



Do homeopathic medicines provoke adverse effects? A systematic review

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Objective: To evaluate the safety of homeopathic medicines by critically appraising reports of adverse effects published in English from 1970 to 1995.

Method: Systematic review on information regarding adverse effects of homeopathic medicines identified using electronic databases, hand searching, searching reference lists, reviewing the bibliography of trials, and other relevant articles, contacting homeopathic pharmaceutical companies and drug regulatory agencies in UK and USA, and by communicating with experts in homeopathy.

Results: The mean incidence of adverse effects of homeopathic medicines was greater than placebo in controlled clinical trials (9.4/6.1) but effects were minor, transient and comparable. There was a large incidence of pathogenetic effects in healthy volunteers taking homeopathic medicines but the methodological quality of these studies was generally low. Anecdotal reports of adverse effects in homeopathic publications were not well documented and mainly reported aggravation of current symptoms. Case reports in conventional medical journals pointed more to adverse effects of mislabelled 'homeopathic products' than to true homeopathic medicines.

Conclusions: Homeopathic medicines in high dilutions, prescribed by trained professionals, are probably safe and unlikely to provoke severe adverse reactions. It is difficult to draw definite conclusions due to the low methodological quality of reports claiming possible adverse effects of homeopathic medicines.

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Introduction

Homeopathy has been used by millions of people in different continents for 200 years. Homeopathic medicines (HMs) are prepared according to official homeopathic pharmacopoeias around the world. HMs are diluted and agitated during their preparation. Only medical doctors or licensed health professionals are allowed to practise homeopathy in some countries.

Despite extensive use by health professionals there is little evidence on the safety of HMs. This subject is not commonly referred to in the homeopathic literature and is rarely a focus of attention in conventional

medical journals. Reports are mainly case reports or letters to the editor attributing adverse effects (AEs) to HMs. There is widespread belief by practitioners and patients that HMs are safe but this has not been systematically appraised.

Regulatory agencies, prescribers and consumer protection agencies need reliable information about the safety of HMs. Given the current absence of systematic reviews on the topic, we decided to do a systematic search on the literature to detect, describe and critically analyse AEs associated with homeopathic medicines from 1970 to 1995.

Objectives

- Appraise critically reports of AEs of HMs published in English from 1970 to 1995.
- Evaluate the safety of HMs.

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Method

Operational definitions

A HM was defined as a substance which is potentially toxic or pathogenic that was prepared according to the specifications of homeopathic pharmacopoeias (excluding herbal preparations and non-homeopathic medicines). This includes combination remedies and isopathy but excludes mixed preparations with non-homeopathic components. An AE was considered to be any troublesome and undesirable effect attributed to the intake of a HM in doses usually administered therapeutically in humans. This included psychological symptoms, physical symptoms and signs, laboratory values obtained using biological samples, laboratory values on data obtained directly from patients and other factors relating to quality of life.

Information sources

Computerized biomedical databases: MEDLINE, TOXLINE, EMBASE, MCAT/AMED; HOM-INFORM; hand searching of the *British Homeopathic Journal* and proceedings of congresses and symposia; contacting homeopathic pharmaceutical companies and drug regulatory agencies in UK (Committee on Safety of Medicines) and USA (Food and Drug Administration); review of the bibliography of trials and other relevant articles; contact with colleagues and experts in homeopathy.

Inclusion criteria

Papers published in medical journals and books that report AEs of homeopathy:

- Conventional and homeopathic journals
- Language: English
- Only in man
- Observational (patient case, series of cases) or experimental (clinical trials or homeopathic pathogenetic trials (HPTs) with more than one volunteer)
- Years: 1970–1995.

Exclusion criteria

- Theoretical, speculative or opinion papers without concrete evidence
- Reports referring to herbal or non-homeopathic medicines.

