of cancer cells, with DNA fragmentation, increased caspase 3 and Bax protein expression, reduction of BcI2, Apaf and citochrome c release. Effect similar to cisplatin on cancer cell survival

Marzotto et al., 2014 [34]	Italy	Gene expression regulation	Gelsemium sempervirens	2c, 3c, 5c, 9c, 30c	SH-SY5Y human neuroblastoma	POSITIVE Changes in the expression of 56 genes on microarray test
Olioso et al., 2014 [35]	Italy	Gene expression regulation	Gelsemium sempervirens	2c	SH-SY5Y human neuroblastoma	POSITIVE Downregulation of most genes in a human neurotransmitter and regulator panel
Siqueira et al., 2013 [36]	Brazil	Effect of influenza virus nosode	Influenza A (A/Aichi/2/68 H3N2)	30x	Biological risk; viral content; effect on MDCK cells and J774G8 murine macrophages	POSITIVE No cytotoxicity; morphological changes in MDCK; changes in MDCK mitochondrial activity; reduced PFK-1 activity in MDCK; increased TNF-α production by macrophages
Huh et al., 2013 [37]	South Korea	Anti-inflammatory activity	Rhus toxicodendron	4x, 30x, 30c, 200c	Primary culture of mice chondrocytes	POSITIVE Increased COX-2 mRNA expression; but for 200c, all HDs inhibited collagen II expression, suggesting chondrocyte dedifferentiation; 30x increased PgE2 release
Lima et al., 2013 [38]	Brazil	Effect of FSH in HD	FSH	6cH, 12cH, 30cH	Survival, activation and growth of ovine preantral follicles	POSITIVE Increased follicle survival and activity; greater follicle and oocyte growth compared to controls; maintenance of follicle viability and ultrastructural integrity after 7-day culture
Mukerjee et al., 2013 [39]	India	Anticancer effect	Thuja occidentalis	30cH	Benzopyrene-induced DNA damage in mice perfused lung cells	POSITIVE Increased cell viability; inhibition of benzopyrene-induced stress through ROS and HSP-90 reduction and glutathione increase
Bishayee et al., 2013 [40]	India	Anticancer action mechanism	Condurango	30cH	Modulation of histone acetylation/dea -cetylation in HeLa human cervical carcinoma cells	POSITIVE Cytotoxic effect; reduced HDAC2 activity; reduced DNA synthesis and cycle cell arrest in G1
Arora et al., 2013 [41]	India	Anticancer action	Sarsaparilla, Ruta graveolens, Phytolacca decandra	30cH, 200cH, 1000cH, 10000 cH	Kidney adenocarcino-ma ACHN (Sars), colorectal carcinoma COLO-205 (Ruta), breast carcinoma MCF-7 (Phyt)	POSITIVE Cytotoxic effect; reduced cell proliferation; apoptosis induction; no effect on non-cancer MDCK cells (Sars)
Preethi et al., 2012 [42]	India	Anticancer action mechanism	Ruta graveolens, Carcinosum, Hydrastis canadensis, Thuja	200c, 1000c	Dalton's lymphoma ascites	POSITIVE Apoptosis induction

			occidentalis			
Ive et al., 2012 [43]	South Africa	Intoxication self-recovery	Arsenicum album	6cH, 30cH, 200cH	MT4 human lymphocytes exposed to arsenic trioxide (As_2O_3)	POSITIVE Increase cell viability; maximum effect 3 days after treatment with Ars 200cH
Oliveira et al., 2012 [44]	Brazil	Immune effects	Mercurius solubilis	6cH, 12cH, 30cH	Mice peritoneal macrophages	POSITIVE Morphological changes typical of the activated state; increased IFNχ and IL-4 secretion; increased NO and ROS production
Das et al., 2012 [45]	India	Gene expression	Arnica montana	30c	Escherichia coli subjected to ultraviolet irradiation	POSITIVE Reduction of DNA damage and oxidative stress; upregulation of gene repair genes
De et al., 2012 [46]	India	Intoxication self-recovery	Arsenicum album	30c	Escherichia coli exposed to sodium arsenine	POSITIVE Reduction of intoxication effects through inhibition of ROS production
Soto et al., 2011 [47]	Brazil	Cell viability	Avena sativa, Pulsatilla nigricans alone and combined	6cH	Sperm motility; cell membrane and acrosome integrity; mitochondrial membrane potential in swine sperm	NEGATIVE
Frenkel et al., 2011 [48]	USA	Anticancer effect	Carcinosinum, Phytolacca decandra, Conium maculatum, Thuja occidentalis	Carc 30c, Con 3c, Phyt 200c, Thuj 30c	MCF-7 (E+ P+) and MDAMB-231 (E- P-) human breast adenocarcinoma	POSITIVE Reduced cell viability; cycle arrest in G1. Carc and Phyt activity equivalent to 0.12 μM paclitaxel
Hofbauer et al. 2010 [49]	Austria	Mechanism of action in gastric ulcer	Nux vomica, Calendula officinalis	10c, 12c	KATO-III human gastric carcinoma cells	POSITIVE Reduced gene expression of H. pylori-induced heparin-binding epidermal growth factor
Patil et al. 2009 [50]	India	Immunomodulating action	Rhus toxicodendron	6cH, 30cH, 200cH, 1000cH	Human PMN function	POSITIVE Increased chemotaxis; increase of oxidative processes; intracellular fungicide action against C. albicans
Stiegling-Vlitalis et al., 2009 [51]	Germany	Physiological effect	Atropine	6x, 32x, 100x	Rat isolated ileum contractility	NEGATIVE

HD: high dilution; FSH: follicle-stimulating hormone; PMN: polymorphonuclear cells; C. albicans: *Candida albicans*; ROS: reactive oxygen species; HSP-90: heat shock protein 90; HDAC2: histone deacetylase 2; USA: United States of America; E+/E-: estrogen receptor positive/negative; P+/P-: progesterone receptor positive/negative; COX-2: cyclooxygenase 2; PgE2: prostaglandin E2; PFK-1: 6-phosphofructo-1-kinase; TNF-α: tumor necrosis factor alpha; IFNχ: gamma interferon; IL: interleukin; NO: nitric oxide; MT: mother tincture; PBMN: peripheral blood mononuclear cells; mRNA: messenger RNA; H. pylori: *Helicobacter pylori*; MRSA: Methicillin resistant *Staphylococcus aureus*; T3: triiodothyronine; L. amazonensis: *Leishmania (L.) amazonensis*

Discussion

One single previous review on *in vitro* HDs effects was published by Witt el. in 2007 [23]. In that review, *in vitro* effects were defined as the ones induced by HDs on molecular or cellular systems; the same definition was used in the present review. However these 2 studies differ as to their aims: Witt et al. sought to analyze the quality of studies through a score. In turn, we sought to establish whether HDs induce evident effects on *in vitro* models, as the results have more objective and less complexity compared to *in vivo* models and clinical trials and reproduce effects observed in clinical practice and laboratory research.

The present review included 28 studies that met the inclusion criteria, corresponding to 2.8 studies/year, on average. The previous review by Witt el al. located 67 studies, being 46 published in peer-reviewed journals from 1932 to 2005, corresponding to 0.63 articles/year [23]. Therefore, one might infer that the publication rate considerably increased in the past decade, in parallel to the greater institutionalization of homeopathy in many countries. In addition, 19 studies conducted with HDs above Avogadro's number published from 2010 to 2015 were replications of previous experiments [52-53].

The vast majority of the analyzed studies (n= 20; 71.4%) were performed in just 2 countries, Brazil (n= 9; 32.1%) and India (n= 11; 39.3%); the remainder of the studies was conducted in South Korea (n= 2), Italy (n= 2), South Africa, USA, Austria and Germany (n= 1, respectively). Predominance of Brazilian and Indian studies was previously reported [54]. As reasons, one might mention the high degree of institutionalization of homeopathy in these 2 countries, being homeopathy acknowledged as an official medical specialty, included in the public health system and health insurance. In addition, homeopathy (clinical and pharmaceutics) is taught at universities, which facilitates the access to resources for research.

Both experimental models and parameters exhibited wide heterogeneity. In this regard, the results of the present review agree with the ones reported by Witt et al. [23]. In addition, some of the articles reported on later stages of long-term research projects, some of them started in the 1990s.

Within such context, the studies conducted by Guedes et al., at School of Medicine, University of São Paulo, and a European multicenter group chaired by Endler, Interuniversity College for Health and Development, Graz, Austria, stand out. Tadpole metamorphosis is a highly complex and well-studied process, highly sensitive to thyroid hormones. Tadpole tail resorption is a focus of much interest among researchers as experimental system for the study of cell death [55]. Along more than 25 years, Endler et al. conducted countless multicenter experiments with many variations of the basic parameters to prove the hypothesis that non-molecular information is conveyed in biological systems [56]. In addition to showing that thyroxin (T4) in HD slows down metamorphosis in *Rana temporaria*, those authors succeeded in establishing a highly reproducible experimental model [53,57]. In turn, the group chaired by Guedes confirmed Endler et al.'s findings in another species, *Rana catesbeiana,* and also showed that triiodothyronine (T3) in HD alters the effect of T3 in pharmacological dose on apoptosis [31, 58-60].

Among the analyzed studies, the ones on the effects and mechanisms of action of HDs in cancer stand out (n= 8; 28.6%), having their point of departure in research started by

Khuda-Bukhsh more than 35 years ago in India [61]. Khuda-Bukhsh was chair of Department of Zoology, Kalyani University, India, and currently is emeritus professor at the same school, having published 118 studies in reputed scientific journals. Still regarding studies on cancer, the one conducted by Frenkel et al. [48] at the prestigious MD Anderson Center, Houston, TX, USA, is deserving of mention. We should further observe that the activity of HDs was equivalent to the one of standard chemotherapy agents, such as cisplatin and paclitaxel [33,48].

The analyzed studies tested a wide variation of HDs in decimal and centesimal scale; in the vast majority of cases HDs exceeded Avogadro's number. The HD most frequently used was 30cH (10^{-60}) (n= 18), followed by 6cH (10^{-12}) and 200c (10^{-400}), corresponding to 9 studies each.

In relation to the recent identification of nanoparticles (NPs) in HDs [62,63] one study investigated the nanoparticle structure of HD and found differences between mother tincture and dilution 6cH; the latter exhibited NPs with 20 nm of diameter [27]. Curiously, one study reported presence of phenol and flavonoid traces even in HD [32].

In Witt et al.'s review, 76% of the studies reported positive outcomes [23]. Differently, in our review only 7.14% of the studies did not detect any effect of the tested HD. One of those studies [47] sought to establish the mechanism of the beneficial action of homeopathic medicines *Avena sativa* and *Pulsatilla nigricans* to improve human and animal fertility [64,65]. The results indicated that such effect might not be attributed to action on the sperm viability.

The other study [51] is the last in a series started in the 1990s on the effects of HD on well-established physiological models, namely, parasympathetic transmitters. In 1997, Cristea et al. [66] reported action of HD of *Belladonna* – homeopathic medicine prepared from *Atropa belladonna* L., the main alkaloid of which is atropine – on rat isolated duodenum contractility. This study was replicated 3 times, including 2 doctoral dissertations defended at Leipzig University, Germany [67-69]. More recently, Nieber et al. [70] tested atropine and *Belladonna* 100d (10^{-100}) on rat isolated ileum; both HD reduced the amplitude of contractions. Similarly, Alecu et al. [71], from Cluj-Napoca University, Romania, tested the possible action of *Belladonna* 7cH (10^{-14}) as antagonist to pilocarpine-induced muscarinic receptor blockade. The results showed that administration of *Belladonna* 7cH after atropine and before pilocarpine reestablished saliva hypersecretion in rats (< 0.0001). Differently, Siegling-Vlatikis et al. [51] did not detect any effect of atropine 6d, 32d or 100d on acetylcholine-induced isolated ileum contractility in rats.

Many different cellular and subcellular actions were evidenced, reiterating results obtained in clinical practice and *in vivo* animal models. The studies by Lima et al., State University of Ceará, Brazil, showed that follicle-stimulating hormone (FSH) 6cH (10^{-12}) increases the viability, survival rate, early activation rate and hormone production in ovine preantral follicles [25,26,38].

Several studies reported reduction of cancer cell viability, with inhibition of cell proliferation, cell cycle arrest, production of reactive oxygen species (ROS), mitochondrial membrane depolarization, DNA damage, promotion of apoptosis and interference in DNA acetylation/deacetylation [27,28,33,39-42,48].

Similarly, HD were shown to modulate gene and protein expression. In regard to inflammation, studies reported increased expression of cyclooxygenase (COX)-2 mRNA, with increased prostaglandin (Pg) E2 production [29, 37]. In a long series of studies (35, 72-75), the group chaired by Bellavite, University of Verona, Italy, approached the anxiolytic action of homeopathic medicine *Gelsemium sempervirens*. Through sophisticate techniques, such as microarray assay, these authors showed that such action is due to regulation of several genes involved in the mechanism underlying anxiety [35,76].

To be sure, Khuda Bukhsh had suggested 20 years ago that HD act through regulation of gene expression [77]. This hypothesis was tested in dozens of experiments in a wide variety of models. In 2013, it was effectively shown, by means of microarray assay, that the effect of *Condurango* 30cH and *Hydrastis canadensis* 30cH on the gene expression profile of HeLa cells was significantly different compared to placebo in regard to more than 100 genes [78].

As another example of research conducted with *in vitro* biological models, the pioneering work by Passeti et al., Federal University of ABC, São Paulo, Brazil, deserves particular mention. These authors showed that homeopathic (*Belladonna*) and isopathic (diluted and agitated bacteria) HD increase the sensitivity of methicillin-resistant *Staphylococcus aureus* (MRSA) to oxacillin. This group of researchers had previously demonstrated that these same medicines in dilutions 12cH and 30cH were able to significantly inhibit *in vitro* growth of *Streptococcus pyogenes*, while *Arnica montana* promoted bacterial growth [79]. One needs not emphasize the relevance of these findings in the present time, when the presence of multidrug resistant bacteria is felt in everyday clinical practice.

Still concerning infectious diseases, Holandino et al. [80], from Federal University of Rio de Janeiro (UFRJ), have for some time been testing a nosode prepared from the influenza virus. Their studies evidenced a protector effect in clinical practice, which might be accounted for by the action of this medicine in various steps of the anti-infection response, including macrophage activation. Macrophages were also analyzed in a study by Oliveira et al. [81}, in which *Mercurius solubilis* induced morphologic changes typical of the activated state of these cells, increased interferon (IFN)γ and interleukin (IL) 4 secretion and increased nitric oxide (NO) and ROS production.

