

## REVIEW

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### A CRITICAL REVIEW OF THE POSSIBLE BENEFITS ASSOCIATED WITH HOMEOPATHIC MEDICINE

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**OBJECTIVE:** To evaluate the recent scientific research progress on homeopathy.

**METHODOLOGY:** Homeopathy was evaluated in terms of its clinical research; *in vitro* research, and physical foundations. The Medline database was the main reference source for the present research, concerning data of approximately the last 10 years. Secondary references (not available in this database) were obtained by means of direct requests to authors listed in the primary references.

**RESULTS:** Clinical studies and *in vitro* research indicate the inefficacy of homeopathy. Some few studies with positive results are questionable because of problems with the quality and lack of appropriate experimental controls in these studies. The most recent meta-analyses on the topic yielded negative results. One of the few previous meta-analyses with positive results had serious publication bias problems, and its results were later substantially reconsidered by the main authors. The sparse *in vitro* homeopathic research with positive results has not been replicated by independent researchers, had serious methodological flaws, or when replicated, did not confirm the initial positive results. A plausible mechanism for homeopathic action is still nonexistent, and its formulation, by now, seems highly unlikely.

**CONCLUSIONS:** As a result of the recent scientific research on homeopathy, it can be concluded that ample evidence exists to show that the homeopathic therapy is not scientifically justifiable.

**DESCRIPTORS:** Homeopathy. Complementary and alternative medicine. Pseudo-science.

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Homeopathy, introduced by the German physician Samuel Hahnemann at the beginning of the 19th century, consists of the treatment of the symptoms of a disease by means of ultra-diluted substances. These substances are chosen based on the assumption that they would cause the same symptoms in healthy subjects if ingested in measurable amounts. Minerals, vegetables, or substances obtained from living organisms may be used in the preparation of homeopathic medicines. Supposedly, the effect of these substances becomes stronger the more they are diluted. An

important step in their preparation is called the *succussion*: “shakes” that are applied to the substance after each dilution stage. Although mostly recommended for small afflictions, sometimes radical statements about the effectiveness of homeopathy are made, for instance, concerning the treatment of AIDS<sup>1</sup>.

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In Brazil, homeopathy is accepted as a medical, pharmaceutical, and veterinary specialty. Homeopathy also has an accepted medical status in England, India, and some States of the United States (Arizona, Connecticut, and Nevada), and its use is widespread in many other countries<sup>2</sup>. The amount of research on homeopathic topics rose substantially in the last 20 years. The analysis of its scientific status, therefore, can already take into account a large number of studies, and such an analysis is obviously important, both in terms of general scientific advancement and for health financing reasons.

The objective of the present study was to critically review and assess the current scientific status of homeopathic medicine. This review focused on the performance of homeopathy in clinical trials, on its state-of-the-art in basic research, and on its physical foundations. References were basically obtained with the help of the Medline-Pubmed database and were restricted to (approximately) the last 10 years. Secondary references, not available in this database, were also identified by means of direct contact with primary authors.

### Clinical trials

Probably the best strategy for assessing the effect of homeopathy is through the results of its clinical trials. Many good quality studies of the last 12 years have yielded negative results, for instance, concerning systematic reviews and meta-analyses<sup>3-11</sup>; infections of the upper respiratory tract and allergic rhinitis<sup>12,13</sup>; post-operative ileus<sup>14</sup>; asthma<sup>15</sup>; warts<sup>16-18</sup>; pain relief and muscle soreness<sup>19-23</sup>; treatment of adenoid vegetation<sup>24</sup>; chronic headache<sup>25-28</sup>; ear inflammation<sup>29,30</sup>; eczema<sup>31</sup>; arthritis<sup>32,33</sup>; bruising<sup>34,35</sup>; anxiety<sup>36</sup>; “provings” (see below) with belladonna, arnica, Pulsatilla and mercury<sup>37-41</sup> and “aggravations” (“good” worsening of symptoms, said by homeopaths to precede patient recovery)<sup>42</sup>.

