

Homeopathy: from tradition to science?

Giulio Viganò · Paola Nannei · Paolo Bellavite

Received: 28 July 2014 / Accepted: 18 October 2014 / Published online: 12 December 2014
© Springer-Verlag Italia 2014

Abstract Homeopathy is a form of therapy based on the similarity (“*similia similibus curantur*”, like cures like), whose popularity is increasing but whose scientific basis is still under discussion. Starting from the premise that it is a “holistic” medicine, programmatically aimed at the whole person in its entirety and individuality, here we go through an overview of his history, basic concepts and scientific evidence. This therapy was founded by Samuel Hahnemann in the late 18th century, although similar concepts existed previously. It has spread around the world in the 19th century, in part because of its success in epidemics outbreaks, but declined during most of the 20th century. Its popularity was increased in the late 20th and early 21st century in many parts of the world and today stands the problem of its integration with conventional medicine. There are different schools of homeopathy. Homeopathy is controversial mainly because of its use of highly diluted medicines, but there is growing evidence that is not a mere placebo. There is a significant body of clinical research including randomized clinical trials suggesting that homeopathy has an effectiveness in curing many symptoms and in improving the quality of life of patients. Cohort studies, observational and economic have produced favorable results. Despite the long history of scientific controversy, homeopathy is an “anomaly” of modern medicine that deserves further investigation for its potential scientific and ethical merits.

Keywords Integrative medicine · Homeopathy · History of medicine · Holistic care · Evidence-based medicine · Person-centered medicine

Introduction

Homeopathy is one of the CAMs (complementary and alternative medicines) mostly widely used in Europe. It arose from repeated clinical observations by the German doctor, Christian Friedrich Samuel Hahnemann, in the 18th century, which led him to reformulate a treatment principle, ‘the law of similars’, which was already known in the history of medicine.

After a period of progressive decline, homeopathy is currently spreading throughout the world and there is an urgent need for scientific confirmation of its mechanism of action and of its usefulness. Scientific research on homeopathy is increasing: in the year 2000 the PubMed databank reviewed 1,675 studies under the keywords “Homeopathy” or “Homeopathic” [1], while at the time of editing this paper (October 2014) the number of studies is as high as 5,535. However, there is still no consensus about the real efficacy of this therapeutic method or about the modality of action of ultramolecular or high dilutions (HDs). It is therefore essential that further studies be conducted.

Bearing in mind the “holistic” nature of the homeopathic approach and of the proofs, however incomplete, of its efficacy, the issue arises of a possible integration of this therapy with conventional medicine, especially in certain clinical areas in which the therapeutic effectiveness of the latter has not been attested, or else to shorten the course of those pathologies for which watchful waiting is the standard practice.

Any effective attempt at integration must be based on knowledge of the field; to this end, our study presents the

G. Viganò (✉) · P. Nannei
Italian Society of Homeopathy and Integrative Medicine, Milan,
Italy
e-mail: viganog70@gmail.com

P. Bellavite
Department of Pathology and Diagnostics, University of Verona,
Verona, Italy

essential points of homeopathic theory, with particular attention to its humanistic aspects, but also taking recent scientific evidence into account.

Homeopathy: person-centered therapy

Homeopathy is a clinical-therapeutic method which aims to restore the level of health of some organism (human, vegetable or animal). It is based on principles first articulated by its founder Samuel Hahnemann in his fundamental work “Organon”: (a) experimentation (‘proving’) on healthy people of substances which are capable of perturbing the healthy state and of causing at least partial manifestation of symptoms (something like an “artificial” physiopathologic alteration), which are as close as possible to the totality of symptoms characteristic of the natural disease ([2], §106). (b) The principle of similarity or ‘law of similars’, and the choice of remedies in accordance with that law: a homeopathic remedy is capable of treating a patient who presents symptoms similar to those which the same substance has caused in experiments on a healthy individual ([2], §51). In classic homeopathy a single remedy must be chosen which has a characteristic spectrum of action and which can cure all the physical, energetic and mental symptoms of the patient (‘specific remedy’) ([2], §147). (c) The administration of minimal doses, potentised in such a way that the chosen substance can develop its potential force to the maximum level ([2], §128).

It should be noted that in homeopathy (which term derives from ‘homeo’ = similar + ‘pathos’), the Greek word ‘pathos’ is used with its original meaning of ‘suffering’. The patient manifests his or her suffering through objective and subjective symptoms, not all of which can be directly ascribed to a single ‘nosological entity’ or illness.

Although inspired by earlier theories, it was on the basis of the principles outlined above and of his extensive clinical experience that Hahnemann organized its methodology, carrying out numerous studies and experiments following specific rules [2], with the collaboration of other doctors.

Hahnemann considered the human being to be a biological unit animated by vital energy (‘Dynamis’) which when balanced, and therefore in a state of health, maintains a truly admirable harmony between all the components of the living organism which are involved in various functional and reactive activities ([2], §9). So Hahnemann’s idea of therapy was oriented toward the patient as a whole person rather than just to his illness, to the organism (the material instrument of life) and to disturbances of the Dynamis which animates it with sensitivity and will ([2], §15). In today’s terminology, this is a therapeutic approach which takes into account the whole person in his or her completeness and complexity.

