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ORIGINAL PAPER

Harm in homeopathy: Aggravations, adverse drug events or medication errors?

C Endrizzi[1], E Rossi[1,*], L Crudeli[2] and D Garibaldi[2]

[1]*Homeopathic Clinic, Reference Regional Centre, Campo di Marte Hospital, AUSL 2 Lucca, Italy*
[2]*Pharmaceutical Department of Health Services, AUSL 2 Lucca, Italy*

Background: **The assessment of harm arising from the use of homeopathic medicine is much discussed, but there is little published data on the subject.**
Aim: **To study prospectively adverse drug events related to homeopathic medicines.**
Setting: **The data were gathered between 1 June 2003 and 30 June 2004 during follow-up visits consecutively carried out at the Homeopathic Clinic, Campo di Marte Hospital, Azienda USL 2, Lucca (Italy). They refer to effects following the administration of a homeopathic medicine, prescribed according to the classical homeopathic method.**
Methods: **Reports collected by a homeopathic doctor (not the prescribing doctor) on the nature and intensity of the effect, dose and frequency of administration, time relationship between the drug use and the adverse events, challenge, unchallange possible concomitant factors, causality (improbable, unlikely, possible, probable, certain).**
Results: **Out of 335 homeopathic consecutive follow-up visits between 1 June 2003 and 30 June 2004, nine adverse reactions were reported (2.68%) including one case of allergy to lactose, excipient of the granules.**
Conclusions: **Adverse events to homeopathic drugs exist and are distinguishable from homeopathic aggravations, but are rare and not severe.** *Homeopathy* **(2005) 94, 233–240.**

Keywords: homeopathy; adverse events; adverse effects; aggravations

Introduction

The international scientific community is discussing the effectiveness and risks of non-conventional therapies, for homeopathy in particular the debate is conditioned by results produced in clinical trials that are still controversial, compared to other practices such as phytotherapy and acupuncture. Despite some positive clinical evidence, from reviews or meta-analyses[1–3] many authors are still cautious or sceptical about accepting that homeopathic medicines have effects beyond those of placebo.[4]

We agree that there is a need to maintain open the discussion on scientific validity of non-conventional therapies,[5] and to reflect on, and continually review, scientific rigour, and not only of so-called alternative practices.[6] Contributions free of prejudice and carried out with methodological rigour are desirable in view of the scale of use of non-conventional therapies, and homeopathy in particular.

Ernst and collaborators,[7] found a prevalence of use of non-conventional medicines in varies countries, ranging from 9% to 65%. According the Italian National Institute of Statistic (ISTAT),[8] almost 9 million people (15.6% of the Italian population) used non-conventional therapies in 1997–999, with homeopathy being the most frequently used (8.2% of the population). In Tuscany, where we operate, around 20% of the population had used at least one of the non-conventional therapies, especially homeopathy and manipulative therapies, in 3 years according to a study conducted on behalf of the Tuscan Regional Health Department's Epidemiological Observatory.[9]

The ISTAT data are of particular interest when they report that 70% of the group studied turned to alternative practices in the expectation of a lower

*Correspondence: Elio Rossi, Ambulatorio di omeopatia, Padiglione D—Ospedale Campo di Marte, 55100 Lucca, Italy
E-mail: omeopatia@usl2.toscana.it
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toxicity; the belief that natural therapies are harmless has encouraged self-prescribing. In 1987, Fisher proposed a system of recording the adverse effects of non-conventional therapies,[10] yet little research has been conducted on the question of the risks of homeopathy. Notifications of serious consequences are mostly to case reports.[11-15] In some instances, these concern the use of so-called 'homeopathic products' (that is medicines containing, amongst other things, homeopathic medicines in low dilutions, or not prescribed in accordance with homeopathic principles).[16] The problem of the risks of homeopathic treatment is also important for the official registration of homeopathic medicines, for which the European directives (92/73 CEE) and Italian legislation (D.L.vo 185/95, law 347/97) provide a form of 'simplified' registration (where formal proof of clinical efficacy is not necessary) provided that the harmlessness is guaranteed.