Detailed comments on many of these studies are published<sup>2,5,43</sup>. Some studies were at first considered to be of good methodological quality, in which positive results were found, concerning, for example, allergic rhinitis and childhood diarrhea<sup>44,45</sup>. These studies, however, could not be independently replicated<sup>13,46</sup>, and some methodological flaws were later detected in their designs<sup>47,48</sup>. The present review could not identify any homeopathic clinical trial that was positively

replicated by an independent group<sup>49,50</sup>.

In 1990, Hill and Doyon<sup>3</sup> reviewed 40 randomized double-blind studies, and concluded that “*The results do not provide acceptable evidence that homeopathic treatments are effective*”. In a review of the scientific literature concerning pediatric homeopathy, Kurz<sup>4</sup> concluded that “*The review of studies carried out according to current scientific criteria revealed—at best—a placebo effect of homeopathy*”. Linde and Melchart<sup>6</sup>, in a review of homeopathic studies on “individualized homeopathy” (one of the current schools of homeopathic treatment), stated that “*...when the analysis was restricted to the methodologically best trials no significant effect was seen*”. Ernst and Pittler<sup>7</sup> in a review of the scientific literature on the homeopathic preparation - arnica, concluded that “*The claim that homeopathic arnica is efficacious beyond a placebo effect is not supported by rigorous clinical trials*”. One of these authors, in another review<sup>8</sup>, states: “*It is concluded that the trial data available to date do not suggest that homeopathy is effective in the prophylaxis of migraine or headache beyond a placebo effect*”, and, more recently<sup>10</sup>, that: “*...(in this review) there was no condition which responds convincingly better to homeopathic treatment than to placebo...*”.

In 1991, Kleijnen *et al.* published a meta-analysis<sup>51</sup> that reported a small positive effect for homeopathic treatments. However, the authors emphasized the fact that clear conclusions were not feasible, since most studies had a very low methodological quality, which could severely bias the results. Similarly, Linde *et al.*<sup>49</sup>, in a 1997 review of more than 100 studies, identified a favorable result for homeopathy. Also in this case, however, the authors admitted that publication bias could introduce an effect that was “dif-

ficult to estimate”. In addition, they stated that: “*...we found little evidence of effectiveness of any single homeopathic approach on any single clinical condition*”.

The magnitude of the bias and the quality of the studies in these reviews is illustrated by a positive study that, when re-assessed, actually revealed no effect of homeopathy over placebo (the original analysis used an inadequate statistical methodology). However, the inadequate study was still accepted in these reviews and considered to be of good quality<sup>53,54</sup>. Similarly, the French government commissioned a high-quality trial with the objective of confirming (or not) 2 preliminary positive homeopathic studies of poor quality. This new trial did not yield any positive results, but all 3 studies were included in the reviews<sup>55</sup>.

Moreover, the presence of bias was later confirmed<sup>56-58</sup>, by means of a visual test that allowed for the identification of a publication bias in the “positive studies” direction. Another approach was the reproduction of the analysis of Linde *et al.*, but taking into account only those studies judged to be of the highest quality<sup>59</sup>. The conclusion of this new analysis was that: “*...homeopathic remedies are associated with the same clinical effect as placebo*” and that: “*... applying strict criteria, a meta-analysis of dilute homeopathic remedies shows no effect over placebo whatsoever*”<sup>59</sup>.

Also, in a re-assessment of their work<sup>60,61</sup>, the main authors of the 1997 review stated that: “*...there was clear evidence that [homeopathic] studies with better methodological quality tended to yield less positive results*”, and that: “*The evidence of bias weakens the findings of our original meta-analysis... It seems, therefore, likely that our meta-analysis at least overestimated the effects of homeopathic treatments*”.

Finally, 2 other recent reviews<sup>11,62</sup>

concluded that no effect can be detected when studies of better methodological quality are considered, and still another, specifically dealing with the *post-operative ileus* condition<sup>63</sup>, found negative results for the studies in which homeopathic preparations had been highly diluted.