It is worth emphasizing the extent to which classic homeopathic medicine, ever since Hahnemann’s time, has always worked on treating the whole human being. So James Tyler Kent (1849–1916), a well-known American 19th century homeopath, stated that the homeopathic doctor must treat the patient’s mental, emotional and spiritual elements along with his/her body [3]. Illness has a profound meaning for the patient who is ill; it manifests in a certain period of his/her existence, is experienced in a personal and original way, and belongs wholly to the person who has generated it. It is always a single, organic manifestation, albeit with multiple aspects. The fragmentation of illness into hundreds of thousands of large and small illnesses which can be nosologically classified has certain advantages, above all that of allowing the subdivision of patients into identifiable groups according to precise diagnostic criteria, which makes it possible to investigate which drugs are most effective for each specific pathology. Nevertheless, this approach, which is closest to the criteria of “evidence-based medicine”, has dispelled the differences between individuals, neglecting their diverse subjective experience of suffering and often neglecting their personal identity as patients. This prompted the Nobel Prize winner for medicine, Alexis Carrel, to affirm that “The sick person has been divided into various regions, each of which has its own specialist. Such a specialist devotes himself to the study of a tiny part of the body, but in this way he remains so ignorant of the rest that he cannot even be said to know this part perfectly” [4].

So homeopathy sets out to satisfy the demand currently felt by both medicine and society [5–7], which is that the patient be considered as a whole person, in his/her physical and spiritual entirety.

Historical background

The principle of similarity on which homeopathy is based has its roots in antiquity, and can be traced through centuries of the history of medicine. Among the earliest proponents of the doctrine was Hippocrates (460–367 B.C.), who is regarded as the first representative of rational medicine in the western world. He observed empirically that “through the similar the disease develops and through use of the similar the disease is healed. So that which causes urinary tenesmus in the healthy, cures it in disease. Coughing is provoked and healed through the same agent in exactly the same way as in the case of urinary tenesmus” [8]. Theophrastus Bombastus von Hohenheim (1493–1542), the German naturalistic doctor and philosopher better known as Paracelsus, was a more recent representative of this line of thought. He formulated the doctrine of signatures (‘signa naturae’), according to

which the therapeutic properties of plants or minerals can be deduced from some similarity between their forms or colours and various parts of the human body: sharply pointed leaves for stabbing pains, iris-like *Euphrasia* flowers for eye diseases, topaz to treat jaundice because both are yellow, and so on [8]. Obviously this type of reasoning by analogy lends itself to attack from current scientific thinking, but historically it played a role in keeping the principle of similarity alive, so that Hahnemann was eventually prompted to examine it experimentally.

After taking a degree in medicine at Erlangen in 1779 and practising for about a decade, Hahnemann (1755–1843) abandoned the medical profession, recognizing its limitations and therapeutic inadequacies. Thereafter he dedicated himself to the translation of scientific texts, and then between 1790 and 1796 he formulated his own doctrine, declaring the universal value of the principle of similarity, which is the cornerstone of homeopathy.

Hahnemann's had his first inkling of this doctrine in 1789, while he was translating a book by W. Cullen, a doctor and professor at the University of Edinburgh. Cullen claimed that the therapeutic power to treat fever of cinchona (Jesuits' bark), which was widely used to treat malaria, could be attributed to a "corroborating" action on the stomach. Hahnemann knew that there were many other substances more bitter and astringent than cinchona which were ineffective against malaria, and he found it intriguing that Cullen in the same work should report among people who worked with quinine a clinical picture of psychophysical toxicosis which was rather similar to the symptoms of malaria. Hahnemann's next step was to test the effects of cinchona on himself, taking a certain quantity every day. While he was taking the drug he experienced fever, shivering and other malaria-like symptoms. This led him to postulate a healing principle: that which can produce a set of symptoms in a healthy individual, can treat a sick individual who is manifesting a similar set of symptoms. The father of homeopathy thought that the therapeutic efficacy of cinchona must be due to the fact that this substance caused symptoms which were similar to those it treated.

In 1796 Hahnemann published an article which can be regarded to all intents and purposes as the birth certificate of homeopathy. In this work, "Essay on a new principle for ascertaining the curative powers of drugs, and some examinations of the previous principles" [9], the law of similars was first defined in a systematic way.

The first complete homeopathy textbook was published in 1810 under the name of "Organon of Rational Art of Healing" [10]. Nine years later, in 1819, a second edition was published with the title "Organon of Healing Art"; further editions followed, until the sixth was published posthumously in 1921. The other two fundamental works

on homeopathy are "Materia Medica Pura" and "Chronic Diseases". *Materia Medica Pura*, a compilation of "homeopathic proving" reports, published in six volumes between Vol. I in 1811 and Vol. VI in 1827. Revised editions of volumes I and II were published in 1830 and 1833, respectively. There are 61 medicines contained in these volumes. There were 37 provers. In the "Chronic diseases" Hahnemann revises and elaborates on the therapeutic approach to the patient according to the theory of "miasms" [11].