Data-extraction forms

Five different forms were developed for extracting data on:

- General information and characterization of HMs
- Methodological aspects of clinical trials and HPTs and incidence of AEs
- Judgement on causation for each AE reported in clinical trials or case reports

- Features of collected AEs
- Judgement on the quality of the paper.

A pilot test on the forms was done for HPTs, clinical trials and case reports. We assessed the causality of AEs of HMs using four categories as suggested by Naranjo: definite, probable, possible, doubtful.¹

Paper analysis procedures

All clinical trials and case reports were independently reviewed by the two authors. HPTs were analysed by the first author. All papers were reviewed according to predefined criteria and analysis protocol for case reports, HPTs and clinical trials. When there was disagreement the first author had the final decision.

Results

We found 19 reports of clinical trials (out of 55), 19 case (or case series) reports and 15 HPTs from documents published between 1970 and 1995 with data on AEs of homeopathy in English. The number of documents which referred to AEs of homeopathy, compared to the total number of retrieved papers, was not satisfactory. This was particularly noted in reports of clinical trials or patients' cases. Meta-analyses or systematic reviews of controlled trials of homeopathy published up to now either do not report on AEs of HMs or state that included trials did not report any AEs. When reported, the quality of information on AEs of the reviewed papers was in general low and lacking crucial information for determination of causality for the HM.

Clinical trials

The mean overall incidence of AE in the homeopathic group (number of subjects with at least one adverse event of the total number of subjects taking a HM) was 9.40 and in the placebo group was 6.17 (for 12 trials where there was information on both placebo and homeopathic AEs). The relative risk of HMs (ratio of incidence of AE in homeopathic treated patients to incidence of AE in placebo-treated persons) compared to placebo was 1.52. Our analysis of clinical trials with reported AEs showed mild and transient AEs which could possibly be attributed in some cases to HMs—mostly headaches, tiredness, skin eruptions, dizziness, bowel dysfunction such as diarrhoea or loose stools and, more frequently, aggravations of symptoms following the administration of HMs. These effects are not very different from the effects noted in placebo groups in clinical trials. From our sample, 36 reports did not mention at all safety information regarding AEs and only 2 included details of how they collected information on AEs during the trial. Two trials with more than 30 patients in each group (control and verum) reported no AEs in either group.

Case reports

Very few case reports or series of cases described new AEs for HMs used in treating patients. Most papers published in homeopathic journals reported aggravation of pre-existing symptoms following the administration of HMs. Papers published in conventional medical journals pointing to AEs of HMs were very rare. In all cases but one (a mixture of grass pollens) they treated AEs of combination remedies in which homeopathic dilutions are mixed with mother-tinctures of plants or low concentrations of toxic metals or acids. The level of causal association was also low in homeopathic or conventional medical journals' reports according to our analysis. Many homeopathic or isopathic medicines, isolated or in combination, in a wide range of dilutions were associated with AEs: Pollens, *Pulsatilla*, *Baryta carbonica*, *Sulphur*, *Calcarea carbonica*, *Sepia*, *Belladonna*, *Ipecacuahna*, *Phosphorus*, *Borax*, as well as combination products mislabelled as 'homeopathic products'. From this analysis it is impossible to state that one particular medicine is provoking more AEs than the others in our sample.

HPTs: there was a great heterogeneity in the methodological quality of reports making it very difficult to draw reliable conclusions on the pathogenicity of the tested medicines. Referring to a subsample of trials published in the UK we found 1 was uncontrolled, 12 used a parallel group design and 2 used a crossover design. All trials had studied different medicines, with varying dilutions (from 3X to 200C). The mean overall incidence of pathogenetic effects was 54.3%. The mean incidence of symptoms per sensitive volunteer was 18.8. Overall there was an average of 267 effects per trial (range 0–1100). The effects were not very different in nature from placebo effects occurring in phase I clinical trials in healthy volunteers.