In turn, Bonamin et al. [82], from Paulista University, São Paulo, Brazil, sought to explain how *Antimonium crudum* develops its previously demonstrated *in vivo* anti-inflammatory and immunomodulating effect (reduced monocyte migration to the infection site; increase of the B cell population in the local lymph nodes). The results showed that *Antimonium crudum* increases macrophage spreading and parasite (*Leishmania amazonensis*) internalization in macrophages, while it has no effect on parasite intracellular digestion, i.e., it has no parasiticide properties. However, production of chemokines (CCCL2) able to attract monocytes is inhibited by treatment. The final result is inhibition of the parasite cycle in the host tissue. This example shows how data gathered in *in vitro* fundamental research, by providing information on the mechanism of action of medicines on the parasite-host relationship, might help clinical practitioners find adequate treatment protocols, particularly when the epidemic genius is used as ground for population-based treatment.

Similarly, relative to leukocytes, Patil et al. [83] found increase of chemotaxis, oxidative processes and intracellular fungicide action against *Candida albicans* with treatment with *Rhus toxicondrendon*, a medicine known for its anti-inflammatory action.

Conclusions

In vitro studies indisputably demonstrate the biological activity of HD above Avogadro's number and account for their effect in clinical practice. Most of the analyzed studies were conducted in countries in which homeopathy is officially recognized, which facilitates the access to resources for research. The information gathered at the cell level helps explain the cell regulation mechanisms triggered by homeopathic treatment. This information might contribute to improve clinical protocols and also understand their limitations.

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Effects of homeopathic high dilutions on plants: literature review

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Abstract

Background: Among the non-conventional assumptions of homeopathy, the use of medicines in high dilutions (HD) is a cause for objections and skepticism among the scientific community, trained within the dose-dependency paradigm of classic pharmacology. Research aiming at evidencing the effects of homeopathic HD has resource to several experimental models (*in vitro*, plants and animals). Aim: To describe the results of studies with high methodological quality that demonstrated positive effects of homeopathic HD on plants. Methods: Taking reviews published until 2015 as reference source, we updated the information through addition of data from recent studies included in database PubMed. Results: From 167 experimental studies analyzed, 48 met the minimum criteria of methodological quality, from which 29 detected specific effects of homeopathic high dilutions on plants through comparison to adequate controls. Conclusions: Despite the substandard methodological quality of most experiments, studies with systematic use of negative controls and reproducibility demonstrated significant indisputable effects of homeopathic HD on plants.

Keywords

Homeopathy; High dilutions; Agriculture; Plants; Phytopathological models; Review

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Introduction

Since homeopathic treatment is grounded on non-conventional assumptions (therapeutic similitude, pathogenetic investigation of medicines on healthy individuals and use of highly diluted and agitated medicines selected according to the full set of characteristic symptoms and signs of patients) its acceptance is resisted by the medical and scientific community, which ignores its specificities and the evidences that support it [1,2]. Used to large and increasing doses that have contrary and palliative action relative to the manifestations of disease, doctors and investigators do not consider the application of a treatment based on infinitesimal or minimal doses of medicines that cause similar disorders to the ones to be cured. This even though they do consider the advances of research in immunotherapy and nanotherapy, based on grounds similars to the ones of homeopathy.

Among the homeopathic assumptions, use of serially diluted and agitated medicines (potencies, high dilutions – HD) with concentration less than 1 gram-molecule (above Avogadro's number, 6.02×10^{-23}) is the reason for the greatest criticism among skeptics, who adhere to the dose-dependent model of modern pharmacology. Denying any plausible effect to homeopathic HD in living beings [3,4], critics attribute the patent improvements induced by homeopathic treatment to the patient-doctor relationship and placebo effect.

To evidence the efficacy of homeopathic medicines in the treatment of diseases and the effectiveness of HD in biological systems, clinical and experimental studies are conducted with human beings, animals, plants, cell cultures, etc. In the present review we describe scientific evidences for the effect of homeopathic HD on plants found in the past decades.

By comparison to other types of studies, research on plants has countless advantages such as: large sample size; large datasets; short duration; low cost; absence of placebo effect; and absence of the ethical issues that apply to animal and human research. However, there are some disadvantages too: systematic pathogenetic trials of medicines have not been conducted with plants that would result in a homeopathic materia medica specific for plants, necessary for the selection of individualized medicines for each plant species and disease type, as we have asserted all along the past decade [5-8]. Then, some relevant parameters or artifact cannot be controlled, which interfere with the development and health of plants and hinder the reproducibility of experiments.

Studies assessing the effect of homeopathic HD on plants are known since 1926 [9]; the first literature review was published in 1984 [10]. Several reviews described the effects of homeopathic medicines on plants [11-16] and analyzed the factors related with improvement of the methodological quality of experiments and corresponding publications (detailed description of experiments, randomization, blinding, control group, statistical analysis of results, systematic use of negative controls and reproducibility, among others).

It should be noticed that systematic use of negative controls (placebo group not subjected to any other intervention) is the ideal method to ensure the stability of a system, exclude false-positive results and assess the specific effect of HD [16]. Reproducibility excludes false-positive results, thus ensuring the scientific quality of experiments [14-17]. As a result of the efforts to improve the methodological quality of

studies, the number of articles on homeopathic fundamental research in peer-reviewed journals considerably increased in the past 2 decades [18], being an indirect indicator of improvement in the experiments.

In the 3 main reviews that analyzed the use of homeopathic medicines in plants [11-13] the experimental results were clustered into 3 groups: a) models using healthy plants [11] useful to investigate issues related with homeopathic potencies and to perform homeopathic pathogenetic trials; b) phytopathological models [12] which are ideal to study the use of homeopathy for management of plant diseases and pests, which is allowed for and used in organic agriculture (agrohomeopathy) [12]; and c) models using plants subjected to abiotic stress (mineral toxicity, salinity, pH, etc.) [13] in which HD of the same stressors are used to re-establish the plants' health.

As mentioned above, the lack of a homeopathic materia medica specific for plants including a large number of signs and symptoms in different species does not allow for the application of the therapeutic similitude principle, and consequently for individualized treatment of diseases and other disorders of plants. In addition to empirical application of homeopathic medicines to various plant disorders, studies evidence the efficacy of biotherapy or isotherapy (therapeutic identity principle) for management of diseases and mineral and chemical imbalance through administration of HD of the biotic (viruses, fungi, bacteria, insects, pests, etc.) and abiotic (toxic agents, NaCl, etc.) stressors that cause such disorders to neutralize them [16-20].

The main aim of the present review was to describe studies that evidenced effects of homeopathic HD on plants, which were clustered in tables according to the 3-group classification mentioned above. Then, based on criteria for methodological quality, we described the most significant experiments and lines of research, including some pursued in Brazil.

Materials and methods

The sources for information on the studies included in the present review were the aforementioned reviews [11-16]. The experiments with the highest methodological quality (Manuscript Information Score – MIS $\geq$ 5) published from 1979 onward were selected. Since the 3 previous reviews analyzed articles published from 1920 to 2015, to update the dataset we added studies published from 2015 to 2017 located through a search in database PubMed using keywords "homeopathy" AND "plant"; "homeopathy" and "agriculture". We also described some Brazilian initiatives for homeopathic research on plants.

Results

The articles that met the inclusion criterion (MIS $\geq$ 5) were clustered into 3 main groups (healthy plants, phytopathological and abiotic stress). The corresponding data were synthesized and described in individual tables.

Table 1. Main studies on the effect of homeopathic high dilutions on healthy plants

Author; year	Species	Aim	Parameters	Treatment	Control	Frequency and mode of application	Effects
Endler et al., 2015 [21]	Wheat	Effect of gibberellic acid in HD on seedling growth in autumn vs. winter-spring	Stalk length	Gibberellic acid 30x	Water; potentized water	Treatments applied to Petri dishes containing seeds	In all autumn experiments gibberellic acid 30x reduced** seedling growth. Results for winter-spring were inconsistent
Majewsky et al., 2014 [22]	Gibbous duckweed (*Lemna gibba*)	Effect of gibberellic acid in HD on seedling growth	Growth rate	Gibberellic acid 14x to 30x	Water; potentized water	Seedlings were kept in Becker glass with nutritive solution and 1 treatment	Increase** of the growth rate with some HD; the plant development-al stage seems to influence response to treatment
Hribar-Marko et al., 2013 [23]	Wheat	Whether seed pre-treatment with gibberellic acid in molecular dose increases the effect of gibberellic acid in HD on seedling growth	Seedling length	Seeds were pre-treated with gibberellic acid in molecular dose (10^{-5}, 10^{-4}, 10^{-3}); treatment with gibberellic acid 30x	Water; potentized water	Application of 2 ml of pre-treatment in Petri dishes containing seed; 4 h later, application of 4 ml of treatments	In the group pre-treated with water gibberellic acid 30x reduced** seedling growth. In the groups given gibberellic acid in molecular dose, the lower the concentration the greater the effect of HD to reduce seedling growth
Kiefer et al., 2012 [24]	Wheat	Effect of gibberellic acid in HD on seed germination	Winter wheat seeds	Gibberellic acid 30x	Water; potentized water	Treatments applied to Petri dishes containing seeds	Gibberellic acid 30x reduced** the germination rate in the 2009-2010 experiments; no difference in 2011. This divergence might be due to poorer seed viability and season of the year
Endler et al., 2011 [25]	Wheat	Effect of gibberellic acid in HD on seedling growth in different seasons of the year	Seedling length	Gibberellic acid 30x	Water; potentized water	Treatments were applied to Petri dishes containing seeds	Gibberellic acid 30x reduced** seedling growth. Best effect in autumn. Causes for difference

							might be poorer seed viability, season of the year and temperature
Pfleger et al., 2011 [26]	Wheat	Effect of gibberellic acid in HD on seedling growth	Seedling length	Gibberellic acid 30x	Water; potentized water	Treatments were applied to Petri dishes containing seeds	Gibberellic acid reduced** seedling growth
Santos et al., 2011 [27]	*Verbe-na gratis-sima*	Effect of *Phosphorus* on plant growth and essential oil concentration	Growth parameters and essential oil content	*Phosphorus* 5cH, 6cH, 9cH, 12cH, 15cH, 18cH, 21cH, 24cH, 27cH, 30cH	Water; hydroalco-holic solution	Treatments applied 3 times per week, 100 ml per vase, along 3 months	Some HD, especially 9cH, increased** plant height and branch and leave dry mass; increased essential oil production
Scherr et al., 2009 [28]	Gibb-ous duck-weed (*Lemna gibba*)	Influence of HD	Growth rate	Gibberellic acid, *Argentum nitricum*, kinetin and *Lemna minor*	Water; potentized water	Plants selected per similar number of leaves and size; kept in Becker glass with treatments	Gibberellic acid 15d, 17x, 18x, 23x and 24x reduced** growth rate
Sukul et al., 2009 [29]	Lady's finger	Influence of plant regulators (CCC, chlorocholine chloride; MH, maleic hydrazide) on plant development	Growth and physiologic-al variables	CCC 30c, CCC 200c, CCC (with copper nanoparti-cles) 30c and MH 30	Potentized hydroalco-holic solution	Leave spraying of treatment diluted 1:550, twice per day, 2 days	All treatments increased** plant growth, chlorophyll content, protein and water amount in leaves; CCC30c with copper nanoparticles was more effective than CCC30c
Baumgart ner et al., 2008 [30]	Dwarf pea	Effect of gibberellic acid in HD on seedling growth	Shoot length	Gibberellic acid 17x and 18x	Water; potentized water	Seeds immersed into treatments 24 h	Gibberellic acid 17x enhanced** growth of seeds harvested in 1997
Sukul et al., 2008 [31]	Pigeon pea	Effects on plant growth	Growth and physiologi-cal variables	CCC 30c, CCC 200c, CCC (with copper nanoparti-cles) 30c and MH 30	Potentized hydroalco-holic solution	Leave spraying of treatment diluted 1:550, 8 days	All treatments increased** plant growth, chlorophyll, protein and sugar content

Scherr et al., 2007 [32]	Gibbous duckweed (*Lemna gibba*)	Effects of HD on growth rate	Growth rate	*Argentum nitricum*, copper sulfate, gibberellic acid, 3-indol acetic acid, kinetin, lactose, *Lemma minor*, methyl jasmonate, metoxuron, *Phosphorus*, potassium nitrate and *Sulphur* 14x-30x	Water; potentized water	Homogeneous plants (number of leaves and size) were placed in Becker glass with nutritive solution; then 46.2 ml of treatments were added	*Argentum nitricum* 24x, 28x, 29; kinetin 14x, 16x, 20x, 26x, 27x, 30x; *Phosphorus* 21x, 25x, 29d influenced** growth rate all along the assessment period
Baumgartner et al., 2004 [33]	Dwarf pea	Effect of plant hormones in HD on seedling growth	Seedling length	Gibberellic acid, kinetin, auxin, abscisic acid 12x to 30x	Water; potentized water	Seeds immersed 24 hours into treatments and placed to germinate	Gibberellic acid 13x, 15x, 17x, 23x; kinetin 19x increased** seedling growth
Chapman 2004 [34]	Lettuce	Effect of homeopathic medicines on plant growth	Plant size and weight	*Sulphur* and *Silicea* in HD	Potentized water	Treatments applied with plants on soil	*Silicea* and *Sulphur* 1LM influenced** plant development
Andrade et al., 2001 [35]	*Justicia pectoralis* Jacq	Effect of HD on *J. pectoralis* growth, coumarin production and electromagnetic field	Growth variables, coumarin yield, electromagnetic field	J. pectoralis, coumarin, guaco, *Phosphorus, Sulphur, Arnica montana*, humic acid 3cH	70% ethanol; 70% ethanol 3cH	Weekly spraying (9) of 2.65 ml/plant of solution (10 drops/l water)	J. pectoralis, humic acid, *Arnica Sulphur* and *Phosphorus* 3cH increased** coumarin yield
Brizzi et al., 2000 [36]	Wheat	Effect of *Arsenicum album* on seed germination	Number of non-germinated seeds	*Arsenicum album* (As_2O_3) 23x to 45x	Water; potentized water	Treatments were applied to Petri dishes containing seeds	HD 30d, 35x, 40x, 42x, 45x enhanced** a seed germination
Betti et al., 1994 [37]	Wheat	Effect of *Arsenicum album* on germination	Germination rate	*Arsenicum album* (As_2O_3) 23x, 25x, 30x, 35x, 40x, 45x	Water; water 30x	Treatments were applied to Petri dishes containing seeds	HDs 40x and 45x increased** seed germination
Pongratz & Endler, 1994 [38]	Wheat	Effect of silver nitrate in HD on germination and seedling development	Seedling size; germination rate	Silver nitrate 24x	Water; dynamized water	Seeds immersed in treatments	Silver nitrate 24x enhanced seedling development
Endler & Pongratz, 1991 [39]	African violet	Effect of indole butyric acid on plant development	Rooting and new leave development	Indole butyric acid 33x	Potentized water	Plant immersion	Enhanced rooting