Traditional methodology

Hahnemann's first book, *Organon of Healing Art*, is still regarded as the fundamental guide to applying the homeopathic method. Conceivably this is the only two-century-old book which is still used in current medical practice: this intriguing fact may be due either to the lack of updating of this medical discipline or to the presence in its theory of some principle of timeless validity. The concepts set out in this work constitute the first attempt in the history of medicine to codify the principles and laws which govern the states of health and disease. Hahnemann proposes the homeopathic method to treat both acute and chronic pathologies, a method based above all on the principles he had set out in the *Organon* (from § 61 to § 69) [2]: "if the stronger well-marked (characteristic), and peculiar symptoms of the disease are covered and matched by the same medicine with similarity of symptoms ..., the few opposite symptoms also disappear of themselves after the expiry of the term of action of the medicament, without retarding the cure in the least" (§ 67) and "In homoeopathic cures they show us that the uncommonly small doses of medicine required in this method of treatment are just sufficient, by the similarity of their symptoms, to overpower and remove the similar nature disease" (§ 68).

The homeopathic doctor's objective during a clinical examination is to find a remedy whose own pathogenesis includes the symptoms presented by the patient during his illness. To reach this objective the doctor uses two instruments: the *Materia Medica* and the *Repertory*. The first is a collection of signs and symptoms (physical, psychological and sensory) caused by administration of a given substance in a high percentage of healthy subjects during proving, while the second is in practice a list of symptoms and the homeopathic remedies associated with them. In fact, two individuals may react to the same *noxa patogena* with symptoms which are similar but not identical. The doctor's aim during the examination is to personalize the therapy as far as possible by comparing the patient's symptoms with the pathogenesis of homeopathic remedies. It is important to find out not only which signs

and symptoms are present, but also the conditions in which they improve or worsen ('modality'), the mental states they cause, how they manifest throughout the day, and so on. All this makes it clear why the same pathology in different individuals may require different homeopathic remedies.

The careful drawing up of a medical history and the doctor's attention to the whole person with his/her individual peculiarities are not so much the result of a specific ethical position as the methodological consequence of the search for the right remedy following the criterion of similarity. In this sense the homeopathic approach is consistent with that of modern 'complexity sciences' [12], pursued in other domains of medicine [13–15], and is opposed to the reductionist tendencies of biotechnological medicine.

The approach to acutely ill patients

In acute pathologies the patient usually presents a limited number of symptoms which do not vary much from one individual to another. For this reason application of the principle of similarity is simpler and the number of remedies from which to choose is reduced. Obviously, individual reactions of the patient (type of sweating, variations in temperature, thirst, prostration, etc.) are always present, and this helps the homeopath to choose the most suitable remedy.

According to Hahnemann, acute pathologies are due to sudden alterations in manifestation of the vital principle; their evolution is variable, but normally is short term [2] (§72). He classifies acute manifestations into two categories: (a) individual diseases such as traumas, ailments due to occasional causes (cold, heat, overeating, etc.), or worsening of chronic illnesses, (b) collective diseases which strike many individuals at the same time and which can be sporadic or epidemic (§73). To cure acute illnesses, the doctor must first determine the most likely occasional cause (§4–5) and then on the basis of the law of similars, select the remedy which as far as possible covers the patient's symptoms in their totality.

The approach to chronically ill patients

The homeopathic approach to such patients requires a profound knowledge of the *Materia Medica* and use of the *Repertory* in order to personalize the treatment as much as possible. In these cases the law of similars is to be applied bearing in mind not only the clinical picture presented by the patient at the time of the medical examination, but also variations in the symptoms which have occurred over time, any other pathological tendencies of the patient and his/her family history. Hahnemann had already specified that the methodological approach to patients who were

chronologically ill should be based on the consideration of a number of points: physical constitution, moral and intellectual character, activities, way of life, habits, social situation, family relationships, age, sex life, etc. (§ 4, 5, 71, 73).

Given the complexity of this approach to chronic illness, the choice of the right remedy can be arrived at by evaluating certain points which have gradually emerged over time: miasms, constitution, and sensitive type.

Miasms

After 20 years of homeopathic practice, Hahnemann began to tackle the fundamental problem of chronic illnesses which did not respond, or responded only partially, to an apparently correct remedy; he published his conclusions in the text, "Chronic Diseases" [11]. In certain cases patients were not completely cured, or else they continued to have relapses or new symptoms despite the right prescription. This observation led Hahnemann to revise his theory and posit the existence of unknown external agents ('miasms') which, after infecting the organism, begin to manifest by causing a series of symptoms. Today this concept seems very limited [16, 17], but it should be borne in mind that until 1860, the year of Pasteur's discovery, the effects of microbes as agents of pathogenesis was practically unknown, so that discussion centred on miasmatic diseases due to miasms or 'effluvia', meaning organic substances in the air which emanated from swamps. Very few individuals suspected that these agents of infection might be living organisms. Hahnemann was among these few: 35 years before Pasteur, in a study of the treatment of Asian cholera (1831), he gave the following definition of miasm: "the cholera miasm finds a favorable element for its multiplication, and grows into an enormously increased brood of those excessively minute, invisible, living creatures, so inimical to human life, of which the contagious matter of the cholera most probably consists" ([18], page 851). In Hahnemann's view, a miasm affects the organism so profoundly as to render it insensitive to the action of homeopathic remedies selected according to the symptoms present at the time of the medical examination. These symptoms are only part of a more complex situation which must be seen in its totality if the patient is to be properly treated. From this point of view the various symptoms presented throughout the patient's life are regarded as an evolution of an original "infection", which must be taken into consideration if a complete and lasting cure is to be effected.