Conclusions

HMs, prepared according to homeopathic pharmacopoeias and prescribed by trained practitioners in high dilutions, appear to be a safe intervention from a quantitative and qualitative perspective. There is a very small risk of toxicity of HMs when compared to placebo in randomised controlled trials using pure HMs and the symptoms produced by HMs and placebo are minor and comparable. This conclusion should be interpreted cautiously since the mode of assessment of AEs in our sample was not described in almost all cases. On the other hand, this conclusion cannot be applied to so-called 'homeopathic products' prepared using many various herbal and mineral components, in very low dilutions or even undiluted. There is anecdotal evidence that such products could do harm to patients and this needs to be addressed by rigorous studies.^{2,3}

HMs are thought, from conventional wisdom, to be very safe because of the high dilutions of the original

substances. Conversely, it is a traditional belief among homeopathic researchers and prescribers that HMs should produce large numbers of pathogenetic effects when given to healthy volunteers. A systematic review of 45 HPTs published in the UK from 1945–1995 showed that there was a large overestimation of pathogenetic effects, especially when trials were of low methodological rigour.⁴ This finding was consistent with a previous paper pointing out the existence of several flaws (from the perspective of modern methodological standards) in Hahnemann's original directions for conducting HPTs, still used by some investigators.⁵ The large number of pathogenetic effects produced by insufficiently controlled or un-controlled pathogenetic trials deserves to be severely criticised and possibly deleted from homeopathic materia medica.

The issue of homeopathic aggravations should be more fully explored in a future systematic review and in clinical trials. The results we obtained from clinical trials could be ambiguously interpreted as a direct effect of the medicine (in this case should be considered as a transient adverse effect) or as the lack of effect of the medicine (meaning the suppression of effective treatment or the natural course of disease, particularly in acute diseases). Also one needs to consider the way practitioners are informing patients on the possibility of such aggravations after using HMs, thus creating expectations.

Our review explored only English language papers. This could be a major drawback as there is a large amount of clinical literature in German, French, Spanish and Portuguese. However, it is our impression the conclusions would not be different, given the reports of some authors studying AEs of homeopathy in other contexts. In France, for instance, Aulas *et al* reported, in addition to case reports we had already included in our review, almost 30 cases of AEs reported to a pharmacovigilance unit in Lyon.⁶ Mostly they were similar to a placebo effect and in two other cases AEs were attributed to mislabelled 'homeopathic medicines' with several components and at least one non-diluted substance.

We did not explore the issue of indirect risks associated with homeopathic prescribing. One can assume they are present given the insufficient evidence of efficacy for most health problems currently treated with HMs, the possibility of misdiagnosis and the overreliance on the power of homeopathic therapeutics. We came across some reports in conventional medical journals in which the use of pure or mislabelled HMs delayed a more appropriate conventional treatment.^{7,8}

Underreporting of AEs of medicines is common in the medical literature. In conventional medicines, according to Venulet⁹ only 21% of 1379 publications contained adequate information to determine causality and most of these did not include sufficient information to interpret the clinical significance of AEs. We

think this phenomenon is a greater problem in homeopathy due to the longstanding belief that HMs are safe and do not cause harm. This fact needs to be taken into consideration regarding our conclusions since we worked with published reports, mainly published in homeopathic journals by sympathizers of homeopathic therapeutics.

We think there should be more effective ways of reporting AEs of HMs. More than a decade ago, Fisher proposed that a reporting system for AEs of complementary medicine should be set up.¹⁰ Unfortunately his suggestion appears to have been ignored. We would like to exhort the homeopathic establishment to set up a monitoring system with clear and distinct instructions for observation of aggravations or new AEs after using HMs. Editors of scientific journals could have a special section (maybe in letters to the editor) to publish short reports of AEs of HMs. HPTs should not be approved by Ethics Committees if they are not well controlled and of rigorous designs. Randomised controlled trials using HMs should seriously take into account the assessment of outcomes on safety, with particular questions addressing the occurrence of AEs in patients. If this is accomplished we think it will be possible, in the near future, to get the true incidence of AEs of homeopathic medicines.

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