A review of data from 1970 to 1995,[17] highlighted a higher incidence of adverse drug events in homeopathic medicines compared to placebo in placebo-controlled trials, although these were generally minor and transient. The authors conclude that homeopathic medicines prescribed in high dilutions by doctors with experience in homeopathy, are generally safe and reaffirm the necessity of accurate clinical research. One of the potential harms relating to non-conventional treatment relates to patients' wish to discontinue conventional therapy inappropriately.[18]

Terminology

There is difficulty in describing adverse events to a homeopathic medicine with conventional terminology.[19,20]

According to WHO Adverse Reaction terminology (WHO Technical Report N° 498/1972) an adverse reaction (ADR) is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or disease therapy, or for the modification of physiological function. Adverse events (AE) do not necessarily have a causal relationship with the treatment. In the CONSORT (Consolidated Standards of Reporting Trials) statement an ADR is an event for which the causality link to the tested intervention is well established and strong.[21] They advise using the term AE to describe harmful events occurring during a trial, because of the difficulty in knowing whether it is related to the intervention or not. The Guidelines for Good Clinical Practice (GPC)[22] distinguish between harmful reactions to marketed medicinal products and the response to new medicinal products or their new use, for which the causal relationship between a medicinal product and an AE is at least a 'reasonable possibility'.

We have followed Nebeker and Barach,[23] who include under the term adverse drug events harm caused by the drug (adverse drug reactions and overdoses) and harms from the use of the drug (including dose reduction and discontinuations of drug). One specific difficulty encountered in homeopathy is that of distinguishing between a genuine adverse drug event and those reactions known as 'homeopathic aggravation' which, on condition that certain criteria are met, are considered to be favourable reactions to treatment.

Objectives of the study

The objectives of this prospective observational investigation are:

- A general assessment of the harm of homeopathic treatment.
- Problems relating to the method of homeopathic prescription.
- Problems that strictly concern the characteristics of the homeopathic prescription.
- Analysis of possible interaction with other medicines (conventional and non-conventional).

Materials and methods

Since 1 June 2003, a prospective observational study has been underway at the Campo di Marte Hospital, Lucca (Regional Centre of Reference for Homeopathic Medicine) in order to monitor possible adverse drug events to homeopathic remedies taken after the first consultation at this clinic.

The only inclusion criteria was a least one follow-up visit during the observation period. All patients who had a follow-up visit during the observation period (June 2003 June 2004) were asked to communicate possible unpleasant sensations, experienced during or after homeopathic treatment, and were questioned by a homeopathic doctor, not the original prescriber, about the type of effect and intensity, (indicated by the patient on a visual analogue scale - (VAS), necessity of treatment of the clinical AE, the time relationship between taking the homeopathic medicine and the AE, response to discontinuation of therapy (dechallenge[23]) or drug readministration (rechallenge[23]), and possible concomitant factors.

We used the 'Report card for Surveillance of Phytotherapy and Dietary supplements' of the Ministry of Health and the Italian Institute of Health (I.S.S.)[24] adapted to homeopathic requirements by the addition of medicine, dose, frequency, and intensity of the effect indicated by the patient, and five levels of causality (improbable, unlikely, possible, probable, certain). The case reports recorded were submitted to Pharmaceutical Department of Health Services at Campo di Marte Hospital, Azienda USL 2. We also followed the criteria[25] for causal assessment suggested by the Italian Ministry of Health, on a case-by-case basis. These criteria are very similar to those of Nebeker and Barach.[23]

In order to standardise as far as possible the data gathering and to render the typology of the prescription less inhomogeneous (at least in the formulation of the posology) it is normal practice in our clinic to start homeopathic treatment with the 50-millesimal potencies (Q)[26] on a scale of progressive dilutions starting from the LM6 , with therapy cycles of 15–45 days duration. For intercurrent acute diseases we used low potencies from 6 to 30CH, after interrupting the constitutional treatment. It is said that the 50-millesimal dilutions are associated with lower incidence and intensity of the homeopathic aggravations.[27] The computerised clinical record WinChip[28] used for recording data.

The patients gave permission for the information to be used for research purposes and their personal data were anonymised by the attribution of an unique numerical code corresponding to each patient.

Since November 2003, our clinic has a Homeopathic Medicine Information and Pharmacovigilance Service, periodically publicised in daily papers, magazines and other media, to which users have telephone access. A homeopathic doctor replies to the users' queries (explanations of homeopathic medicine, possible interactions in physiological states such as pregnancy and lactation, possible interference with conventional medicines) and receives information on harm by passive surveillance.