There have been many variations of the miasms theory during the history of homeopathy and it is still the subject of much discussion. While it is obviously outdated from the point of view of modern pathology, it is still used in some

schools as an informative criterion which can facilitate the choice of remedy.

Constitutions

This concept derives from theories expounded by Dr. Nebel at the beginning of the 20th century which were later taken up by other doctors, particularly Leon Vannier [19]. They noted that some patients who were sensitive to the action of calcium carbonate presented similar morphological and psychological characteristics and similar morbid tendencies. The same observation could be made regarding subjects sensitive to other calcium salts (calcium phosphate and calcium fluoride). This concept evolved during the 1920s, and was both extolled and attacked to an excessive extent. Nowadays three fundamental constitutional types tend to be recognized: sulphuric, carbonic, phosphoric, with a further secondary type (fluoric) which according to many experts is not an independent type and can therefore be combined with the others.

In the light of modern genetic discoveries, the theory of constitutional types should not be seen as a rigid definition of patient categories. However, the fact remains that the chance to determine a patient's constitution facilitates the homeopath in the choice of a remedy for chronic illness in the absence of other supporting information.

Sensitive typology

The notion of the “sensitive typology” arose from experiments using various homeopathic remedies. During these provings the early homeopaths noticed that in some subjects a great number of clearly defined symptoms manifested. Clinical experience demonstrated that such individuals had certain characteristics in common (morphology, temperament, morbid tendencies, and so on), and that the pathologies they presented throughout their lives were often cured by the very substance to which they had shown particular sensitivity during the provings. From the practical point of view, knowing a patient's sensitive typology helps to choose the right remedy to treat his/her chronic illness.

Homeopathic schools

It is worth noting that in the course of its history, homeopathy has seen many doctrinal debates and variations in the way it is applied. Two main divisions are currently recognized: unicism and pluralism (see also http://www.echamp.eu/fileadmin/user_upload/Brochures/Homeotherapy_-_Definitions_and_Therapeutic_Schools.pdf).

The unicist homeopath is more faithful to Hahnemann's methods; he or she studies and treats the patient as a unique

and organic whole. Only one remedy is prescribed at a time, to cover the overall picture of individual dysfunction. The pluralist form, which allows the prescription of more than one remedy at a time, is also called clinical homeopathy. It originated in France and has spread all over the world. It involves the prescription of one or more remedies chosen on the basis of the patient's more important symptoms.

Other therapies exist which, although they have many points in common and although they make use of homeopathic remedies, cannot be identified with true homeopathy; they include isotherapy, homotoxicology and anthroposophy. There are also homeopathic medicines produced with complex formulations, containing several components. These formulations are often sold over the counter (OTC) to treat specific symptoms like sore throat, cough or insomnia, but their use does not constitute a true homeopathic treatment.

Further distinctions have arisen between those who propose the use of low dilutions/dynamisations (small doses by weight of medicinal substances which have been diluted following homeopathic procedures) and those who propose the almost exclusive use of high dilutions/dynamisations (so-called infinitesimal doses or high ‘potency’ homeopathic remedies).

Research

In homeopathy, medicines are used at extremely low doses and also at ‘ultramolecular’ dilutions (high dilutions, HDs). This term describes those remedies in which the original substance is unlikely to be present: the dilution is superior to Avogadro's number (6.002×10^{23}), in other words more than 23 DH or 12 CH. This paradox has always provoked heated debate about the efficacy of homeopathy, with detractors [20, 21] and supporters [22, 23]. Even today, 25 years after Poitevin's and Benveniste's publications [24, 25] about the “memory of water”, the controversy has not died down. Both basic research in this field and studies of clinical efficacy have made considerable progress in recent years, and although the mechanism of action of HDs has still not been completely clarified, knowledge has advanced to the point where the clinical efficacy of homeopathic dilutions seems plausible.

Furthermore, in the face of widespread scepticism in academic circles, homeopathic remedies retain a solid popularity among European populations. In Italy [26], Norway [27], Germany [28] and Switzerland [29], homeopathy is very frequently chosen to treat paediatric patients. Even general practitioners often prescribe homeopathic remedies when conventional therapies prove relatively or completely ineffective [30].

So the subject evidently requires further examination, with an analysis of what can be learned from both basic and clinical research.

Basic research

Even if homeopathy is based on the law of similars, its principal axiom, research has focused on the study of HDs, aiming to understand whether and how they work and to draw attention to their possible biological action.