As can be seen, the relationship between the lack of quality in a homeopathic study and its positive results arises in numerous studies, and some authors repeatedly warn against the fact that “alternative and complementary” medical journals create a serious publication bias in the field<sup>64</sup>. Thus, the message that consistently emerges is that homeopathic studies with positive results are those of low methodological quality, in which double-blind characteristics could not be assured, that had statistical methodological flaws or that were published in less rigorous journals<sup>54-67</sup>. For instance, in the study mentioned by Linde *et al.*, only 20% of the trials could actually be considered as “blind”<sup>67</sup>.

In addition, other reasons for positive results can be noted:

- homeopathic preparations with a relatively low dilution may still retain pharmacological properties<sup>68</sup>. Even if these effects were not specific for the problem being addressed, the masking of the “intervention” group could be thus compromised.

- There are documented cases in which homeopathic medications had been adulterated<sup>69-71</sup>. For instance, Kerr and Saryan<sup>69</sup>, in an analysis of homeopathic preparations in the United States, found arsenic in 2 out of 6 tested samples. Also, in a recent review 120 samples of “alternative medicine” medications (including homeopathy), Gupta *et al.*<sup>71</sup>, in India, found that 38% of them were contaminated with corticosteroids. An older study in the United States<sup>70</sup> detected a similar proportion.

Another homeopathic research

topic that has yielded fully negative results is the one of “homeopathic provings”<sup>37-41</sup>. This is a fundamental procedure for the definition of homeopathic prescriptions. In these provings, arbitrary substances are given to a small number of healthy volunteers, and the subsequent symptoms are recorded by the volunteers. As mentioned, homeopathic prescriptions are then developed from the assumptions that these substances, ultra-diluted, could cure these same symptoms in sick subjects. For instance, in a recent experiment that tried to submit these assumptions to a double-blind test<sup>38</sup>, 47 volunteers were divided in 2 groups, one receiving a placebo, and the other, ultra-diluted belladonna. It was not possible to observe any discernible pattern in the symptoms reported by the 2 groups. Another interesting older example concerns an experiment on homeopathic *Pulsatilla*<sup>40</sup> in which subjects received either a placebo or the homeopathic preparation in a cross-over design. No differences could be detected between the 2 groups, and an interesting result was that during the first month, clear symptoms were reported by all patients, probably due to the “novelty” characteristic of the study.

### Physical foundations and *in vitro* research

The modern *in vitro* homeopathic research can be said to begin with the work of the French immunologist Jacques Benveniste, during the 1980s. In 1988, this researcher reported that in his laboratory, conclusive proof of homeopathic effects had been identified. According to him, water could retain a “memory” of its solutes and, with

this memory, cause the degranulation of basophil cells *in vitro*, even after the solute had been diluted to 10<sup>-120</sup>.

Benveniste’s study<sup>72</sup> was accepted for publication in the *Nature* journal, as long as a committee, assigned by the journal, could make an *in loco* replication attempt. This committee, however, concluded that<sup>73</sup>:

- the experiments were not double-blind;
- they “worked better” when performed by a specific member of Benveniste’s team;
- when the experiments did not work, they were discarded;
- no adequate statistical control methods were employed;
- when replicated with better controls, no effect could be detected.

In summary, “...an extensive series of experiments which are statistically ill-controlled, from which no substantial effort has been made to exclude systematic error, including observer bias, and whose interpretation has been clouded by the exclusion of measures in conflict with the claim...”.