Pongratz, 1990 [40]	Wheat	Effect of silver nitrate on germination and seedling development	Seedling length; germination rate	Silver nitrate 24x	Potentized water	Seed immersion	Increased** seedling development
Noiret & Claude, 1979 [41]	Wheat	Effect of copper sulfate in HD on germination and seedling growth	Dry and fresh weight	$CuSO_4$ 5c, 7c and 9c	Water; potentized water	Seed immersion	Reduction** of analyzed variables

** Statistically significant difference

Table 2. Main studies on the effect of homeopathic high dilutions on phytopathological models

Author; year	Species	Aims	Parameters	Treatment	Controls	Frequency and mode of application	Effects
Shah-Rossi et al., 2009 [42]	*Arabido-psis thaliana*	Effect of HD on plants infected with *Pseudomonas syringae*	Infection rate of leaves	30 substances 30x	Water; potentized water	Plants fully plunged upside-down for 30 sec into 20 ml of treatments; 1.5 ml of dipping solution dropped onto center of each plant rosette from which leaked into soil, the remainder was added to irrigation solution	Biplantol reduced infection**
Datta, 2006 [43]	Mulberry	Effect of *Cina maritima* on root-knot disease of mulberry	Growth and infection variables	*Cina* 200c and *Cina* MT before and after inoculation	90% hydroalco-holic solution	Plants were sprayed 4 times, every 3 days, with 10 ml of treatment; *Cina* MT diluted 1:40 and Cina 200c 1:20	Treatments increased** length and fresh weight of branches and roots, number of leaves/plant and foliar area; and reduced** gall number/plant; treatment before inoculation was more efficacious

Sukul et al., 2006 [44]	Lady's finger	Effect of homeopathic medicines on plants infected with nematode *Meloidogyne incognita*	Root gall number and nematode population	*Cina* 30c, Santonin 30c	Water; hydroalcoholic solution 30c	Spraying for 10 days, starting 7 days after inoculation. Each plant received 5-10 ml of treatment diluted in water 1:1000	Treatments reduced** root gall number and nematode population; and increased soil population
Betti et al., 2003 [45]	Tobacco	Effect of As_2O_3 on tobacco plants inoculated tobacco mosaic virus	Hypersensitivity lesions	As_2O_3 5x, 45x, 5cH and 45cH	Water; potentized water	10 disks of the 3rd or 4th inoculated leave from each plant were placed in Petri dishes with 15 ml of treatments	Decimal HD, 45x in particular, reduced** the number of hypersensitivity lesions
Sukul et al., 2001 [46]	Tomato	Effect of *Cina maritma* in HD on *Meloidogyne incognita*	Root gall number and nematode population	*Cina* 200c and 1000c	Globules impregnated with 90% hydroalcoholic solution	Leave spraying of 10 ml/plant of treatments (7.2 mg globules/ml distilled water), once per day, 10 days	*Cina* 200c reduced** gall number/plant; both HD reduced** the root nematode population
Sukul & Sukul 1999 [47]	Cowpea	Effect of *Cina maritma* on *Meloidogyne incognita*	Gall number; nematode population	*Cina* 1000c	Globules impregnated with 90% hydroalcoholic solution	Leave spraying	Reduction of gall number and root and soil nematode population

** Statistically significant difference. MT: mother tincture

Table 3. Main studies on the effect of homeopathic high dilutions on plants subjected to abiotic stress

Author; year	Species	Aims	Parameters	Treatment	Controls	Frequency and mode of application	Effects
Brizzi et al., 2011 [48]	Wheat	Effect of *Arsenicum album* 45x on germination of seeds previously exposed to As_2O_3	Germination rate	*Arsenicum album* 45x	Distilled water; distilled water 45x	Seeds were exposed to As_2O_3 30 min and rinsed (60 min) with water before treatments, heated 30 min at 20, 40, 70 and 100ºC (5 min)	*Arsenicum* 45x enhanced** seed germination; efficacy was not changed by heating up to 40ºC, but decreased at 100ºC

Jager et al., 2011 [49]	*Lemna gibba*	11 substances in HD on plant growth following exposure to As_2O_3	Number and foliar area; leave color	*Arsenicum album*, nosode, gibberellic acid, arsenic and other substances in various dilutions	Water; succussed water	Exposure to As_2O_3 48 h (intoxication), then plants were transferred to other containers with the treatments	*Arsenicum album* and nosode increased** the growth rate of plants
Jager et al., 2010 [50]	*Lemna gibba*	Effect of 3 substances in HD on plant growth after exposure to As_2O_3	Foliar area	*Arsenicum album*, nosode and gibberellic acid in various dilutions	Water; potentized water	Exposure to As_2O_3 48 h (intoxication), then plants were transferred to other containers with treatments	*Arsenicum album* and nosode increased** the growth rate of plants
Lahn-stein et al., 2009 [51]	Wheat	Effect of *Arsenicum album* in HD on germination of seeds exposed to As_2O_3 and seedling growth	Shoot growth	*Arsenicum album* 45x	Distilled water; distilled water 45x	Seeds exposed to As_2O_3 30 min, rinsed with water (60 min) and applied 3.3 ml of treatment	Reduction** of seedling growth
Binder et al., 2005 [52]	Wheat	Effect of *Arsenicum album* on seeds exposed to As_2O_3	Seedling growth	*Arsenicum album* 45x	Distilled water; water 45x	Seeds exposed to 0.1% As_2O_3 30 min, rinsed with water (60 min); treatments were placed in Petri dishes containing seeds	Reduction** of seedling growth
Brizzi et al., 2005 [53]	Wheat	Effect of As_2O_3 in HD on growth of plants exposed to sublethal dose of As_2O_3	Seedling length	As_2O_3 5x, 15x, 25x, 35x and 45x	Distilled water; potentized distilled water; diluted, not agitated As_2O_3	Seeds exposed to As_2O_3 30 min, rinsed with water (60 min) and applied 3.2 ml of treatments	As_2O_3 45x increased** seedling growth
Brizzi et al., 2000 [54]	Wheat	Effect of *Arsenicum album* on germination of seeds exposed to As_2O_3	Germination rate	As_2O_3 30x, 40x, 42x, 45x	Distilled water; potentized distilled water; diluted, not agitated As_2O_3	Seeds exposed to 0.1% As_2O_3 30 min, rinsed with water (60 min); treatments were placed in Petri dishes containing seeds	$As_2O_3$40x, 42x and 45x enhanced** germination of seeds exposed or not to As_2O_3; diluted As_2O_3 had no effect on germination
Betti et al., 1997 [55]	Wheat	Effect *Arsenicum album* 45x on seeds exposed to As_2O_3	Shoot and root growth	*Arsenicum album* 45x	Distilled water	Single application of 3.2 ml of treatments per container	24% increase** of shoot growth

** Statistically significant difference

Discussion

Recent reviews on the effect of homeopathic HD on plants [11-13] performed until 2011 analyzed 167 experimental studies described in 157 articles. These reviews were performed by a same group of authors, who applied a specific scale (MIS) to assess the methodological quality of studies. Scores (0 to 2) were attributed to 5 items: experiment design; materials; measurement instruments; potentization techniques; and type of controls.

Relative to the 167 analyzed experimental studies, global assessment [16] showed that 84 (50%) included statistical analysis and 48 (29%) attained the minimum score required (MIS ≥ 5) for adequate interpretation of results. 29 studies (17%) used adequate controls to detect specific effects of homeopathic HD; these studies found significant effects with HD over Avogadro's number. 10 studies (6%) systematically used negative controls (placebo group).

Among 48 experimental studies with MIS ≥ 5, wheat was the species most often used (23 studies), followed by dwarf pea and gibbous duckweed (3 studies each). Homeopathic agents most frequently used were: silver nitrate (9 studies), arsenic (8 studies), gibberellic acid (6 studies) and *Cina maritima* (4 studies). Various HD were tested; linear relationship was not found between HD level and effect size. Some studies applied a broad range of HDs to one same experimental model; the results showed that some HDs were active, while others were not. In healthy plants, some HD enhanced germination, while others inhibited it, which evidences the biphasic effect of the various concentrations [16,36].

Analysis of the reviews [16] showed that among 86 studies conducted with healthy plants [11] 43 (50%) included statistical analysis; 29 (34%) had MIS ≥ 5; 15 (17%) used adequate controls; and 5 (6%) systematically employed negative controls [28,30,32,33]. Among 44 studies that tested phytopathological models [12] 19 (43%) included statistical analysis; 6 (7%) had MIS ≥ 5; 6 (7%) used adequate controls; and 1 (2%) systematically employed negative controls [42]. Among 37 studies with plants exposed to abiotic stress [13], 22 (68%) included statistical analysis; 13 (35%) had MIS ≥ 5; 8 (22%) used adequate controls; and 4 (11%) systematic use of negative controls [48,50-52].

To assess the reproducibility of homeopathic experiments in plants, which might confirm the validity of isolated results, recent reviews [14,15] clustered studies per line of research. Among the models with healthy plants, experiments belonging to lines of research 'wheat seedlings & silver nitrate' [9,38,40,56,57), 'dwarf pea and gibberellic acid' [30,33], 'wheat seedlings/stalk growth & gibberellic acid [21-23,25,26] and 'wheat seedlings/germination & gibberellic acid' [24,58] stand out. Among the models with plants exposed to abiotic stress and following treatment, experiments of 'intoxication of wheat seedlings with arsenic & *Arsenicum album*' [48,53-55,59] predominated.

In the first review of studies of HD on plants, in 1984, Scofield [10] called the attention to methodological flaws in study design and development among the analyzed experiments, including: inadequate sample size; no statistical analysis; no detailed description of methods (selection and preparation of medicines, dose, mode of application, etc.) or controls; no double-blinding; inadequate control and reproducibility of experiments; and inadequate outcome measures, among others.

In addition to the aforementioned flaws, easily corrected through rigorous observance of the assumptions of the scientific method, aspects intrinsic to homeopathy make systematization and improvement of experiments difficult, such as the complexity inherent to selection of individualized medicines and application of HD. However, analysis of the studies published in the past decades evidenced a qualitative leap in the research conducted with homeopathic HD in plants, including suggestions for improvement of the design, development and description of this type of experiments [17,60-64].

Although systematic use of negative controls and reproducibility ought to be routine components of future studies with homeopathic HD on plants to ensure the system stability, exclude false-positive results and confirm the validity of results, some aspects might hinder their internal or external reproducibility, such as: relevant parameters that cannot be controlled; inadequate outcome measures; and inherent irreproducibility. Many false-positive results might be related to artifact, be the result of contamination, systematic deviation or random noise of the experimental design, while they are mistakenly interpreted as effects of treatment [14,15].

According to Baumgartner [17,60,65] the reproducibility of homeopathic experiments is a complex issue, as a function of the many factors involved, for which reason interactive approaches are needed.

As mentioned above, we need to stress once again the need for researchers to congregate around the production of a homeopathic materia medica specific for plants, a project launched in Brazil in 2003 [5-8,20,66,67]. The availability of such materia medica is an indispensable requirement for the selection of individualized medicines for treatment of the various plant disorders and diseases. This need recently reasserted by other authors [13,16,22], such materia medica would allow for the application of the classic therapeutic similitude principle based on the similarity between the signs and symptoms elicited by homeopathic medicines during homeopathic pathogenetic trials on plants and the signs and symptoms exhibited by the plant species to be treated. Except for isotherapy – which employs HD of pathogens to prevent and/or treat the harmful effects they themselves cause (analogously to immunization and immunotherapy in humans, respectively), the vast majority of medicines used for homeopathic treatment of plants is empirically and unspecifically selected (without description of the method of selection used), but analogically from the signs and symptoms described in the traditionally materia medica (result of pathogenetic trials of substances on human beings).

As a complementary suggestion and reproducing our work with modern drugs in the past decade (with the goal to use them based on the similarity between the adverse effects they induce and the signs and symptoms of patients, see *New homeopathic medicines: use of modern drugs according to the similitude principle*, www.newhomeopathicmedicines.com) [68-73] a homeopathic materia medica for plants might begin by the survey, systematization and organization of the signs and symptoms elicited in plants by the various substances commonly used in agricultural practice (mineral, pesticides, fertilizers, etc.) to be later complemented with classical homeopathic pathogenetic trials.

To illustrate the validity of this method, the study by Betti et al. [45] employed arsenic trioxide (As_2O_3) to reduce the severity of infection with the tobacco mosaic virus (TMV). The medicine was selected based on the classical therapeutic similitude

principle, i.e., similarity of signs and symptoms, once the authors observed that application of As_2O_3 in toxic dose to tobacco leaves caused lesions similar to the ones of TMV-induced hypersensitivity. The results showed that homeopathic treatment with As_2O_3 in HD significantly increased the plant resistance to TMV, assessed based on the number of hypersensitivity lesions.

Betti's group also succeeded in reducing the symptoms caused by fungus *Alternaria brassicicola* to cauliflower with As_2O_3 35x. This medicine was selected based on a pathogenetic trial of 1mM As_2O_3 on cauliflower, which resulted in symptoms similar to the ones induced by the fungus [74].

Similar studies conducted in Brazil detected similarity between the pathogenetic signs and symptoms of eucalyptus oil on bean plants and the ones caused by fungus *Pseudocercospora griseola,* namely, the etiologic agent of angular leaf spot [66,75]. Studies on reduction of infection of bean plants with *P. griseola* are still incipient, but point to possible control of angular leaf spot with potentized eucalyptus oil [76] via activation of biochemical mechanisms of plant defense [77].