The most widely credited hypothesis to explain the mechanism of action of homeopathic medicines relates to understanding whether and how water may be able to retain information. As mentioned above, this theory, known as the “memory of water”, sparked intense controversy [31–33] which is still open [34, 35]. More recent studies suggest that in appropriate circumstances, aqueous or hydroalcoholic solutions can memorise and transmit information about substances which have been progressively diluted in them [36, 37]. Rey’s studies on thermoluminescence [38, 39] are of particular interest. This technique is used in the study of solids, particularly crystals. The researcher demonstrated that lithium chloride 15 CH and sodium chloride 15 CH produce thermoluminescence which is characteristic of the original solutions of their respective salts and different from that of the solvent. This result, which was confirmed by an independent research group [40], has been attributed to peculiar modifications to the network of hydrogen bonds found in very dilute solutions of each salt. Other researchers have measured modifications of the physical parameters of ultradilute homeopathic solutions using pH measurement, electrical conductivity, isothermic calorimetry [41, 42] and other electronic devices [43–46]. On the basis of these studies it can be affirmed that there exists a measurable difference between the chemical–physical parameters of water and those of ultradilute homeopathic solutions, even though these are chemically identical to water. These differences have been attributed to the formation of specific molecular “clusters” [47, 48] or “coherence domains” [49, 50] induced by dynamisation, which alter the molecular structure of the water itself [51].

Another fundamental line of research involves hormesis, which is closely related to the principle of similarity. Hormetic responses are characterized by modest stimulation of a specific function at low doses and inhibition of the same function at high doses. In recent years numerous articles have been published which demonstrate that the dose–response hormetic curve is a very common biological phenomenon which is highly generalisable [52]. A vast database is now available which gives evidence of the occurrence of the dose–response hormetic curve in the toxicological literature [53]. The recent concept of

“postconditioning hormesis” is particularly interesting: it describes the phenomenon whereby minimal toxic stimuli have a beneficial effect on a biological system which has previously been exposed to high toxic stress of a similar nature [54–56]. However, it would not be correct to identify the phenomenon of hormesis *in toto* with the homeopathic concept of similarity [57–59], although there are remarkable points of contact between the two.

A recent meta-analysis which evaluated 67 *in vitro* experiments in 75 research publications about homeopathic dilutions had very interesting results. It found that 75 % of all the studies conducted on ultramolecular dilutions (HDs) showed that they had some effect [60].

Finally it is worth remembering the *in vitro* studies on degranulation of basophils, which aim to identify a reproducible biological reaction in order to study the effects of homeopathic dilutions. The earliest studies showed an inhibition of degranulation using ultramolecular dilutions of anti IgE antibodies [24], but reproduction of these results proved impossible. Subsequent studies, using a different methodology, gave positive results using ultramolecular dilutions of histamine [61–63]. Several independent laboratories [64–67], but one [68], were able to reproduce these results.

Clinical research

The primary aim of basic research is to understand whether and how homeopathic medicines, or more generally substances at high dilutions, can have effects on living systems. Clinical research, on the other hand, must evaluate the safety and efficacy of homeopathic remedies. One further aspect concerns their mechanism of action, in other words whether their action can be considered tantamount to that of placebos. When evaluating the evidence for or against the efficacy of homeopathy it must be emphasized that the question of the placebo effect, although very important, is not the same question and does not tell the whole story [69].

The standard method for evaluating the clinical efficacy of a medicine is the double-blind, randomized clinical trial (RCT). Various meta-analyses have been carried out in recent years to evaluate the efficacy of homeopathic remedies. The first was published in 1991 and included 105 trials with results which could be evaluated; 81 of these trials gave positive results [70]. However, the researchers judged the methods used in the majority of the studies insufficiently rigorous for definitive conclusions to be drawn, although they held that a positive effect of homeopathy was plausible.

Another meta-analysis was published in *The Lancet* in 1997 [71]. This article selected 185 studies, 89 of which satisfied the researchers’ criteria of quality and fitness for

statistical analysis. The odds ratio of these 89 trials was 2.45 (95 % CI 2.05, 2.93) in favour of homeopathy. 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. However, we found insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition. Further research on homeopathy is warranted provided it is rigorous and systematic” [71].

In 2005 Shang et al. [72] published a meta-analysis which included 110 RCTs of homeopathic and 110 RCTs of conventional medicines. In both groups of trials the majority of studies found a positive effect of the drug compared with placebo. When the analysis was restricted to studies judged to be of high quality and which had a large number of subjects, the odds ratio of homeopathy (eight studies) was 0.88 (95 % CI 0.65–1.19) whereas that of conventional medicine (six studies) was 0.58 (0.39–0.85); these results led the researchers to conclude that the effects of homeopathy were no different from those of placebo. This paper provoked various objections about the criteria used to select the studies for inclusion, and whether it was possible to compare data from such different trials [73–77]. The criteria used to select these trials are fundamental if we are to avoid including in the statistical analysis trials which might falsify its results. This was the main objection made to Shang’s study, along with the criticism that far too few studies were included and that they were too different from one another to allow application of the calculations typical of meta-analyses [23, 78]. Furthermore, it has been shown that flawed statistical methods were applied: The funnel plot, used by Shang et al. [72] is flawed when applied to a mixture of diseases, because studies with expected strong treatment effects are, for ethical reasons, powered lower than studies with expected weak or unclear treatment effects. [79].