We classify adverse reaction to homeopathic medicines as follows:

Homeopathic aggravation: an initial aggravation of the patient's symptoms, followed by an improvement.

The homoeopath welcomes such a reaction when assessing the patient's response to the medicine, provided that it is accompanied by a general improvement of the patient and as the intensity and duration are kept to a minimum.

Notwithstanding the difficulty of expressing the response to homeopathic medicine in conventional pharmacological terminology, we hypotheses that aggravations are comparable to a 'adverse reaction dose-dependent' (*ADR-type A*), according to Rawlins and Thompson's, classification,[19,20] a predictable consequence of an excess of the primary action of the medicine. An aggravation symptom is recognisable by its pattern of onset[29] and with regard to exposure to the medicine therefore it could also be described as a time-dependent ADR, using Aronson and Fermer's new dose-time-susceptibility (DoTS) classification, although this also refers to the pharmacokinetics of the drug to its bioavailiability and to modification of its concentration. These factors have no equivalent for an homeopathic medicine.

Adverse drug event with aggravation of symptoms, not followed by an improvement. Such reactions may be due to:

(a) administration of a partially similar medicine, and not in harmony with the patient's symptom picture;
(b) administration of a suitable medicine but with an incorrect posology: ill-timed or too frequent repetition of the medicine; or too high a potency.

Adverse drug event not expected with the appropriate prescription. Such reactions may be attributable to:

(a) The subject's hypersensitivity, reacting excessively and in an unexpected manner to the homeopathic medicine (*proving* effect). This kind of proving effect differs from homeopathic aggravation in that new symptoms are produced, rather than the reappearance of patients' old symptoms.
(b) Incorrect prescription. In this case the reaction may coincide with a spontaneous worsening of the disturbance that has been incorrectly treated.

These types of reaction could be considered according to the current ADR classifications, as type B (hypersensitivity reactions).[12,20] Such reactions are often unexpected (thus time independent), or they can arise from the first dose of the treatment, or from continued and repeated exposure to the medicine (intermediate or late reaction).

The concept of susceptibility, so important in the homeopathic tradition, must be understood here not just in the sense of morphologic, genetic, environmental or pathological characteristics that make the patient more vulnerable and sensitive to the action of the pharmacological substance, but also in the sense of a highly individualised sensitive milieu, typical of the patient, comprising all the above factors, in such a way that these factors become or may become triggering or predisposing causes. According to our understanding the emphasis should be placed on a homoeo-dynamic adjustment, characterised by a holistic rather than a linear auto-organisation of the system[30] 'orientating' and conditioning the terrain, enabling it to 'resonate' with the homeopathic medicine.[31] Thus the criteria of sensitivity outlined in the ADR DoTS classification cannot be adapted to the assessment of the following reactions.

We adopted the following criteria for establishing a causal relationship between the ADR and the homeopathic treatment:

(a) The reaction reoccurs with the same medicine at least twice.
(b) The reaction ceased upon suspension of treatment and reoccured with recommencement of the homeopathic therapy (positive dechallenge and rechallenge) in the absence of concomitant and predisposing conditions.
(c) A clear correlation between the subject's symptoms and symptoms produced in provings of the medicine. In this case it usually involves new symptoms never experienced by the subject before, in absence of concomitant conditions.
(d) The symptoms referred to as undesirable are the same as those presented by the subject before

treatment but with a greater intensity or frequency (homeopathic aggravation).

(e) There are no concomitant conditions that have any bearing on the unwanted symptoms reported by patient.

Causality is rated as follows:

Grade 4. Certain: there is an clear relationship between the symptoms as expressed by the subject and the effects of the medicine, with the same medicine being given at least twice (symptomatological coherence); positive dechallenge/rechallenge; absence of concomitant and predisposing factors (concurrent disease or other drugs or chemicals), or cannot be explained by these.

Grade 3. Probable: the effect is related to the therapy (symptomatological matching or time relationship with positive dechallenge); it is unlikely to be attributable to concurrent predisposing factors.

Grade 2. Possible: the effect related to the therapy in terms of symptomatology, but could be explained by predisposing factors present; information on drug withdrawal may be unclear.