Conclusions

Effect of homeopathic HD on plants was demonstrated in various experimental models with satisfactory methodological quality. These studies systematically employed negative controls and exhibited reproducibility, with consequent reduction of the odds of false-positive results; thus the validity of the results is confirmed.

In addition to the confirmation of the effect of HD on various biological systems, the positive results of homeopathic experiments with plants lend support to the plausibility of homeopathic treatment for human diseases, as factors doctor-patient relationship and placebo effect – commonly mentioned by skeptics to account for the improvement observed in homeopathic clinical practice – are absent.

The methodological flaws of the older studies notwithstanding, the advances in homeopathic research on plants made in the past decades – as a function of the advantages proper to this experimental model and of an increasing interest in the use of homeopathy in agroecology - point to a promising field of research to elucidate the particularities of the mechanism of action of homeopathic HD and to broaden the scope of their therapeutic use.

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Clinical research in homeopathy: systematic reviews and randomized clinical trials

Silvia Waisse·

Abstract

Background: Systematic reviews and randomized clinical trials (RCT) are considered to have the highest level of evidence. Aim: To perform a descriptive review of systematic reviews and RCT on the effectiveness and efficacy of homeopathy. Methods: Data from the report published by Liga Medicorum Homeopathica Internationalis (LMHI) in 2014 were updated by means on a search conducted in database PubMed. Results: 7 systematic reviews with meta-analysis were located, 6 of them concluded that the effects of homeopathy are not compatible with placebo effect; only 1 systematic review arrived to the opposite conclusion, but was severely criticized due to methodological flaws. A total of 19 RCT were published along the analyzed period; 84.2% had at least one positive outcome. Conclusions: Based on the available evidences of the highest level it is not possible to assert that the effects of homeopathic are exclusively placebo effect. On the opposite, specific effects were detected in several studies.

Keywords

Homeopathy; Efficacy; Effectiveness; Systematic review; Meta-analysis; Randomized controlled trials

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Introduction

While we were writing the present article, homeopathy was officially equated to conventional medicine in Switzerland in the terms of mandatory coverage. This decision was made after a 6-year test period (2012-2017) of inclusion of various modalities of complementary and alternative medicine (CAM) upon the population's demand, following demonstration of their effectiveness. Indeed, 2/3 of the Swiss population voted to include CAM in the list of health care procedures paid by the government. However, the final decision had to take into consideration the objections raised by conventional medicine, according to which CAM is inefficacious and harmful [1].

The investigators entrusted the assessment of homeopathy within the Swiss government Complementary Medicine Evaluation Program (PEK) asked themselves: how to produce an answer satisfactory to society and at the same time complying with the requirements of scientific medicine? The answer was: through health technology assessment (HTA), which does not merely assess the efficacy of an intervention, as systematic reviews and meta-analyses do, but also and more especially its effectiveness in the real world, adequacy, safety and economy, i.e., a quite broader and information-rich scope. The conclusion was that there is sufficient evidence for preclinical (experimental) effectiveness and clinical efficacy of homeopathy, as well as for its safety and economy compared to conventional medicine [1].

It is safe to assume that this type of approach is the most judicious for assessment of health interventions. Yet, these studies demand much time (the just mentioned Swiss study needed 5 year preparation and 2-year execution) and funding, which is not easily available. Therefore, in their stead, investigators seek for evidences of effectiveness and clinical efficacy, for which various grading systems were developed. One of the most widely used among such systems, the one formulated by Oxford Centre for Evidence-based Medicine, establishes 5 levels of evidence (with some sublevels) being systematic reviews of randomized clinical trials (RCT) and individual RCT considered as the highest level [2]. Thus being, in the present study we analyzed systematic reviews and individual RCT to establish whether the clinical effects of homeopathy represent or not placebo effect.

The reference source was a previous analysis of such studies published until mid-2014 conducted by Liga Medicorum Homeopathica Internationalis (LMHI) [3]. We updated the data to include the ones published from mid-2014 to the present time through a search in database PubMed without language restrictions. The search was restricted to database PubMed to facilitate the access of the data to readers. For the same reason we did not consider less available sources, such as meeting proceedings and dissertations, among others.

Systematic reviews with meta-analysis

Up to this moment, 1,015 records are included in database CORE-Hom/HRI [4] corresponding to studies of any nature of homeopathic outcomes from RCT to observational studies. A large number of such studies were subjected to systematic

review with meta-analysis. From 1991 to the present time 7 large systematic reviews with meta-analysis were conducted, the results of which are described next.

The first systematic review was performed by Kleijnen et al. in 1991 [5]. These authors analyzed RCT published in any language assessing outcomes of homeopathic treatment in which participants were randomly allocated to groups intervention (homeopathy) or placebo. The studies were also subjected to analysis of methodological quality (emphasizing large sample size; randomization; double blinding; adequate description of patients' characteristics; accurate description of intervention; relevant and well described effect measures; and data presentation in a way to allow readers to verify data and analyses).

The systematic search retrieved 107 studies described in 96 articles; the overall methodological quality of the studies was low. For this reason, the authors chose to analyze only the articles with better methodological quality (score ≥ 60/100).

Fourteen studies tested classical homeopathy (individualized treatment), 18 applied one and the same homeopathic treatment to all patients with a comparable diagnosis, in 26 more than 1 medicine was prescribed to each patient, and 9 were on isopathy (use of the same agent that causes disease subjected to dilution and agitation).

While 42 studies did not include sufficient data for assessment and interpretation of outcomes, their heterogeneity did not allowed for combined analysis. These flaws notwithstanding, the authors inferred that the positive results indicated statistically significant difference relative to the main outcomes between the groups. Thus they concluded: "Evidence is to a large extent positive"; there was no publication bias, i.e., the journal chosen had no relationship with the outcomes; and finally "**The amount of positive evidence even among the best studies came as a surprise to us. Based on this evidence we would be ready to accept that homeopathy can be efficacious, if only the mechanism of action were more plausible**" (our emphasis).

In 1996 Boissel et al. [6] published a report addressed to the Commission of European Communities; the data were re-analyzed in 2007 [7]. This study consisted of a systematic review with meta-analysis of RCT on any disease published or not until June 1998. The authors located 118 records, from which 16 (representing 17 comparisons) were included for analysis for a total of 2,617 patients.

The results were synthesized through the combination of the p values of the primary outcomes of each individual study. For the 17 comparisons combined p was 0.000036, however, with reduction to non-statistically significant level (p= 0.08) when the studies of poorer quality were progressively excluded in sensitivity analysis. Yet the authors concluded "**There is some evidence that homeopathic treatments are more effective than placebo**" (our emphasis).

The following systematic review was performed by Linde et al. in 1997 [8]. These authors considered RCT with sufficient information, after data extraction, to calculate outcome rates in both groups, i.e., intervention and placebo. As in Kleijnen et al.'s study [5] also they included studies with classical homeopathy (single individualized medicine), medicine(s) for definite conditions (here designated as 'clinical homeopathy'), medicine combinations ('homeopathic complex formulas') and isopathy. The quality of studies was assessed by means of Jadad's scale (good quality: > 3) and a *ad hoc* scale (good quality: > 5).

Systematic search located 186 records, which were reduced to 89 after application of the inclusion/exclusion criteria. The studies, published from 1945 to 1995, had 118 participants, on average, and corresponded to 24 different clinical conditions; 37% employed low potencies (1d to 8d, 1c to 4c), 22% medium potencies (9d to 23d, 5c to 11c) and 37% high dilutions (over 23d or 11c). 29% of the studies had high quality (Jadad's and *ad hoc* scales); 45% studies scored ≥3 on Jadad's scale and 38% ≥ on the *ad hoc* scale.

The global odds ratio (OR) was 2.45 favorable to homeopathy (95% confidence interval – 95%CI: 2.05-2.93). To remind briefly, OR= 1 means that exposure does not influence the outcome odds, OR > 1 means that exposure is associated with higher outcome odds, and OR < 1 means that exposure is associated with lower outcome odds [9]. In turn, OR for the studies with high quality was 1.66 (95%CI: 1.33-2.08), being the results patently favorable to homeopathy. In addition neither sensitivity nor subgroup analysis eliminated the statistical significance of the results. OR of the studies with positive results decreased by 27% when publication bias was considered, however, once again without loss of statistical significance.

The authors concluded that "**The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo**" (our emphasis) and that "We believe that a serious effort to research homeopathy is clearly warranted despite its implausibility".

The following year Line and Melchart published a new review [10] which exclusively included individualized homeopathic studies. The authors considered randomized or quasi-randomized clinical trials comparing individualized homeopathic treatment to placebo, no treatment or other treatment. The quality of studies was assessed through a checklist and 2 scores. Studies with sufficient data were jointly subjected to quantitative meta-analysis.

This review analyzed 32 articles that met the inclusion criteria; 28 involved comparison to placebo, 2 to other treatment and 2 to both, for a total of 1,778 patients and variable quality. Among the placebo-controlled studies, 19 had sufficient data for inclusion in meta-analysis, which indicated that homeopathy was more effective than placebo (pooled rate ratio 1.62; 95%CI: 1.17-2.23). However, when analysis was restricted to the studies with better quality significant effect was not detected. The authors concluded "**The results of the available randomized trials suggest that individualized homeopathy has an effect over placebo**" (our emphasis).

In 2005 was published a meta-analysis performed by Shang et al. [11] which analyzed 110 homeopathic RCT (44% clinical homeopathy, 32% complex formulas, 16% classical homeopathy, 1% isopathy and 1 non-classifiable study) matched to 110 conventional medicine RCT per diagnostic category (diseases). On the first and main analysis, which included all the selected RCT, more homeopathic studies had high methodological quality (19% vs. 8%) and in both groups the studies with smaller samples and poorer methodological quality reported more beneficial therapeutic effects. Heterogeneity was lower among the homeopathic RCT, which could not be attributed to chance. Bias was similar in both groups.

Upon restricting analysis to the studies with better quality - larger sample size, being 8 homeopathic and 6 conventional medicine studies, OR was 0.88 (95%CI: 0.65-1.19) for the homeopathic RCTs and 0.58 (95%CI: 0.39-0.85) for the conventional medicine

ones – in this case, OR < 1 was defined as beneficial effect. Considering the presence of bias, the authors concluded "there was weak evidence for a specific effect of homeopathic remedies, but strong evidence for specific effects of conventional interventions. **This finding is compatible with the notion that the clinical effects of homeopathy are placebo effects**" (our emphasis).

The last 2 meta-analyses were chaired by Mathie in 2014 and 2017 [12,13] comprising RCT with individualized and non-individualized homeopathy, respectively, for any clinical condition. The former analyzed 32 RCT for 24 different clinical conditions, and the latter 75 RCT for 48 different conditions, with median n= 43.5 and n= 62.5 patients per study, respectively. In both cases, studies with high methodological quality were very few, just 3 in each review.

In the 2014 review, 22 RCT had data extractable for meta-analysis. Pooled OR was 1.53 (95%CI: 1.22-1.91; p< 0.01) favorable to homeopathy. There was no evidence of publication bias. In analysis of the group of RCT with reliable evidence, pooled OR was 1.98 (95%CI: 1.16-3.38; p= 0.013). According to the authors, the results indicate that "**Medicines prescribed in individualized homeopathy may have small, specific treatment effects**" (our emphasis).

In the 2017 review, 54 RCT had data extractable for meta-analysis. The overall standardized mean difference (SMD) was -0.33 (95%CI: -0.44 to -0.21; p< 0.001) falling to 0.16 (95%CI: -0.31 to -0.02) following adjustment for publication bias. It is worth to observe that SMD is an effect measure used when several studies assess one same outcome, but in different ways, for which reason the results ought to be standardized on a uniform scale before they can be pooled [14]. When improvement is associated with lower scores on the outcome measure, SMD < 0 denotes how much efficacious the analyzed treatment is compared to placebo, and reciprocally SMD > 0 denotes how much less efficacious the analyzed treatment is compared to placebo [15].

Following adjustment for publication bias, the authors concluded that the results led to **rejection of the null hypothesis, i.e., that across the entire range of clinical conditions that have been researched, the main outcome of treatment using a non-individualized homeopathic medicine cannot be distinguished from that using placebo** (our emphasis). In subgroup analysis (RCT with the best quality) pooled SMD fell to a non-significant value, -0.18 (95%CI: -0.46 to 0.09), which indicates that **non-individualized homeopathy was not different from placebo on the basis of reliable evidence** (our emphasis).

A considerable number of reviews of homeopathy for specific clinical conditions were performed. One analysis of such studies up to mid-2014 was published by LMHI [3]. The reviews found favorable results for homeopathy in: upper airway infections and allergies, childhood diarrhea, influenza, postoperative ileus, rheumatic disorders, allergic rhinitis, vertigo and anxiety. This analysis is available online, readers might access it at http://www.lmhi.org/downloads/articles/lmhi-sc-framework-2014-june-15-2015.pdf. Next we updated the data from 2014 to the present time.

Boehm et al. [16] surveyed the literature on homeopathy for fibromyalgia and located 10 case reports, 3 observational studies, 1 non-randomized clinical trial and 4 RCT. The latter were subjected to meta-analysis, which found that homeopathy was effective to reduce the tender point count (SMD: -0.42; 95%CI: -0.78 to 0.05; p= 0.03), pain

intensity (SMD: -0.54; 95%CI: -0.97 to -0.10; p= 0.02) and fatigue (SMD: -0.47; 95%CI: -0.90 to -0.05; p= 0.03) compared to placebo. On those grounds the authors concluded there is "**sufficient basis for discussing the possible benefits of homeopathy for patients suffering from fibromyalgia syndrome**" (our emphasis).

Banerjee et al. [17] analyzed RCT assessing the effects of any modality of homeopathic treatment on allergic rhinitis published until December 2015. Primary outcomes were: improvement of symptoms and global quality of life score. The authors located 11 records, 6 corresponding to isopathy, which were not considered adequate for inclusion in meta-analysis. The overall quality of the studies was low; only 3 studies with variable quality were included for meta-analysis. **The results evidenced favorable results for homeopathy in the improvement of nasal** (relative risk – RR: 1.48; 95%CI: 1.24-1.77and RR: 1.27; 95%CI: 1.10-1.46, respectively) **and eye** (RR: 1.55; 95%CI: 1.22-1.80 and RR: 1.37; 95%: 1.21-1.56) **symptoms at 2 and 4 weeks** (our emphasis). However, the authors observe that the low or uncertain methodological quality of the evidences demand caution upon drawing sound conclusions.