To overcome these difficulties, Mathie et al. [23] conducted a review of research on homeopathy from 1950 to 2011. They identified 498 studies, from which they selected 263. The aim of their work was to define a method for studying and cataloguing RCTs carried out in the field of homeopathy, in order to clarify the issues raised by previously published RCTs and also to find a group of studies on which to base future systematic reviews. This review of the literature led Mathie to evaluate the use of homeopathy in 89 clinical conditions. It was found to have given decidedly positive results in three types of pathology, fibromyalgia, influenza, and allergic rhinitis. In a further 47 conditions homeopathic medicine gave results which were generally positive, in 33 the results were unclear, and in six the results were basically negative. Of the 164 peer-reviewed papers included in the analysis, 71 (43 %)

demonstrated an effect of homeopathic medicine, 9 (6 %) gave a negative result and 80 (49 %) were inconclusive. These results are in line with those of a similar study which evaluated 1,016 systematic reviews of RCTs in allopathic medicine, published in the Cochrane Library: 44 % of the reviews gave a positive result, 7 % a negative and 49 % an inconclusive result [80].

Observational clinical studies should also be mentioned, since they can make a useful contribution to the development of research in the field of homeopathy and to evaluation of its efficacy [81–84]. While it is true that RCTs are the standard method for testing the effectiveness of drugs, it is equally clear that their structure is not completely appropriate for studying such complex medical acts [85] as the choice of a homeopathic remedy may prove to be. Observational clinical studies are increasingly being used in conventional medicine also, because their lower statistical validity is balanced by the advantage that they can be carried out in conditions which more accurately reflect the real methods used by health workers and the environments in which they work. The results of clinical observation studies may be considered a valid adjunct in the field of homeopathic research. These studies have decidedly positive results [69, 86, 87].

Integration

Although there is still a lot of doubt about the efficacy of homeopathic medicine, it is widely used throughout the world, obviously with regional variations. The European Commission estimated in 1997 that 27 % of the population had used homeopathic remedies. They are also very popular in India and Latin America. Some nations include homeopathy in their national health systems: UK, Brazil, Mexico, India, Pakistan and Sri Lanka [88]. In Europe, CAMs and especially homeopathy are increasingly demanded by the public and pose the questions related to integration with mainstream medicine [89–91]. In Italy, the use of homeopathic medicine has evolved in a peculiar way [92]. According to an investigation by ISTAT, the number of users increased from 2.5 % of the population in 1991 to 8.2 % in 2000, later stabilizing at 7 % in 2005 (ISTAT document 2007), making it the most popular form of alternative medicine in Italy.

This widespread interest in the use of homeopathy is a point of departure for the promotion of greater integration between conventional medicine and homeopathic practice. Obviously, that can only be based on the following essential requirements:

(1) Promotion of clinical research to evaluate the real efficacy of homeopathy.

The current situation of uncertainty about its validity is an inescapable fact, from which it follows that further studies are necessary.

(2) Appropriate courses of study and training, with certification of the level of instruction.

(3) Evaluation of the cost-effectiveness of homeopathic compared with conventional medicine. Useful studies of this kind have been conducted in France, Germany and Italy [84, 93–96]. They showed substantially equivalent costs for the two types of treatment, with better outcomes for those patients whose doctors also used homeopathic medicines.

There have been a number of attempts at integration in various countries. One notable example is the collaboration between Dr. Prasanta Banerji and various American universities and research centres, which has resulted in the formation of an international team charged with evaluating the efficacy of certain homeopathic protocols for the treatment of neoplastic pathologies [97, 98]. The Joint Action “European Partnership on Action against Cancer” (EPAAC) also works in the field of oncology. This project, initiated in September 2009 by the European Commission with the support of numerous partner agencies, aims to reduce the number of cancer cases in all member states. The Regione Toscana (regional administration of Tuscany) is a participant in this project; its aims are to collect and analyze scientific evidence about the use of complementary medicine in oncology, and to devise criteria for the most accurate disclosure of this scientific information.

In UK more than 400 general practitioners use homeopathy along with conventional medicine in their daily practice, and within the National Health Service there are five hospitals using integrated medicine which offer homeopathic treatments. The Royal London Hospital for Integrated Medicine (RLHIM) is the largest public institution for integrated medicine in Europe, offering an approach to diagnosis and therapy based on both conventional and homeopathic medicine. In Italy too, doctors at the Ospedale Petruccioli at Pitigliano have since February 2011 offered homeopathic medicine to those hospitalized patients who request it. This is the result of developments in legal and clinical practice promoted by the Tuscany regional administration in order to integrate complementary medicine into the National Health Service [99, 100].

A particularly well-integrated branch of medicine is paediatrics. A survey of 1,233 Italian paediatricians conducted by the Società Italiana di Pediatria (SIP) in 2011 revealed that 23 % of those interviewed used CAMs (complementary and alternative medicines). The most commonly used forms were herbal medicine (82.4 %) followed by homeopathy (74.9 %).

Our everyday clinical experience suggests that homeopathy and conventional medicine can be integrated in the treatment of both acute and chronic illness. For acute pathologies we first try homeopathic remedies which are useful in treating the overall clinical picture, resorting to conventional medicine only if there is an inadequate response. Fundamental to this course of action is the support given by studies which on the one hand confirm the efficacy of homeopathy, and which on the other hand exclude that postponing any more aggressive therapy involves any risk for the patient. The treatment of acute middle ear infection is a good illustration of the way we work. The international literature confirms both that it is possible to wait 72 h from the onset of symptoms before beginning antibiotic treatment [101], and that homeopathic medicine is effective in this situation [69, 102].