Grade 1. Unlikely: the symptomatological expression of the ADR does not match symptoms produced during provings of the medicine; or there is an absence of dechallenge/rechallenge and there are possible predisposing factors.

Results

From 1 June 2003 to 30 June 2004, 335 follow-up visits were carried out on 181 patients undergoing homeopathic treatment, with data relating to the use of the 50-millesimal dilutions (Q). During the period 1 June 2003–30 June 2004, a total of 335 consecutive follow-up visits were monitored. These visits were carried out in 181 patients. Inclusion criteria were: at least one follow-up visit during the observation period.

There was a minimum of one follow-up visit and a maximum of seven; 79/181 (43%) had three consecutive visits, 36/181 (19.8%) four. The average frequency of consultations was 1.7 months (range 1 13 months). 29% of patients men and 71% women, the average age was 20.6 years (14 months 68 years). 79/181 patients had their initial consultation during the period of the study. 102/181 (56%) had already had a first consultation before 1 June 2003.

The most frequently examined pathologies in the 181 patients were respiratory pathologies (asthma 11.1%, relapsing acute respiratory infections 9%), followed by dermatological problems of allergic type (7.6%), psychological pathologies including anxiety-depressive syndromes (9%), digestive tract pathologies such as gastritis and irritable bowel syndrome (9%), menopausal disturbances (6.2%) and headache (4%).

The homeopathic medicines prescribed were mostly polycrests: *Pulsatilla pratensis* (11.4%), *Lachesis mutus* (9.9%), *Silicea terra*, *Sulphur* (7.6%), *Arsenicum album* (6.1%), *Sepia officinalis* and *Ignatia amara* (5.3%), then *Natrum muriaticum*, *Lycopodium clavatum*, *Nux vomica*, *Phosphorus*.

Nine cases (2.68%) of adverse drug events were recorded, including one case of allergy to the excipient of the granules (lactose) (Table 1). In one case the AE appeared after using a 30CH medicine, administered during a flare-up, thus presumably an ill-timed repetition.

These AEs were scored 3 or 4 of certainty that the event is linked to a medicine; the intensity of response is between 2 and 10/10 (as scored by the patient); in spite of the intensity of the subjective perception of the clinical symptom, no medical therapy was required to treat any of the AE.

Conclusion

Adverse reactions during classical homeopathic treatment have been observed in our study at a rate of 2.68% (9 of 335 cases). Amongst these reactions one case of lactose intolerance (verified by diagnostic tests) with inflammation of oral mucosa stands out. Adverse effects were generally mild, not requiring specific treatment.

The nine reports of adverse drug events recorded in our study were interpreted as follows (Table 1): in 4/8 cases the AE can be attributed to a homeopathic prescription identified as inappropriate, either due to a too frequent repetition of the medicine or to an incorrect potency; in 2/8 cases the administration of an only partially similar medicine; one unforeseen reaction in the case of lactose allergy (1/8); one case (1/8) of intense homeopathic aggravation (accompanied by an amelioration of the inflammatory symptomatology of the ear for which the child had been brought to the clinic) and one reaction (1/8) probably due, not only to the homeopathic medicine (aggravation), but also to a hormonal disturbance in a patient affected by amenorrhoea, bulimia and an anxiety-depressive state, whose menstrual cycle with a preceding sensation of hunger resumed upon administration of the medicine.

Discussion

This incidence is in line with the findings of Anelli *et al*[32] on adverse effects during homeopathic treatment, in which 2.7% of patients experienced a side effect related to homeopathic therapy. Riley *et al*[33] in their study of homeopathic and conventional therapy in recurrent infections of the primary respiratory tract found an incidence of 7.8% of adverse effects in children treated homeopathically, a higher level than that observed by us, but much lower than that reported by the corresponding group receiving conventional therapy (22.3%). The differences between our

Table 1 Data referring to adverse effects appearing during the course of homoeopathic therapy reported in follow-up visits 1 June 03–30 June 04: 9/335 (2.68%)