Interestingly, also the occurrence of adverse effects of homeopathic treatment was subjected to systematic review and meta-analysis. In 2016, Stub et al. [18] analyzed RCT published from 1995 to 2011. The authors located 41 studies, for a total of 6,055 patients; 39 studies were included for meta-analysis. Adverse effects were reported in 68% of the studies (n= 28) without significant difference compared to the control group (OR: 0.99; 95%CI: 0.86-1.14). In other words, as the authors stated, adverse effects are commonly reported in studies on homeopathy, being that **the proportion of patients with adverse effects is similar among the ones treated with homeopathy and conventional medicine** (our emphasis).

Recent randomized controlled trials

To complete the present summary description of clinical studies on homeopathy, we next describe RCT published from 2014 to the present time, and thus not included in the LMHI report (Table 1).

Table 1. Homeopathic RCT published from 2014 to the present time

Author/year	Model	Outcomes	Results
Teixeira et al., 2017 [19]	Estrogen 6cH, 18c, 24cH vs. placebo	Reduction of global and partial scores (VAS) of endometriosis-related pelvic pain, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and quality of life (SF-36)	POSITIVE Reduction of global score in group homeopathy (p< 0.001); reduction in partial scores for dysmenorrhea (p< 0.001), noncyclic pelvic pain (p< 0.009) and cyclic bowel pain (p< 0.001); group placebo did not show any improvement. Group homeopathy exhibited significant improvement on BDI and 3 SF-36 domains (physical pain, vitality and mental health); group placebo did not show any improvement

Sorrentino et al., 2017 [20]	*Arnica montana* 1000K vs. placebo	Blood/serum drainage volume, drainage duration, perceived pain and hematomas, days of treatment after total mastectomy for breast cancer	MIXED Reduced bleeding and seroma formation (p= 0.03); no difference in the remainder of outcomes
Chaiet et al., 2016 [21]	*Arnica montana* vs. placebo	Ecchymosis extension and intensity after rhinoplasty with	POSITIVE Intervention groups exhibited 16.2%, 39.2% and 20.4% reduction of ecchymosis extension on days 2/3, 7 and 9/10 after surgery, being statistically significant for day 7 (p= 0.097); lesion intensity increased 13.1% on day 1, followed by 10.9% and 36.3% reduction on days 7 and 9/10, being statistically significant for day 9/10 (p= 0.074)
Alizadeh Charanabi et al., 2016 [22]	Individualized homeopathy vs. placebo	Pain intensity (VAS) and quality of life (SF-36); use of conventional analgesics for moderate-to-severe menstrual pain	NEGATIVE All outcomes improved in both groups, without significant difference
Jacobs et al., 2016 [23]	Commercial homeopathic syrup vs. placebo, 3 days	Change in upper airway symptoms 1 h after intake; pooled score (nasal discharge, cough, congestion and sneezing) assessed twice/day along 3 days on a 4-point scale among children 2 to 5 years old	MIXED No difference in symptoms 1 hour after intake. Sneezing, cough and pooled score exhibited significant improvement in group homeopathy on the first 2 assessments
Vilhena et al., 2016 [24]	9 pre-selected homeopathic medicines vs. placebo	Prevention of excess weight gain during pregnancy among women with mental disorders	MIXED No difference in BMI at baseline and pregnancy week 40. 5 min Apgar significantly higher in group homeopathy
Pedrero-Escala et al., 2016 [25]	Adjuvant homeopathic formula vs. placebo, 3 months	Clinical progression (pneumatic otoscopy, tympanometry) of children (2 months to 12 years old) with otitis media with effusion treated with mucolytic agents and inhaled steroids	MIXED No difference in the proportion of cured cases or frequency of adverse effects. Incidence of acute respiratory disorders was lower in group homeopathy (p= 0.009)
van Haselen et al., 2016 [26]	On demand conventional symptomatic treatment vs. homeopathic formula (Influcid®) +	Cure of fever and upper respiratory symptoms and Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21), among children	POSITIVE Group homeopathy required less symptomatic medication. Symptoms cured significantly faster (p= 0.0001). Proportion of children without fever on day 3 was higher. Significant

	conventional treatment, 7 days		reduction on WURSS-21 score ($p< 0.00011$)
Siqueira et al., 2016 [27]	Isopathic formula vs. InfluBio (H3N2 30x) vs. placebo	Number of URI episodes along 1 year among children 1 to 5 years old	POSITIVE Significant different between the 2 isopathy groups and placebo ($p< 0.001$). 30.5% of the children in group placebo exhibited 3 or more URI episodes/year vs. 1/year in group InfluBio and none in group isopathic formula
Zafar et al, 2016 [28]	*Chamomilla* vs. pentazocine vs. placebo	Labor pain in healthy women	NEGATIVE No significant difference between the groups
Morris et al., 2016 [29]	Standard physical therapy vs. homeopathic formula + standard physical therapy, 6 weeks	Pain intensity (VAS); Oswestry Disability Index; lumbar spine range of motion; analgesics; patients from both genders, 45-75 years old, receiving physical therapy for osteoarthritis	MIXED Pain improvement, daily functioning and range of motion significantly better in group homeopathy. No difference in use of analgesics
Macias-Cortes et al., 2015 [30]	Individualized homeopathy vs. fluoxetine vs. placebo	Depression in peri- and postmenopausal women, Hamilton Rating Scale for Depression, Beck Depression Inventory (BDI), Greene scale, response rate (50% reduction from baseline score), remission rate after 6-week treatment	MIXED Homeopathy and fluoxetine improved the score on Hamilton scale compared to placebo. No treatment changed BDI score. Only homeopathy improved score on Green scale compared to placebo ($p= 0.02$); no difference in remission rate; response rate significantly higher in groups homeopathy and fluoxetine ($p= 0.0$)
Frass et al., 2015 [31]	Adjuvant individualized homeopathy	Overall state of health, subjective well-being in cancer patients under standard anticancer treatment	POSITIVE Significant improvement of overall state of health ($p< 0.005$) and subjective well-being ($p< 0.001$) in group homeopathy
Koley et al., 2015 [32]	Individualized homeopathy vs. placebo	3 VAS (pain, stiffness, function loss), score on Osteoarthritis Research Society International after 2-month treatment of patients with knee osteoarthritis	NEGATIVE Significant reduction of scores in both groups ($p< 0.05$) without difference between them
Peckham et al., 2014 [33]	Standard care vs. homeopathy + standard care vs. supportive listening + standard care	Severity of inflammatory bowel syndrome (IBS) after 26-week treatment	MIXED Interim ANCOVA adjusted for IBS severity, age and occupation did not detect difference; post-hoc test revealed significant difference favorable to homeopathy

			compared to standard care; 62.5% of patients in homeopathy arm exhibited clinically relevant changes on IBS severity score (vs. 25.0% in arm standard care alone)
Danno et al., 2014 [34]	*China rubra* 7cH + quinine vs. quinine alone; non-blind allocation	Frequency of quinine adverse effects in women with < 3 months pregnancy and malaria	POSITIVE Lower proportion of patients with adverse effects in *China rubra* group on days 0 and 6 (53.9% and 23.3%, respectively); the proportion of patients with adverse effects did not change in control group (58.9% and 82.5%); 72.4% of patients in group intervention and 97.2% of patients in control group reported at least 1 adverse effect (p< 0.0001)
Chand et al., 2014 [35]	Standard anti TB treatment + individualized homeopathy vs. standard anti TB treatment + placebo	Homeopathy as adjuvant for multidrug resistant pulmonary TB; sputum conversion, weight gain, ESR, Hb, chest x-ray	MIXED No difference in conversion rate; greater weight gain (p= 0.071), ERS reduction (p= 0.068) and Hb increase (p= 0.068) in group homeopathy; greater proportion of radiological improvement (p= 0.002); cure rate increased by 11.4%
Chauhan et al., 2014 [36]	Individualized homeopathy vs. placebo, 18 months	TSH and antithyroid antibodies (TOPAb) in children with subclinical hypothyroidism and autoimmune thyroiditis	POSITIVE Greater proportion of TSH and TOPAb return to normal values in group homeopathy (p< 0.006; p< 0.05); 8 children in placebo group (10.5%) progressed into clinical hypothyroidism
Malapane et al., 2014 [37]	Homeopathic formula vs. placebo, 6 days	Wong-Baker FACES Grading scale, changes in signs of symptoms, among children 6 to 12 years old with acute viral tonsillitis	POSITIVE Significant improvement in group homeopathy in: tonsillitis-related pain, pain on swallowing, pharyngeal erythema and inflammation, tonsil size

TB, tuberculosis; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; VAS, visual analog scale; BMI, body mass index; URI, upper respiratory infection; TSH, thyroid-stimulating hormone

Discussion

Six out of the 7 available meta-analyses are favorable to homeopathy, while only Shang et al.'s [11] attributed the clinical effects of homeopathy to placebo effect. Shang et al.'s study had disproportionate repercussion, leading to assert that the "end of homeopathy" had come [38]. Yet, that study was the target of hard criticism, which is reminded here briefly. For a detailed analysis of the methodological flaws of Shang et

al.'s review we recommend Eizayaga's paper [39] available in Portuguese and Spanish in this journal at http://aph.org.br/revista/index.php/aph/article/view/262/327.

Linde and Jonas [40] stressed 2 among various "fundamental problems" in the presentation and discussion of results. First, the authors did not report the excluded studies nor assessed the methodological quality and OR of all the RCT included in the study, as well as the 8 studies included in the final analysis. Then, considering the approach followed in pooled analysis, restriction to the larger studies led to false-negative results. In addition, since the final analysis was based on only 8 and 6 studies (possibly non-matched per disease) the outcome might be easily due to chance.

In turn, Walach et al. [41] point to the argument that small study bias impregnates any clinical study, which might represent a "mortal blow" to homeopathy, since the OR of the larger studies converge around zero. These authors again stress that the analyzed studies were not described, which is necessary to establish whether they were truly representative as stated by Shang et al. Contrariwise, the 6 studies with conventional interventions were carefully selected.

Fisher et al. [42] put the matching of the studies according to quality into question, as the methodological quality was better in the homeopathy studies. Then, Shang et al.'s conclusions were based on mere 8 and unknown clinical trials, which led Fisher et al. to ask what the results would have been were the 21 homeopathic studies with high quality to have been included. In addition, Dantas [43] stresses the fact that Shang et al.'s argument asserting that study size might be a more precise measurement of study quality than the standards assessment techniques is groundless.

Synthetically, the problems in Shang et al.'s meta-analysis might be summarized as follows, according to Eizayaga [39]: 1) biased grounds: homeopathy is implausible, and thus its results must have other causes; 2) study size is the determinant of study quality; 3) the effects detected in homeopathic RCT might be explained by a combination of methodological flaws and bias, which does not account for the results of conventional RCT; 4) arbitrary selection of studies, with major imbalance, which makes them non comparable, in addition to including 3 conventional interventions that later on were banned by the Food and Drug Administration (USA); 5) arbitrary sub-selection in the final meta-analysis, while the initial criterion established by the authors (matched RCT) was dismissed; 6) when the authors finally communicated the 8 homeopathic RCT used, they were found not to be representative of homeopathy.

A total of 19 RCT on homeopathy published from 2014 to the present time were located in database PubMed. The single source available for comparison is a review from 2015 by Mathie et al. [44} which covered the period from 1995 to 2015 to compare it to the state of the art in 1994 [45].

The annual rate detected in the present review (5.43 studies/year) is smaller compared to Mathie et al.'s [22], 10-12/year, possibly because we restricted the search to database PubMed and only included controlled studies (placebo, no treatment or other treatment).

A little more than one-third of the studies tested individualized homeopathy (n= 7, 36.8%); the vast majority used non-individualized homeopathy/complex formulas, 1 study tested isopathy [27] and another semi-individualized homeopathy (pre-selection

of 9 medicines) [24]. In Mathie et al.'s review [44], almost half of the studies used individualized homeopathy (45.30%).

In the present review, only 15.79% (3/19) of the studies reported negative results; all the others had positive (n= 8, 42.10%) or mixed (n= 8, 42,10%) results. In Mathie et al.'s study [44], 44.44% (16/36) of the studies reported positive results; 30.55% (11/36) reported negative results and 25.0% (9/36) were inconclusive. These data point to possible occurrence of publication bias, which naturally can only be assessed in future systematic reviews with bias analysis. There was not considerable difference between results and homeopathic approach (individualized, non-individualized, semi-individualized or isopathy).

Conclusions

On the basis of the available evidences, considering the ones of highest level (systematic reviews and RCT) only, one might not assert that the effects of homeopathy are exclusively placebo effect. Contrariwise, specific effects were detected. Inasmuch as the mechanism of action of homeopathy is becoming increasingly plausible (see the other articles included in the present dossier), the remaining doubts on its efficacy and effectiveness will be gradually dispelled.

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Potentized estrogen in homeopathic treatment of endometriosis-associated pelvic pain: A 24-week, randomized, double-blind, placebo-controlled study

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Abstract

Objective: To evaluate the efficacy and safety of potentized estrogen compared to placebo in homeopathic treatment of endometriosis-associated pelvic pain (EAPP). Study design: The present was a 24-week, randomized, double-blind, placebo-controlled trial that included 50 women aged 18-45 years old with diagnosis of deeply infiltrating endometriosis based on magnetic resonance imaging or transvaginal ultrasound after bowel preparation, and score ≥ 5 on a visual analogue scale (VAS: range 0 to 10 points) for endometriosis-associated pelvic pain. Potentized estrogen (12cH, 18cH and 24cH) or placebo was administered twice daily per oral route. The primary outcome measure was change in the severity of EAPP global and partial scores (VAS) from baseline to week 24, determined as the difference in the mean score of five modalities of chronic pelvic pain (dysmenorrhea, deep dyspareunia, non-cyclic pelvic pain, cyclic bowel pain and/or cyclic urinary pain). The secondary outcome measures were mean score difference for quality of life assessed with SF-36 Health Survey Questionnaire, depression symptoms on Beck Depression Inventory (BDI), and anxiety symptoms on Beck Anxiety Inventory (BAI). Results: The EAPP global score (VAS: range 0 to 50 points) decreased by 12.82 ($p< 0.001$) in the group treated with potentized estrogen from baseline to week 24. Group that used potentized estrogen also exhibited partial score (VAS: range 0 to 10 points) reduction in three EAPP modalities: dysmenorrhea (3.28; $p< 0.001$), non-cyclic pelvic pain (2.71; $p= 0.009$), and cyclic bowel pain (3.40; $p< 0.001$). Placebo group did not show any significant changes in EAPP global or partial scores. In addition, the potentized estrogen group showed significant improvement in three of eight SF-36 domains (bodily pain, vitality and mental health) and depression symptoms (BDI). Placebo group showed no significant improvement in this regard. These results demonstrate superiority of potentized estrogen over placebo. Few adverse events were associated with potentized estrogen. Conclusions: Potentized estrogen (12cH, 18cH and 24cH) at a dose of 3 drops twice daily for 24 weeks was significantly more effective than placebo for reducing endometriosis-associated pelvic pain. Trial registration: ClinicalTrials.gov Identifier: https://clinicaltrials.gov/show/NCT02427386.