When treating chronic or relapsing pathologies we intervene on various levels. In line with results in the literature [92], we find that the greatest demand is for treatment of relapsing respiratory infections. We use homeopathy as a first line therapy for these patients, both to reduce the number of acute episodes and to reduce the risk of complications which compromise the function of the lower respiratory tract. If these occur, it is sometimes necessary to use antibiotics. In the field of dermatology, there are frequent requests to treat children with atopic dermatitis; in this pathology too, homeopathy can usefully be integrated with the specialist treatments prescribed by dermatologists. The main objective of therapy is moisturization of the skin. Homeopathic treatments can reduce cutaneous itching and inflammation, and shorten the duration of symptoms [103, 104].

Conclusions and prospects

Because it considers the patient as a whole person rather than just his/her illness, homeopathy and other forms of CAM can contribute to “restore the soul to medicine—the soul being that part of us that is the most important but the least easy to delineate.” [105].

As we have seen, a significant effort is being made to evaluate the real efficacy of this therapeutic method. Further studies are necessary to deepen our understanding of the mechanism of action of HDs and to confirm existing results. Work on hormesis is of particular interest, and investigation of the chemical and physical properties of water which confirm the effects of ultra-dilute homeopathic solutions.

We also believe that it is essential to extend clinical research, both by producing RCTs of high quality and by endorsing observational studies of the epidemiological type, which are frequently undervalued. This type of

research has the advantage of being conducted in conditions which more accurately reflect the real methods used by health workers and the environmental conditions in which they are used. Observational studies make it possible to follow homeopathic methodology more closely and an important variety of them, called “clinical verification of homeopathic symptoms”, may serve for improving homeopathic prescription in future [106–109]. Every therapeutic approach, in fact, requires evaluation procedures which take into account its possible mechanisms of action and the context of treatment. RCTs are not always capable of adequately evaluating medical acts requiring particular abilities, such as surgery and acupuncture [110]; it must be borne in mind that finding the correct homeopathic remedy depends on taking a thorough medical history and on an atmosphere of trust, which is lacking in double-blind studies [85, 111, 112]. Judgments about the efficacy of homeopathic therapy, and hence whether it can be integrated with ‘allopathic’ medicine, need to be arrived at using a variety of research methods, blind and open, randomized and observational, because each method gives results which allow evaluations from diverse points of view.

Acknowledgments We thank Associazione Giovanni Scolaro per la Medicina Integrata (Verona, I) for the contribution in translation and editing of the manuscript.

Conflict of interest Giulio Viganò certifies that there is no actual or potential conflict of interest in relation to this article.