Code	*Sex*	*Age*	*Pathology*	*Treatment*	*Effect reported*	*Characteristics of the effect*	*Use of medicine*	*Possible interpretation of effect*
475	M	1	Recurrent respiratory infection	Sulph 30ch, 3 granules 3 × day	Motorial agitation; amelioration of respiratory problems	New symptom, effect lasts for few days Dech. positive Intensity 4.5	Conven-tional therapy reduced	I.H.P. early repetition of remedy Correlation to therapy: probable *Grade 3*
475	M	1	Recurrent respiratory infection	Sulph 30 ch, 3 granules 3 × day	Lactose intollerance (appearing in membrane of oral cavity)	Effects lasts for a week after suspension treatment Intensity 10	Not used	Unforeseeable reaction Correlation to therapy: certain *Grade 4*
644	F	49	Bulimia anxious-depressive state; recurrent headaches; Amenorrhoea	Puls 6 Q, 5 drops 2 × day	Aggravation of bulimia; Menstrual cycle returns; Reduction of headaches	Effect lasts for the duration of the therapy Dech. positive Intensity 8	Conven-tional therapy reduced	Homoeopathic aggravation? Correlation to therapy: probable *Grade 3*
182	M	5	Bronchial asthma	Calc 6 Q, 5 drops 2 × day	Psychomotorial agitation; No significant improvement in respiratory symptoms	New symptom effect lasts for the duration of the therapy Dech. positive Intensity 2	Conven-tional therapy reduced	I.H.P. Only partially similar remedy Correlation to therapy: probable *Grade 3*
524	F	5	Recurrent otitis	Merc 6 Q, 5 drops 2 × day	Conjunctivitis; Amelioration of otitis; prior catarrhal conjunctivitis	Reappearance of old symptom, effect lasts for the duration of the therapy Dech. positive Intensity 4.5	Conven-tional therapy reduced	Homoeopathic aggravation? Correlation to therapy: certain *Grade 4*
420	M	43	Chronic prostatitis	Sulph 6 Q, 5 drops 2 × day	Irritability; No significant improvement in prostate symptoms	New symptom Dech. positive Intensity 5		I.H.P. Only partially similar remedy Correlation to therapy: certain *Grade 4*
992	F	51	Turbinate Hypertrophy	Sulph 9 Q, 5 drops 2 × day	Aggravation of nasal obstruction only with this dilution	Dech. positive Intensity 7	Conven-tional therapy reduced	I.H.P. potency of remedy not adequate Correlation to therapy: probable *Grade 3*
1052	F	44	Anxiety syndrome	Aur.m.n. 9 Q, 5 drops 2 × day	Increased sensation of hunger only with this dilution (effect not revealed with 6Q)	New symptom Dech. and rech. positive Intensity 5.5	No con-comitant medicines	I.H.P. potency of remedy not adequate Correlation to therapy: certain *Grade 4*
1016	M	4	Headache	Puls 6 Q, drops 2 × day	Conjunctivitis; amelioration of headache and associated symptoms	New symptom Dech. and rech. positive Intensity not expressed	No con-comitant medicines	I.H.P. early repetition of remedy Correlation to therapy: certain *Grade 4*

R.H, recovery in hospital: I.H.P, inappropriate homoeopathic prescription; dech., dechallenge; rech., rechallenge.

observations and those of Riley may relate to the fact that they studied paediatric cases with specific acute pathology, and the distinction between probable and certain effects was not as clearly defined in their study as it was in ours.

The low incidence of adverse effects reported in our study, does not seem to be influenced by the rate of patients lost to follow up. In 2004 we carried out an independent telephone survey[34] on all the patients (104) seen from 1 June 2002 to 31 May 2003 who never returned for a follow-up visit after the initial homeopathic consultation, in order to ascertain the reasons for the interruption of the relationship (drop-out). All the drop-outs were sought, 73 (70.2%) were traced.

Analysing the answers given by the patients who did not return (73/104), 36/73 (49%) referred to the effectiveness of the treatment with an improvement in their state of health, and for this reason did not return for the follow-up visit. Some patients were dissatisfied with the consultation or the homeopathic treatment (12.3%), but none of these related to the adverse effects of the homeopathic medicine.