Recently, an allegedly positive replication of this study was reported<sup>74</sup>. This new experiment was performed in 4 European laboratories, and a member of Benveniste’s original team took part in them. This study, however, was only published as a short, non-peer reviewed article, and, apparently, had methodological flaws that could compromise its results. For instance, the authors reported that ¼ of their data had to be discarded, although no clear justification was presented for that. Also, the statistical techniques used appear inadequate. For instance, consider the fractions of *control x treatment* degranulation reported in the study for “laboratory 1”:

| “Laboratory | Control           | Histamine         | number | F     | p      |
|-------------|-------------------|-------------------|--------|-------|--------|
|             | (% degranulation) | (% degranulation) |        |       |        |
| 1           | 45.8              | 36.5              | 123    | 15.35 | .0002” |

Using standard statistical formulae for a 2-proportions t-test<sup>75</sup>, one finds a 95% Confidence Interval of:

95% CI lab 1: [-0.03; 0.21] ; not statistically significant.

Finally, at least 5 other research groups tried to replicate Benveniste's results, not one of them finding a positive effect<sup>76-80</sup>.

More recently, Benveniste stated that the "homeopathic potentialization" of a substance could be sent and recovered through electromagnetic means (for example, through an e-mail message)<sup>81</sup>. The "water memory" thus digitized could then be used to transfer the properties of the original solute to other substances, at long distance. More information on this (still non-substantiated) claim can be found in <http://www.digibio.com>.

Currently, research in this area still continues, basically coordinated by an international consortium named GIRI (*International Research Group on Very Low Dose and High Dilution Effects*, in French). The member list of this group has more than 150 scientists from many countries, and renowned members include the French immunologist Madeleine Bastide. In one of the few studies of the group that appeared in the scientific literature<sup>82,83</sup>, the authors attempted to study the effects of ultra-diluted thyroxine ( $10^{-60}$ ) in the growth of juvenile frogs (see Endler<sup>84</sup> for more details). The authors report on the results of 4 experiments. In the first one, a very highly diluted thyroxine solution was applied to a tank in which juvenile frogs were developing. In the second, this solution was placed inside a sealed vial, which was then placed close to the tank (without contact with the water). In 2 other experiments, a procedure was used to "digitize" the properties of the solution and then to "communicate" them to water in another vial. Basically, in the 2 last experiments, a vial with the thyroxine preparation was con-

nected to a coil wire and to an amplifier. An electric current was then applied to the wire, and "after filtering and noise reduction", the homeopathic effect was, allegedly, transferred to a pure water vial, also connected to the amplifier. In each of the 4 experiments, "diluted water (water  $10^{-60}$ )" was used as control. Results were similar in all the 4 experiments: frog growth was altered whether they were exposed to the ultra-diluted thyroxine, to the closely placed sealed vial, or to the vials to which the "digitized" properties had been transferred. The authors also reported that many other factors, for instance, the time of the year when the experiments were performed, appeared to influence the results.

From these experiments, the authors concluded that the homeopathic effect propagates through electromagnetic waves, which had transferred the homeopathic effect to the frogs. However, the most probable explanation is that the complex and non-blind characteristic of the work allowed for the introduction of bias, which would explain the altered rate of growth in all 4 experiments<sup>85,86</sup>.

Other GIRI members further expanded the implications of these results. For instance, the Belgian researcher William Betz reports that, in a similar situation, when both a placebo and a homeopathic preparation produced the same effect, Madeleine Bastide concluded that the placebo had been "contaminated" by the "homeopathic radiation", arising from the closely stored homeopathic preparation<sup>85</sup>.

Finally, Vickers<sup>87</sup> performed a comprehensive review of the literature concerning "pre-clinical research" in homeopathy, concluding that: "There is a lack of independent replication of any pre-clinical research in homeopathy. In the few instances where a research team has set out to replicate

the work of another, either the results were negative or the methodology was questionable" .

In summary, similarly to the analysis concerning clinical trials, here, also, it is possible to identify a clear relationship between the low methodological quality of a homeopathic study and its positive results.