Keywords

Homeopathy; Endometriosis; Pelvic pain; Homeopathic remedy; Rebound effect; Placebo; Randomized controlled trial

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Related papers:
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Randomized, double-blind trial on the efficacy of homeopathic treatment in children with recurrent tonsillitis·

Sergio E. Furuta[1], Luc L.M. Weckx[2], Claudia R. Figueiredo[3]·

Abstract

Objective**:** The efficacy and safety of homeopathic treatment was investigated on children with recurrent tonsillitis justifying surgery. Methods**:** Prospective, randomized, double-blind clinical trial that included 40 children between ages of 3 to 7 years old; 20 children were treated with homeopathic medication and 20 children with placebo. Follow up was 4 months per child. Assessment of results was clinical by means of a standard questionnaire and clinical examination on the first and last day of treatment. Recurrent tonsillitis was defined as 5 to 7 episodes of bacterial acute tonsillitis per year. Results: From the group of 18 children who completed homeopathic treatment, 14 did not present any episode of acute bacterial tonsillitis; from the group of 15 children who received placebo 5 patients did not present tonsillitis; this difference was statistically significant (p= 0,015). None of the patient exhibited side effects. Conclusions**:** Homeopathic treatment was effective in children with recurrent tonsillitis compared to placebo, 14 children (78%) were no longer indicated surgery. Homeopathic treatment was not associated with adverse events.

Keywords

Homeopathy; Recurrent tonsillitis; Children; Randomized controlled trial

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Introduction

Acute tonsillitis is an acute infectious inflammation of the palatine tonsils; antibiotic treatment is commonly indicated. In the first half of the 20th century, tonsillectomy and adenoidectomy came to be indicated in the presence of minimal symptoms as routine surgery for almost all childhood diseases. Starting in the 1960s, several studies demonstrated the inefficacy of surgery in many cases, and doubts on its indication arose. By that time, research began to be conducted on the immune role of Waldeyer's lymphatic ring, resulting in more conservative and judicious indication of surgery [1].

Homeopathy, formulated by the German doctor Samuel Hahnemann in 1796, is successfully used for prevention and treatment of palatine and pharyngeal tonsil disease, with reduction of the number of patients indicated surgery [2]. However, the literature on the efficacy of homeopathy is scarce.

The present randomized double-blind study sought to assess the efficacy and safety of homeopathic treatment for children indicated tonsillectomy for recurrent tonsillitis.

Materials and methods

Patients

Forty patients cared at the pediatric otorhinolaryngology outpatient clinic of São Paulo School of Medicine, Federal University of São Paulo (EPM/UNIFESP) and São Paulo Hospital were selected from March 2000 to September 2001. Eligible participants were children 3 to 7 years old indicated tonsillectomy for recurrent tonsillitis while they waited for surgery. Patients with systemic diseases or immunodeficiency were excluded.

Bacterial acute tonsillitis was defined as presence of sore throat, fever (> 37.8 ºC), prostration, pain on deglutition, lack of appetite and enlarged neck lymph nodes; hyperemia, swelling and purulent exudate on physical examination [3]. Recurrent acute tonsillitis was defined as 5-7 episodes/year [4].

Participants were randomly and blindly allocated to 2 groups: I- n= 20, subjected to homeopathic treatment for 4 months; II – n= 20, subjected to placebo for 4 months.

Parents/guardians were informed as to the study goals and signed an informed consent form. The study was approved by the research ethics committee of EPM/UNIFESP (ruling no. 012/00).

Treatment

Treatment consisted in administration of 3 homeopathic medicines for all patients in group I, selected according to Costa's [5] and Linhares' [2] experience: 1) individualized constitutional medicine, i.e. chosen based on the similarity of the

patient's physical and mental signs and symptoms as collected during interview and physical examination; remedies were administered in potency 30cH, one single dose; patients were assessed every 4 weeks along 4 months; medicines were selected using Digital Homeopathic Repertory II [6]; 2) *Baryta carbonica* 6cH, daily, along 4 months; the proving of this remedy matches the local characteristics of the palatine tonsils; and 3) isopathic medicine composed of ß-hemolytic *Streptococcus*, *Staphylococcus aureus, Haemophilus influenzae* and Tonsil, 12cH, daily, for 4 months.

Group II received placebo instead of the constitutional remedy, one single dose; placebo instead of *Baryta carbonica* 6cH; and placebo instead of the isopathic combination; the latter 2 daily for 4 months.

Both investigators and patients were blinded to intervention. Randomization was performed by the homeopathic pharmacist who prepared the medicine. The code was broken only after the end of the treatment of all patients. Placebo was 30% ethanol, namely, the solvent used for preparation of homeopathic medicines; ethanol is used as preservative. All the medicines were prepared according to the Brazilian Homeopathic Pharmacopoeia [7].

Clinical assessment included application of a questionnaire once per month for 4 months to investigate the frequency and intensity of tonsillitis episodes. In addition, all the participants were subjected to otorhinolaryngological assessment (oral inspection, anterior rhinoscopy and otoscopy) on the first and last day of treatment, performed by an otolaryngologist from the pediatric otorhinolaryngologicy staff, EPM/UNIFESP.

Patients who developed acute bacterial tonsillitis during the study period were treated with antimicrobial agents. At the end of the study, all the cases with surgical indication were referred to surgery.

Statistical analysis

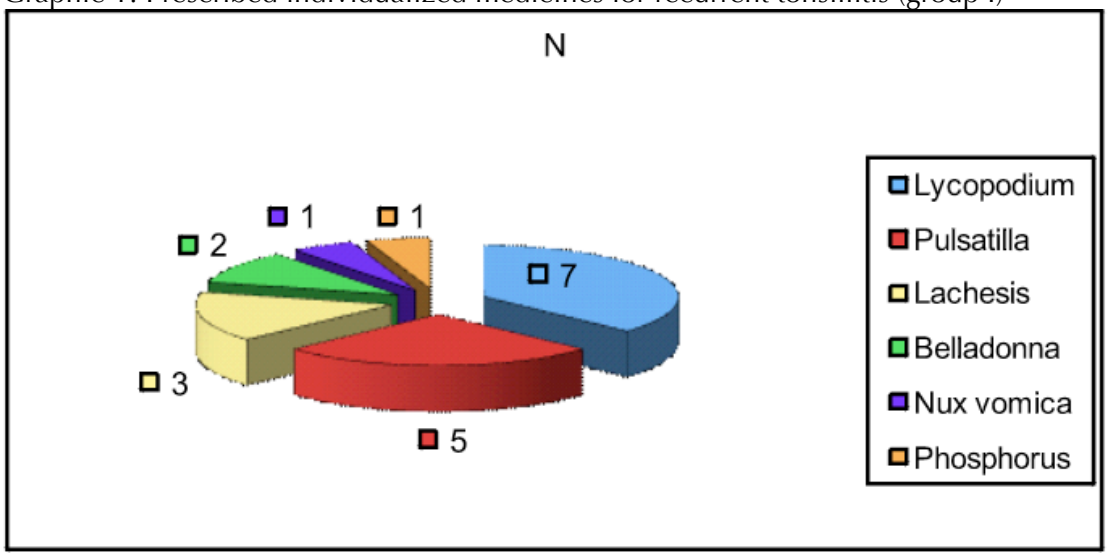
Statistical analysis was performed by means of Fisher's exact test or an extension for tables larger than 2 x 2. The statistical level was set to p= 0.05 (5).

Results

Forty children aged 3 to 7 years old diagnosed with recurrent tonsillitis and surgical indication were initially recruited. However, only 33 patients completed the study. 20 (61%) were female and 13 (39%) male. Seven participants dropped out, being 2 from group I (homeopathy) and 5 from group II (placebo). The 2 children in group I dropped out because they lived too far from the hospital (cases 24 and 37). In group placebo, 1 child moved to another town (case 4), 1 had tonsillitis and febrile seizure (case 22) and 3 dropped out for unknown reasons (cases 14, 27 and 37).

The constitutional medicines selected for children in group I were: *Lycopodium clavatum*, *Pulsatilla nigricans, Lachesis muta, Belladonna, Nux vomica* e *Phosphorus* (Graphic 1).

Graphic 1. Prescribed individualized medicines for recurrent tonsillitis (group I)



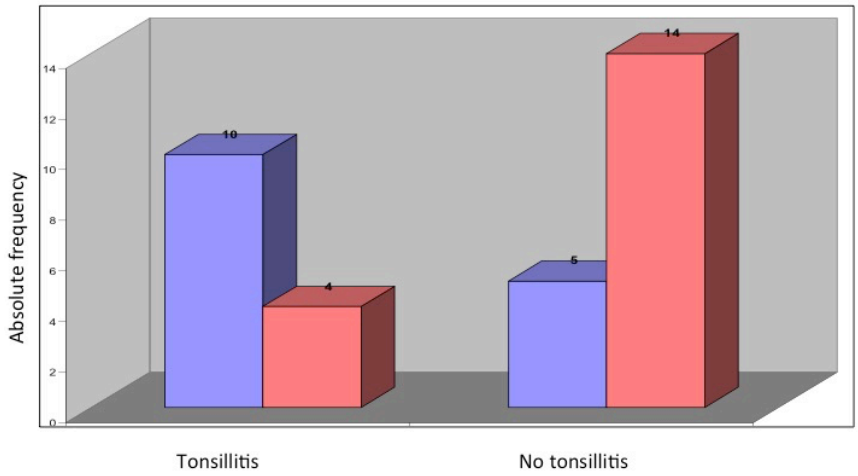
Four (22%) participants in group I (homeopathy) had acute tonsillitis and were treated with antibiotics; 14 patients (78%) did not develop tonsillitis (Table 1; Graphic 2). Ten (67%) patients in group II (placebo) had tonsillitis and were treated with antibiotics (Table 1; Graphic 2); 5 patients (33%) did not have tonsillitis. The 4 and 10 children, respectively, who had tonsillitis were referred to surgery.

Statistical analysis revealed significant difference (p= 0.015) showing greater efficacy of homeopathic treatment compared to placebo. Neither group exhibited adverse events.

Table 1. Clinical progression of participants; Fisher's exact test (p= 0.015)

Group	No tonsillitis	Tonsillitis	Total
Placebo	5	10	15
Intervention	14	4	18
Total	19	14	33

Graphic 2. Clinical progression of participants; Fisher's exact test (p= 0.015) (blue: placebo; red: intervention)



Discussion

Homeopathy is used as option for treatment of recurrent tonsillitis to avoid abuse of antibiotics and reduce surgical indication. In 1941, Lustoza [8] published an article entitled "Throat diseases and their homeopathic treatment", which is valid to this day, thus demonstrating the permanence of homeopathic notions and treatments over time.

The well-known difficulty for randomized double-blind trials of homeopathy is due to need to individualize each treatment, a *sine qua non* for application of the therapeutic similitude principle. Homeopathy approaches the patient as a whole, rather than his/her symptoms or diseases. Application of the therapeutic similitude principle led to select 6 different, individualized medicines for one and the same condition, namely, recurrent tonsillitis. The average duration of the first consultation was 60 minutes. All the participants were seen by one and the same doctor, which limited the sample size.

The placebo effect of a good doctor-patient relationship is a subject of discussion opposing conventional and homeopathic doctors. The former adduce that the efficacy of homeopathic treatment derives from suggestion (placebo effect). The latter cite the use of homeopathy in animals and children, who are not likely to be influenced by their relationship with doctors. Gonçalves, in his study with rats, advocated the experimental model, to avoid the effect of the "doctor-patient" relationship [9].

Although Hahnemann [10] recommended the use of one single remedy for treatment of chronic diseases, in the present study we preferred a combination, including the constitutional remedy, an organ-centered remedy and isopathic agents, as a function of the personal experience of the investigators, Costa [6] and Linhares [2]. It is worth to observe that *Baryta carbonica* is considered a classical remedy for recurrent tonsillitis, according to Cairo [11], Costa [5], Tejada [12], Hom [13] and Linhares [2]. The isopathic combination included remedies prepared from the etiologic agents of disease as starting material, to wit, ß-hemolytic *Streptococcus*, *Staphylococcus aureus* and *Haemophilus influenzae,* which are the most often related to acute bacterial tonsillitis [15,16].

A total of 7 patients (17.5%) dropped out from the study, being 2 (5%) from group I (homeopathy) and 5 (12.5%) from group II (placebo). The latter's higher frequency of dropouts might be attributed to lack of motivation to continue treatment, perhaps due to therapeutic failure.

Most patients who seek homeopathy do so for believing it is more natural and safe than conventional treatment. In the present study, no adverse effects of homeopathic medicines were reported.

Conclusions

The results obtained from the clinical assessment of 33 children aged 3 to 7 years old with recurrent tonsillitis randomly allocated to receive homeopathy or placebo and followed up along for 4 months allows concluding: 1) homeopathic treatment was efficient; 14 patients (78%) from group I was spared from surgery; 2) homeopathic treatment was not associated with side effects.

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Do homeopathic medicines cause drug-dependent adverse effects or aggravations?

Flávio Dantas·

Abstract

Critical appraisal of the safety of homeopathic medicines developed recently. This matter is relevant for decision making by doctors, patients and drug regulatory agencies. Despite the apparent implausibility of the action of homeopathic medicines due to the pharmacotechnical processes of dilution and agitation used for their preparation, there are reports in the conventional medical literature on the toxicity of homeopathic medicines, including apparently life-threatening events. Systematic reviews of randomized controlled trials show that homeopathic medicines cause more adverse effects than placebo, albeit mild and transient. Establishing an online monitoring system for collection of data on the adverse effects of homeopathic, herbal or conventional medicines is relevant for non-biased assessment of the information gathered from consumers and health care providers.