In the literature, reports of adverse effects occurring during homeopathic treatment generally refer to reactions to homeopathic medicines used in low dilutions. Even in our preliminary data[35] referring to spontaneous reports of adverse effects (14 telephone calls received by the Homeopathic Medicine Information and Pharmacovigilance Service, November 2003 June 2004) indicate that 85.7% of the therapies used by the callers, involved multiple homeopathic remedies in low dilution, administered simultaneously or in homeopathic complexes and recommended in 35% of the cases by a person who was not a doctor or pharmacist. In 53% of the cases they were recommended by a medical doctor considered an 'expert' in homeopathy.

We demonstrated that adverse events occur also using so-called high potencies (Q potencies) generally considered harmless and safe. We have attempted to provide a plausible explanation of the appearance of the adverse drug events in patients, according to the classical homeopathic methodological approach. We wondered what proportion of the homeopathic prescriptions that were identified as not appropriate should be taken into consideration as a drug AE or a medication error.

Nebeker *et al*[23] explain the close relationship between adverse drug events and medication errors: any preventable event that causes or leads to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such an event may be related to professional practice, health care products, procedure and system including prescribing.

Medication errors are much commoner than adverse drug events, but they result in harm in less than 1% of cases; conversely, about one quarter of adverse drug events are due to medication errors.

These reports do not include those defined as 'homeopathic aggravation' in the true sense of the word, unless they were of such an intensity as to warrant reporting and require medical intervention (generally by antidoting the medicine). This is because the homeopathic aggravation is a temporary reaction, (usually unreported) and is followed by an amelioration of the patient and disturbance being treated.[29] However, in order to assess the incidence of aggravations, our clinic is currently conducting research aimed at examining the frequency and the intensity of homeopathic aggravation, studied during control visits following an effective prescription.

From the initial information on 102 follow-up visits by 338 consecutive patients from September 2002 to 30 June 2004, 27 cases of homeopathic aggravation have been revealed, an incidence of 26.3%.

Aggravation is frequently encountered in homeopathic clinical practice, and in many cases is considered a necessary stage of the curative process. It is difficult to qualify or record in clinical studies. Recent information comes from an observational study by Pomposelli *et al*[36], in which the results of homeopathic treatment in association with traditional therapies, were examined. In 55 patients affected by arthritic-rheumatic and/or osteoporotic pathology, no adverse effects from homeopathic medicines were reported, but in 16 cases (30.8%), a homeopathic aggravation was reported during the first 6 months of therapy, and in 2 cases (3.7%) during the second 6 month period.

In an analysis of randomised clinical trials, Grabia and Ernst[37] were unable to verify a substantial difference between *verum* and placebo in terms of aggravations. They concluded that: either the aggravation does not exist or the methods used to examine it are inadequate. Furthermore, it is not usual practice to document this effect and distinguish it from ADR.

The homeopathic aggravation is a complex phenomenon which forms part of the system: degree of similitude-potency of the medicine and individual sensitivity and reaction. Each of these factors has a variable contingency, thus an accurate definition of each of the factors is required in order to assess this phenomenon, which is not always possible in clinical studies whose aim is other than that of the precise observation of the homeopathic aggravation. The problem of aggravation brings us back again to the difficulty of labelling reactions with the conventional terminology used in ADRs (we could say that they are type A reactions, but it would be necessary to agree on the concept of dose-dependency, or perhaps it would be better to identify them as time-dependent reactions from the first dose?).

With regard to analysis of interaction with other medicines (conventional and non-conventional), a consideration that has proved relevant is that of Rossi *et al*[38] This study showed that many patients undergoing homeopathic treatment have used or are still using conventional medicine and a clear reduction in

the use of these medicines can be demonstrated during homeopathic treatment, leading to the hypothesis that some of the unwanted effects reported could result from the reduction or untimely suspension of conventional therapy, the study by Pomposelli et al also tends to confirm this hypothesis. The correlation between the reduction of conventional treatment and the appearance of possible ADR, attributed to the homeopathic medicine, also seems possible in many of the passive surveillance telephone reports. Nevertheless, in the AE reported up until now in this study, the presenting clinical symptoms do not appear to be linked to the reduction of the pharmacological therapy prescribed for the pathology.

Another reflection should be made about the potential psychological 'impact' of a medicine in well-informed subjects. Galatti and Caputi[39] pointed out that certain kinds of information can modify the patient's perception. We wonder if the perception of symptoms as perceived as unpleasant by patients undergoing homeopathic treatment could be improved through a better understanding by the patient of homeopathic therapy.

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