Still concerning the physical mechanisms of homeopathy, it is not possible to identify differences between homeopathic preparations and pure water by means of a nuclear magnetic resonance (NMR) analysis<sup>88</sup>. It is well known that homeopathy "violates" the Avogadro number, that is, in a homeopathic preparation above a  $10^{-24}$  dilution, not 1 molecule of the original solute is expected to be found. However, explanations for the putative action mechanisms for homeopathy under these circumstances are only very rarely presented. Worse yet, when examined, these few explanations turn out to be absolutely non-substantiated and non-scientific<sup>43,86</sup>. For instance, in a recent introduction to homeopathy in the *British Medical Journal*<sup>89</sup>, the authors made the (non-referenced) statement that "The complex lattice formations created by water molecules are thought by some to hold the key to ... homeopathy". The reason for such an oblique, unspecific citation must be the long history of non-corroborated search for such water structures, of which a recent example is Lo *et al.*<sup>90-92</sup>.

It should also be noticed that this low concern with a possible mechanism of action leaves unanswered arguments such as<sup>93</sup>: "It is estimated that in 60 seconds a person standing still generates about 100 000 particles – skin fragments, salt, oil droplets, humidity and cosmetics – which are large enough to damage an integrated circuit during its manufacturing process. Even if homeopathic medications were prepared in a room of maximum clean-

*ness, the chance of one of these particles ending in the final preparation would be large. How could the water tell between what is the active substance and what is a sulphur molecule from a hairspray? How can it tell, in its memory, the molecule of the rotten liver of a duck among millions of organic particles that are thrown over it by the simple act of breathing?"*

## CONCLUSIONS

The statement that homeopathy is "discriminated by an "official science" cannot be supported by the results of

the present review. The quantity and quality of the current research in this area indicates that, actually, the rejection of homeopathy as a valid scientific endeavor comes from the fact that the more recent research has thoroughly disconfirmed the main homeopathic hypotheses. Another conclusion concerns the relationship between the quality of a homeopathic study and its positive results. This is a clearly recognized phenomenon, which, for instance, admittedly "contaminated" the meta-analyses conducted in the 1990s that detected a (weak) favorable effect for homeopathic preparations.

In summary, the present review in-

dicates that the weight of the modern evidence clearly disconfirms the hypothesis that ultra-diluted substances could have a noticeable clinical or pharmacological effect in living organisms.

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## RESUMO

ALMEIDA RMVR - Uma revisão crítica da literatura relativa aos possíveis benefícios da medicina homeopática. **Rev. Hosp. Clín. Fac. Med. S. Paulo** 58(6):324-331, 2003.

**OBJETIVOS:** Avaliar os resultados da pesquisa científica em relação aos possíveis benefícios da homeopatia.

**METODOLOGIA:** A homeopatia foi avaliada a partir de sua pesquisa clínica; sua pesquisa *in vitro* ou "pré-clínica" e seus fundamentos físicos. Para tal, foi realizada uma ampla revisão e análise crítica da literatura científica mais recente no tópico. (aproximadamente últimos dez anos). Os trabalhos foram selecionados primeiramente a partir da base de dados

Medline. Referências secundárias (não indexadas nesta base de dados) puderam então ser obtidas por meio de contato direto com autores listados nas referências primárias.

**RESULTADOS:** Tanto estudos clínicos quanto pesquisas *in vitro* e estudos de "provas" homeopáticas apontam para a ineficácia de sua utilização. Alguns poucos estudos com resultados positivos podem ser explicados por problemas de qualidade e (falta de) controles adequados. As meta-análises mais importantes na área forneceram resultados negativos. Uma recente meta-análise com resultados positivos teve sérios problemas metodológicos, e seus resultados foram, posteriormente, substancialmente alterados pelos autores. A pesquisa metodológica *in*

*vitro*, similarmente, apresenta poucos resultados positivos, os quais possuem sérios problemas metodológicos e não puderam ser replicados por pesquisadores independentes. Um mecanismo plausível para a atuação das substâncias homeopáticas é inexistente, e sua formulação, atualmente é altamente improvável.

**CONCLUSÃO:** Como resultado das pesquisas realizadas nos últimos anos, podemos concluir que existe ampla evidência de que a prática homeopática não é cientificamente justificável.

**DESCRITORES:** Homeopatia. Medicina complementar e alternativa. Pseudo-ciência.

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