Keywords

Homeopathy; Patient safety; Adverse effects; Homeopathic aggravation

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Introduction

The safety of homeopathy has been more scarcely addressed than its efficacy. Reasons might be the implausibility of so highly diluted medicines causing adverse effects, or the lack of a reasonable and scientifically consistent explanation for the effects of homeopathic medicines. However, safety is a highly relevant issue for homeopathic doctors, drug regulatory agency and patients. It is also relevant in the assessment of the mental and physical symptoms that appear in ill individuals, thus complementing the information obtained from homeopathic pathogenetic trials (HPT) conducted with apparently healthy individuals.

Homeopathy has been a historical victim of **disinformation** and **deformation** when approached in pharmacology courses of medical schools. A survey of pharmacology textbooks performed in 1985 showed that authors exhibited only 2 attitudes in regard to homeopathy: either they ignored it or affirmed it is not effective, but merely acts as placebo, however, without providing scientific evidences for such strong assertion [1]. This finding was corroborated more than 20 years later in a survey of medical students [2]. The aim of the present paper is to describe the progression of the scientific knwoledge on the safety of homeopathy to bring light into issues related with the occurrence of adverse effects and the differentiation between homeopathy and placebo effect.

Assessing homeopathy safety

Reports of alleged adverse effects caused by homeopathic medicines published in journals without reviewers specialized in homeopathy illustrate a contradiction that might be fed by prejudice, particular interests or blind passions. Is it reasonable to believe that a medicine to which no effectiveness is attributed, but acts through mere placebo effect, might be able to cause pancreatitis? [3]. Or that it might cause severe adverse effects, while it does not have any therapeutic benefits, i.e., it looks more like a toxic than a medicine? [4]. In the 2 just mentioned instances the drugs used contained various plant extracts, which technically disqualifies them as homeopathic medicines. Severe life-threatening risks were attributed in Israel, in 2010, to the use of an over-the-counter homeopathic baby colic formula [5]. Scientists involved with homeopathy gave a different interpretation to that episode [6] by associating those events to the pathogenetic effects detected in HPT conducted with apparently healthy volunteers.

Occurrence of pathogenetic effects following use of an incorrectly prescribed homeopathic medicine is a part of the caseload of experienced homeopaths. To mention just one example, one of the medical students attending the course on Introduction to Homeopathy given at Medical School, Federal University of Uberlândia (UFU), brought her 7-year-old nephew for consultation at the outpatient clinic of the University Hospital. Being obesity the single problem of the child, there was no need for any other prescription but dietary orientation. Yet, on the student's insistent demand, *Calcarea carbonica* 30cH was prescribed in weekly doses. Less than 2 weeks later, the student asked whether the fact that her nephew had stolen money from his grandmother for the first time in life (which he later on returned, probably for feeling guilty) could be attributed to the remedy. Symptom 'steals money' is attributed to *Calcarea carbonica* in many works on homeopathic materia medica and repertories. Mere chance? A pathogenetic effect of *Calcarea carbonica* in a sensitive individual?

The effects of homeopathic medicines on human beings might be scientifically assessed under 2 circumstances: upon their use on apparently healthy volunteers and in patients subjected to homeopathic treatment. In the latter case, undesirable effects or the so-called 'homeopathic aggravation' might occur. The first systematic review on this subjected was published in 2000 by this author and Hagen Rampes [7]. We prepared an *ad hoc* form to extract data from clinical trials, HPT and case reports and assessed methodological aspects of trials and reports of adverse effects. The latter were classified according to the 4 categories of causality formulated by Naranjo et al. [8]: definite, probable, possible or doubtful.

Our study sought to locate descriptions of adverse effects of homeopathic medicines through a search on electronic databases (MEDLINE, TOXLINE, EMBASE, MCAT/AMED; HOM-INFORM), manual search in medical journals (homeopathic or not), meeting proceedings, bibliographies, literature reviews, clinical and other relevant studies published in English from 1970 to 1995. We also surveyed the information provided by homeopathic pharmaceutical companies and drug regulatory agencies in the United States (Food and Drug Administration) and United Kingdom (Committee on Safety of Medicines). In addition, we contacted specialists in homeopathy. All the included clinical studies were independently analyzed by the 2 authors (FD and HR); HPT were analyzed by a different pair of examiners (one of them FD). All the included articles were reviewed according to preset criteria. Individual forms for data collection were developed for case reports, HPT and clinical trials. The quality of studies and causality attribution of adverse effects was independently performed by the 2 examiners; instances of disagreement were solved by consensus.

For the purpose of the study, homeopathic medicines were defined as potentially toxic or pathogenic substances prepared according to the stipulations in homeopathic pharmacopoeias (thus botanicals and non-homeopathic medicines, i.e., not subjected to dilution and agitation) were excluded. Adverse effects were considered as any unpleasant and undesirable effects attributed to a homeopathic medicine administered in the usual doses to humans for therapeutic purposes. The latter included mental and physical symptoms and signs, as well changes in laboratory tests of biological samples or directly obtained from patients, and other factors related with the quality of life of patients.

Randomized controlled trials: The incidence of reported adverse effects was higher in the group that used homeopathic medicines than in the group given placebo (9.40 vs. 6.17, respectively). The odds ratio (OR) for homeopathic medicines versus placebo was 2.09 (95% confidence interval – CI: 1.52-2.88). It should be noticed that these results were strongly influenced by one single study with OR 4.6. The reported effects were usually mild and transient, as Table 1 shows.

From 55 analyzed clinical trials, only 19 reported adverse effects. From these, only 2 provided detail on how information was collected. Eleven studies reported adverse effects with use of both homeopathic medicines and placebo. Two studies with more than 30 patients per group did not report any adverse effect.

Table 1. Adverse effects (AE) of homeopathic medicines reported in clinical trials (1970-1995)

Author; year	Medicines	AE incidence with homeopathic medicines	AE incidence with placebo	Reported AE
Lökken, 1995	*Arnica* 30x	5 / 24	5 / 24	Unspecific complaints (headache, dizziness)
Reilly, 1994	Allergen 30cH	1 / 11	2 / 13	Aggravation
Reilly, 1986	Pollen 30cH	11 / 56	11 / 52	Aggravation
Reilly, 1985	Pollen 30cH	1 / 10	7 / 25	Aggravation
Labrecque, 1992	*Thuja* 30cH, *Antimonium crudum* 7cH, *Nitricum acidum* 7cH	2 / 84	4 / 87	Stomachache, soft stools, skin rash, tiredness
Attena, 1995	*Anas barbariae* 200cH	77 / 783	17 / 790	Aggravation of flu symptoms: muscle pain, low fever, nasal discharge, headache, skin rash, itch, earache
Wiesenauer, 1995	*Galphimia glauca* 4x	0 / 64	1 / 68	Mild nausea in the morning
Ernst, 1990	Plant formula, mother tincture to 4x	0 / 31	0 / 30	None
Jansen, 1992	Individualized medicine 30c to 1000c	0 / 6	1 / 4	Repeated aggravation (placebo)
Jacobs, 1994	Individualized medicine 30c	0 / 43	0 / 44	None
De Klerk, 1994	Individualized medicine 6c to 200c	12 / 86	13 / 84	Irritability, fever, headache, aggressiveness (2), eczema, vomiting, sweating (2), skin rash (2), changeable mood, obstinacy, hyperactivity, ear discharge, constipation, restlessness, cough, stomachache, nausea, epistaxis, seizures, albuminuria

Homeopathic pathogenetic trials: 15 HTP published in the United Kingdom were analyzed. One study did not include controls, 12 employed a parallel group given placebo and 2 had crossover design. The studies tested different medicines in dilutions ranging from 3x to 200c. The global mean incidence of pathogenetic effects was 54.3%, and the mean incidence of symptoms per sensitive volunteer 18.8. Overall, 267 pathogenetic effects were reported per HPT (varying from 0 to 1,100). The reported effects did not differ much from the ones describe as nocebo in phase I studies conducted with healthy volunteers. However, the methodological quality of the studies, assessed by means of an *ad hoc* index, was very low.

Case reports: An extremely very small number of case reports published in homeopathic journals described adverse effects among patients treated with homeopathic medicines. A total of 19 articles describing case reports or case series and information on adverse effects were analyzed. Most articles published in homeopathic journals reported aggravation of previous symptoms following intake of homeopathic medicines. Articles addressing occurrence of adverse effects with homeopathic medicines published in non-homeopathic journals were rare. In all cases (but for 1, in which a mixture of grass pollen was used) the medication consisted of mixtures of diluted homeopathic medicines and plant mother tincture or low toxic concentrations of metals or acids. The causality level was rated very low. Although it was not possible to conclude that any particular medicine induced more adverse effects, instances were reported with use of *Pulsatilla*, *Baryta carbonica*, *Sulphur*, *Calcarea carbonica*, *Sepia*, *Belladonna*, *Ipeca*, *Phosphorus*, *Borax* and isopathic agents.

As described in the original article [7] indirect risks associated with homeopathic prescriptions were not analyzed. However the authors assumed that such risks could occur given the insufficient demonstration of efficacy for most conditions for which homeopathy was indicated, possible flaws in clinical diagnosis (and in the indication of more adequate therapeutic options) and to the excessive trust of some prescribers in the therapeutic potential of homeopathy.

The main conclusions of the study were: a) homeopathic medicines might cause adverse effects, however, they are usually mild and transient; b) adverse effects of homeopathic medicines are possibly underreported; c) there were several instances of mischaracterization of drugs as homeopathic medicines, since they had not been prepared according to the rules described in homeopathic pharmacopoeias; d) the main risks associated with homeopathy are indirect, depending more on the prescribers than on medicines as such. To summarize, pure homeopathic medicines in high dilutions prescribed by qualified homeopathic doctors are probably safe and would very rarely cause severe adverse effects.

What do experienced doctors think about adverse effects of homeopathic medicines? A questionnaire was applied to homeopathic doctors attending an international conference on homeopathic research held in London to investigate their opinion about the safety of medicines, frequency of adverse effects, medicines most associated with adverse effects and communication of possible aggravation/adverse effects to patients. The sample comprised 51 doctors from various countries, who together represented 646 years of clinical experience with homeopathy (mean: 12.9 years); most doctors routinely prescribed one single medicine (85%). Questions were responded on a 5-point Likert scale. Most participants believed that homeopathic medicines are probably safe (92%) although they might cause adverse effects (71%), however, not likely to cause severe damage (75%). According to 58% of the responders, homeopathic aggravation ought not to be included among adverse effects; 26% had the opposite opinion. The frequency of adverse effects observed in practice was low, just occasionally (45%) or seldom (41%). The medicine most associated with adverse effects was *Sulphur* (skin manifestations), followed by *Sepia*, *Lachesis* and *Natrum muriaticum*. Most participants asserted they preferred to inform patients as to the possible occurrence of aggravation following medicine intake, which occurrence is even desirable, because it represents a sign of favorable prognosis. Only 4 doctors reported not to comment with patients about possible aggravation at the time of prescribing [9].

In regard to homeopathic aggravation, Grabia and Ernst [10] published in 2003 a systematic review on the occurrence of this phenomenon following use of homeopathic medicines compared to placebo in controlled clinical trials. A total of 24 studies were included; occurrence of aggravation was very low. Overall, 50 episodes of aggravation corresponded to participants given placebo, and 63 (26% more) to participants given homeopathic potencies.

A prospective study was conducted at a homeopathic outpatient clinic affiliated with the Italian health system with patients treated with classical homeopathy to investigate the incidence of adverse effects. Analysis was performed by a doctor who had not participated in direct patient care. The results showed that only 9 adverse reactions had been reported along 335 consecutive consultations, which corresponds to an extremely low frequency, 2.68%. In turn, among 116 patients cared at the Bristol Homeopathic Hospital who responded a questionnaire on the follow-up visit (after 2-6 weeks), 11% reported adverse effects, 24% aggravation, 27% new symptoms and 18% reappearance of older symptoms [12]. Thorough study of the so-called homeopathic aggravation is needed to improve its management, including more precise knowledge of the medicines and dilutions most associated with such events. To attain accurate knowledge on the adverse effects of homeopathy and increase the safety of treatments, such studies should be prospective and in large-scale, with integrated collaboration of doctors.

In 2012 Posadzki, Alotaibi and Ernst [13] published a systematic review of case reports or case series describing adverse effects of homeopathy. A total of 38 instances were included (1,159 patients); 30 corresponded to direct adverse effects of homeopathic medicines, and 8 to adverse effects appearing during the replacement of conventional by homeopathic medicines. According to the authors, the adverse effects ranged from mild to severe, including 4 deaths; allergic reactions and intoxication were the most common adverse effects. However, those authors mistakenly considered non-diluted mother tincture of poisonous plants (e.g., aconite) or toxics (e.g., arsenic) as homeopathic medicines; *Rhus toxicodendron* was the medicine most frequently involved in such reactions.

Posadzki et al.'s study was the subject of strong criticism, including requests for retraction, since it included misattribution of causality (e.g., bladder cancer appearing 7 years after the use of a homeopathic medicine [14]) or misinterpretation of attribution of the adverse outcome to homeopathy that had not been done by the authors of the original report [15], in addition to flaws in the description of cases. One of the included studies, performed by Brazilian authors [16], reported 2 cases of alopecia following mesotherapy designated as "homeopathic mesotherapy". As a fact, treatment consisted of injection of *Lilium* compositum, *Solanum* compositum, *Thuja* and *Tanacetum* into the scalp of patients with androgenetic alopecia, being these botanicals and not homeopathic medicines. In addition, laboratories make mistakes in the manufacture of medicines, as shown by a study from 1986 on differences between the arsenic concentration informed in the labels of 4 from 6 samples of over-the-counter medicines sold in USA, besides larger amounts of arsenic in 2 of such samples [17].

