

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

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### **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 knowledge 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	<i>Arnica</i> 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	<i>Thuja</i> 30cH, <i>Antimonium crudum</i> 7cH, <i>Nitricum acidum</i> 7cH	2 / 84	4 / 87	Stomachache, soft stools, skin rash, tiredness
Attena, 1995	<i>Anas barbariae</i> 200cH	77 / 783	17 / 790	Aggravation of flu symptoms: muscle pain, low fever, nasal discharge, headache, skin rash, itch, earache
Wiesenauer, 1995	<i>Galphimia glauca</i> 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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