A new systematic review on the adverse effects of homeopathy was published in 2016. This review analyzed clinical trials published from 1995 to 2011 [18], i.e. after the first review conducted by Dantas and Rampes [7]. A total of 28 studies (out of 41) with high methodological quality, according to the Cochrane Collaboration criteria, reported adverse effects. About 68% of them were rated mild and 25% moderate, which

corroborates the results of the 1995 review. Five studies reported homeopathic aggravation, mostly (85%) rated mild. A parallel meta-analysis led the authors to conclude that the proportion of patients who had used homeopathic medicines and had adverse effects was similar to the one of patients given placebo or conventional medicines in randomized trials. However, such similarity was put into question after reanalysis by Mathie et al. [19] which pointed to significant difference in the frequency of adverse effects between homeopathic medicines and placebo (220/2,436 vs. 157/2,400, OR: 1.42) and significantly lower frequency in the case of homeopathy compared to conventional medicines (43/355 vs. 71/401, OR: 0.64). The results of this reanalysis were not debated by the review authors, thus the results obtained by the original systematic review [7] were reaffirmed.

Final considerations

Analysis of the safety of homeopathy medicines and whether they might cause adverse effects involves aspects beyond the purely technical ones discussed in the present review. The latter indicate that homeopathic medicines are active and different from placebo; they were associated with higher incidence of adverse effects compared to placebo in randomized controlled trials, albeit mild and transient. One needs to understand the **simplicity** involved in the discovery and production of homeopathic medicines, which are prepared from substances patently toxic for humans when used in ponderable dose or that cause pathogenetic effects when tested in potentized doses on healthy volunteers. Competition within the pharmaceutical industry and multiple economic interests cannot be omitted in discussions on the efficacy, effectiveness, safety and cost-benefit of homeopathy. Clinical studies sponsored by the pharmaceutical industry tend to favor its new products over the conventional ones when compared to studies funded by other sources or non-profit organizations [20].

If from the ethical point of view respect for the autonomy of both patients – resulting from various determinants, such as expectations, financial cost and quality of life – and doctors – who make decisions based on scientific evidence - is imperative, then society needs to be properly informed as to the results of non-biased studies of homeopathic medicines. At the same time, to avoid premature and fallacious generalizations against homeopathy, special attention should be paid to the surveillance of the diligent practice of homeopathic doctors and laboratories or pharmacies that manufacture homeopathic medicines.

Although the direct risks of homeopathic medicines are very low, indirect risks derived from incorrect medical practice deserve particular attention. **Competence-based medicine** seeks to integrate medical ethics and scientific truth according to each professional's experience [21]. Deviations from correct professional behavior by one or a few homeopathic doctors should not be imprudently attributed to all the professionals, as sometimes is the case. As in the case of other medical specialties, one needs to know how to separate the wheat from the chaff instead of confounding them and contaminating an entire professional community with false allegations.

To conclude, fortunately much advance was made in the knowledge on the safety of homeopathic medicines and homeopathy along the past 2 decades. An editorial published in journal *Homeopathy* in 1999 [22] made several recommendations to improve the monitoring for adverse reactions to homeopathic medicines. Noteworthy

attention was paid to the collection of data on safety in recent homeopathic clinical trials, in addition to several studies conducted in outpatient clinics and new systematic reviews. However, a long path must still be walked to accept that medicine is based on transient truths and must be practiced with full attention and correct intention. Medical wisdom demands from doctors knowledge of their own limits and to admit as true, to be implemented in their practice, only that which is good for themselves and for the others.

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

Flávio Dantas·

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 HPT 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) 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) changes introduced in the design of HPT to become more rigorous and controlled are described. 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 a fee 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 to 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 experiments') 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 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 rigorous experimental design and adequate techniques for control that will help in 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 evidences 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] point to 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 performed 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 of 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. An excess of rigor? In any case, several years later it became known that volunteer #8 (who had moved to another town) had 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 performed 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 yielding 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 were 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, Table 4) 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).

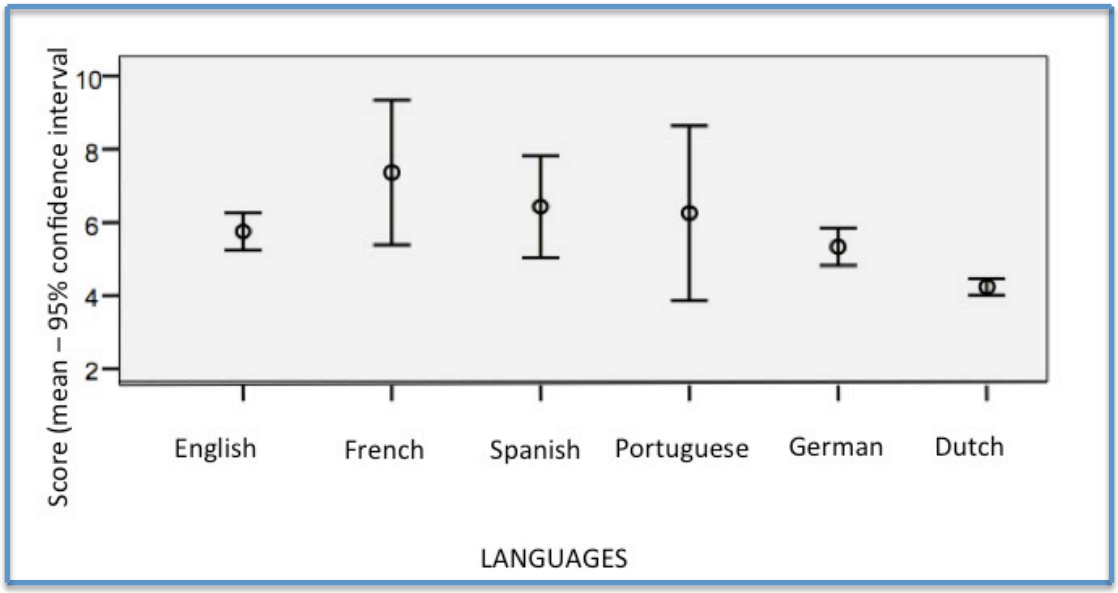
Table 4. Methodological Quality Index for scoring HPT (Dantas score) [46]

	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	One partially stated	One clearly stated or both partially stated	Clearly stated
Criteria for selection of	Not stated	At least one	2 to 4 defined	More than 4 defined

effects		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).

Figure 1. Mean methodological scores by language of publication



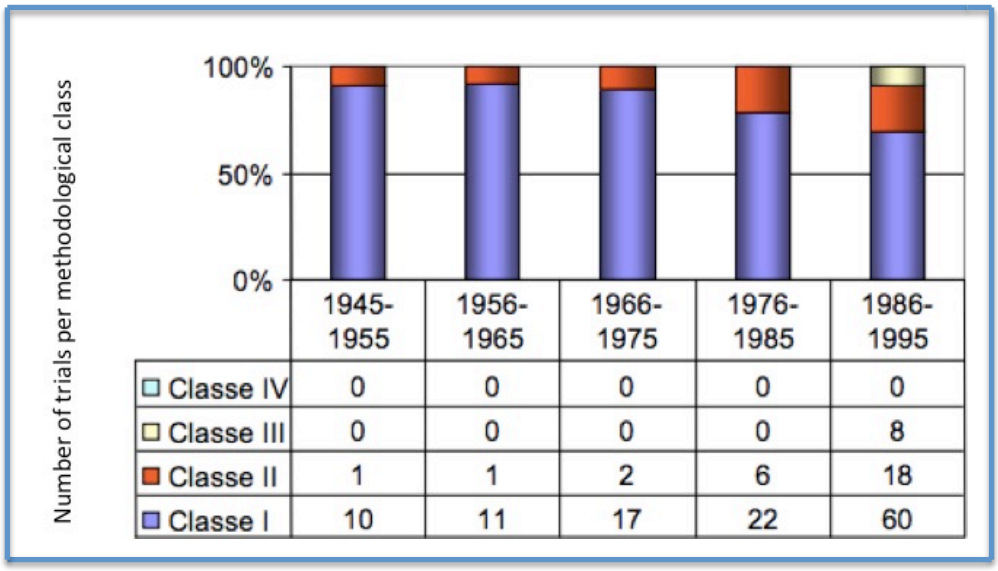
The average score of the analyzed HPT was 5.65, with large predominance of studies with low methodological quality (score 4: 41.5%; 5-6: 34.5%; 7-8: 14%; 9-10: 4.5%; 12: 4.5%; 13: 1.0%); 76% of the studies were included in class I. Only 15 studies described randomization, the first one published in 1961 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 - whether 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 (Figure 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 election 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. Progression of methodological quality per decade, 1945 to 1995 (%)

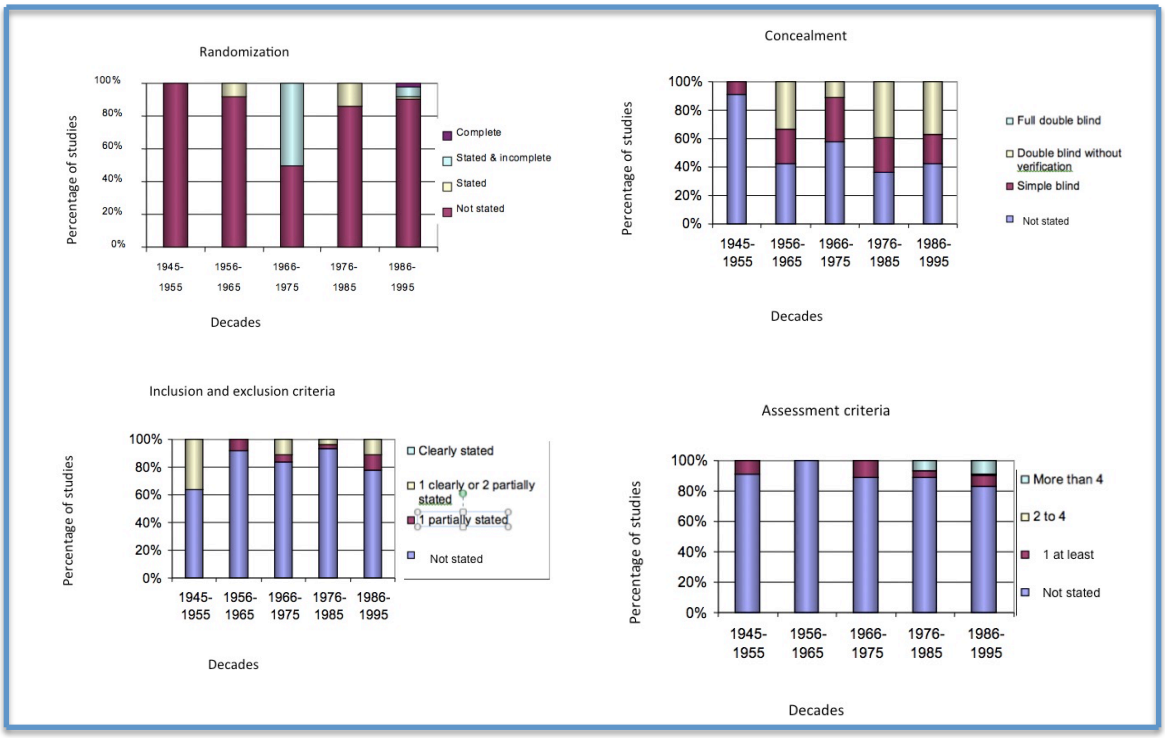


	1945-1955	1956-1965	1966-1975	1976-1985	1986-1995
Classe IV	0	0	0	0	0
Classe III	0	0	0	0	8
Classe II	1	1	2	6	18
Classe I	10	11	17	22	60

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 (Figure 3, [46].

The studies had small sample size (median: 15) and volunteers were often somehow involved in homeopathy learning. There was positive correlation between the Dantas score 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 ones with poorer quality; 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.

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



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 ones with poorer quality.

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 group *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.

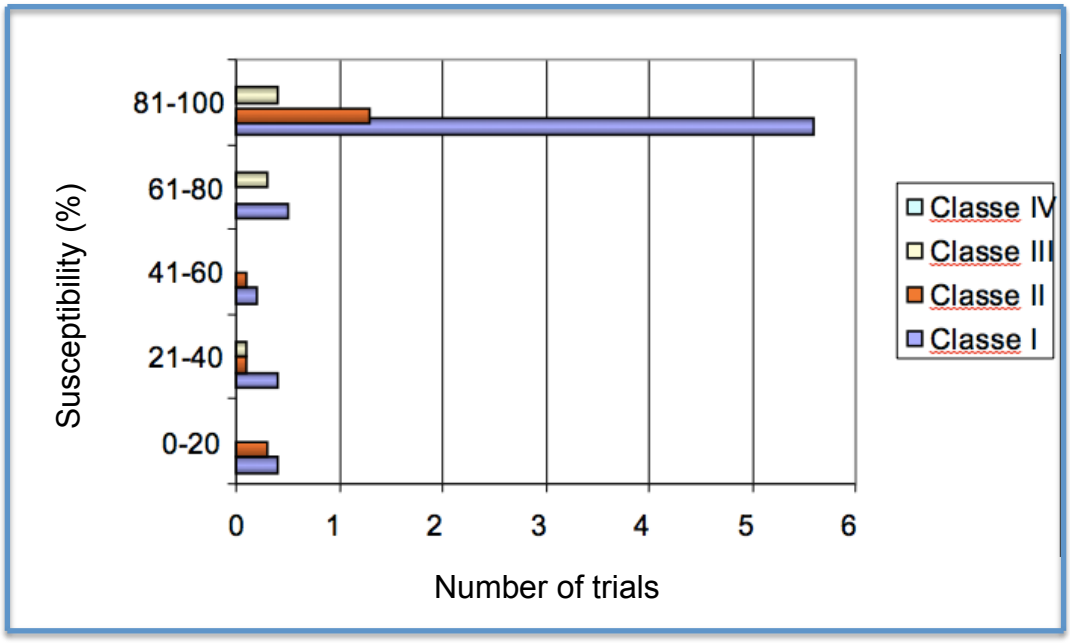
A comparative analysis was performed of the main characteristics of the studies with higher methodological quality (score 12-13) with the same number of studies with the lowest score (4) randomly selected by means of the lottery method following matching per publication year. The results showed that 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 the volunteers' susceptibility was 100%. Only 1 study explicitly stated that no symptom could be attributed to the tested medicine. (Figure 4).

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] which 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.

Figure 4. Percentage of susceptible volunteers according to methodological class



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 the homeopathic clinical logic is particularly meaningful. Indeed, in the present article such concepts were used in the assessment of the relevant and sensitive issue of 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 give 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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