References

- Bellavite P, Conforti A, Lechi A, Menestrina F, Pomari S (2000) *Le medicine complementari: definizioni, applicazioni, evidenze scientifiche disponibili*. Utet-periodici, Milano
- Hahnemann CFS, Reves Joseph (eds) (1842) *Organon of Medicine*, 5, 6 edn. Homeopress Ltd, Haifa
- Kent JT (1919) *Lectures on homoeopathic philosophy*, Memorial edn. Ehrhart and Karl, Chicago
- A Carrel (1945) *Le rôle futur de la médecine*. In: A Carrel, A Lumiere (eds) *Médecine officielle et médecines hérétiques*. Plon Pressences, Paris
- Oberbaum M, Singer SR, Vithoulkas G (2005) The colour of the homeopathic improvement: the multidimensional nature of the response to homeopathic therapy. *Homeopathy* 94:196–199
- Schmidt JM (2009) Is homeopathy a science?—Continuity and clash of concepts of science within holistic medicine. *J Med Humanit* 30:83–97
- Bell IR, Koithan M, Pincus D (2012) Methodological implications of nonlinear dynamical systems models for whole systems of complementary and alternative medicine. *Forsch Komplementmed* 19(Suppl 1):15–21
- L.J. Boyd (1936) *A Study of the Simile in Medicine* (edizione italiana a cura di P. Bellavite: *Il Simile in Medicina*. Medicina Ippocratica, omeopatia e scienza, Ed. Cortina, Verona, 2001). Boericke and Tafel, Philadelphia
- Hahnemann CFS (1796) *Versuch über ein neues Princip zur Auffindung der Heilkräfte der Arzneisubstanzen* (Essay on a new principle for ascertaining the curative powers of drugs), and some examinations of the previous principles. *Hufeland's J* 2:391–439
- Hahnemann CFS (1810) *Organon der rationellen Heilkunde*. Arnoldschen Buchhandlung, Dresden
- Hahnemann CFS (1828) *Die chronischen krankheiten. Ihre eigenthümliche natur und homöopathische heilung*. Arnold, Dresden
- Bellavite P (2003) Complexity science and homeopathy: a synthetic overview. *Homeopathy* 92:203–212
- Paley J (2007) Complex adaptive systems and nursing. *Nurs Inq* 14:233–242
- Mezzich JE, Salloum IM (2008) Clinical complexity and person-centered integrative diagnosis. *World Psychiatry* 7:1–2
- Miles A (2009) Complexity in medicine and healthcare: people and systems, theory and practice. *J Eval Clin Pract* 15:409–410
- Guajardo G, Bellavite P, Wynn S, Searcy R, Fernandez R, Kayne S (1999) Homeopathic terminology: a consensus quest. *Br Homeopath J* 88:135–141
- Bellavite P, Pettigrew A (2004) Miasms and modern pathology. *Homeopathy* 93:65–66
- CFS Hahnemann (1851) *The lesser writings of Samuel Hahnemann* (trans: Dudgeon RE). W Headland Publishers, London
- Vannier L (1965) *La typologie et ses applications thérapeutiques*. Doin-Darren & Cie, Paris
- Garattini S, Berteletti V (2010) Alternative medical practices: flashbacks from the dark ages. *Eur J Intern Med* 21:245–246
- Ernst E (2008) The truth about homeopathy. *Br J Clin Pharmacol* 65:163–164
- Milgrom LR (2008) Homeopathy and the new fundamentalism: a critique of the critics. *J Altern Complement Med* 14:589–594
- Rutten L, Mathie RT, Fisher P, Goossens M, Van WM (2013) Plausibility and evidence: the case of homeopathy. *Med Health Care Philos* 16:525–532
- Poitevin B, Davenas E, Benveniste J (1988) In vitro immunological degranulation of human basophils is modulated by lung histamine and *Apis mellifica*. *Br J Clin Pharmacol* 25:439–444
- Davenas E, Beauvais F, Amara J, Robinson M, Miadonna A, Tedeschi A, Pomeranz B, Fortner P, Belon P, Sainte-Laudy J, Poitevin B, Benveniste J (1988) Human basophil degranulation triggered by very dilute antiserum against IgE. *Nature* 333:816–818
- Rossi E, Bartoli P, Panozzo M, Bianchi A, Da Fré M (2010) Outcome of homeopathic treatment in paediatric patients: an observational study from 1998 to 2008. *Eur J Integr Med* 2:115–122
- Steinsbekk A, Bentzen N, Brien S (2006) Why do parents take their children to homeopaths?—an exploratory qualitative study. *Forsch Komplementmed* 13(2006):88–93
- Du Y, Knopf H (2009) Paediatric homeopathy in Germany: results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Pharmacoepidemiol Drug Saf* 18:370–379
- Marian F, Joost K, Saini KD, von Ammon K, Thurneysen A, Busato A (2008) Patient satisfaction and side effects in primary care: an observational study comparing homeopathy and conventional medicine. *BMC Complement Altern Med* 8:52
- Ekins-Daukes S, Helms PJ, Taylor MW, Simpson CR, McLay JS (2005) Paediatric homeopathy in general practice: where, when and why? *Br J Clin Pharmacol* 59:743–749
- Picart CJ (1994) Scientific controversy as farce: the Benveniste–Maddox counter trials. *Soc Stud Sci* 24:7–37
- Maddox J, Randi J, Stewart WW (1988) “High-dilution” experiments a delusion. *Nature* 334:287–290
- Benveniste J (1994) Memory of water revisited (letter). *Nature* 370:322

34. Chaplin MF (2007) The memory of water: an overview. *Homeopathy* 96:143–150
35. Poitevin B (2008) The continuing mystery of the memory of water. *Homeopathy* 97:39–41
36. Elia V, Napoli E, Germano R (2007) The ‘memory of water’: an almost deciphered enigma. Dissipative structures in extremely dilute aqueous solutions. *Homeopathy* 96:163–169
37. Betti L, Trebbi G, Olioso D, Marzotto M, Bellavite P (2013) Basic research in homeopathy and ultra-high dilutions: what progress is being made? *Homeopathy* 102:151–154
38. Rey L (2007) Can low-temperature thermoluminescence cast light on the nature of ultra-high dilutions? *Homeopathy* 96:170–174
39. Rey LR (2003) Thermoluminescence of ultra-high dilutions of lithium chloride and sodium chloride. *Physica A* 323:67–74
40. Van Wijk R, Bosman S, van Wijk EP (2006) Thermoluminescence in ultra-high dilution research. *J Altern Complement Med* 12:437–443
41. Belon P, Elia V, Elia L, Montanino M, Napoli E, Niccoli M (2008) Conductometric and calorimetric studies of the diluted and agitated solutions. On the combined anomalous effect of time and volume parameters. *J Therm Anal Calorim* 92:459–469
42. Elia V, Baiano S, Duro I, Napoli E, Niccoli M, Nonatelli L (2004) Permanent physico-chemical properties of extremely diluted aqueous solutions of homeopathic medicines. *Homeopathy* 93:144–150
43. Bell IR, Lewis DA, Brooks AJ, Lewis SE, Schwartz GE (2003) Gas discharge visualization evaluation of ultramolecular doses of homeopathic medicines under blinded, controlled conditions. *J Altern Complement Med* 9:25–38
44. Assumpcao R (2008) Electrical impedance and HV plasma images of high dilutions of sodium chloride. *Homeopathy* 97:129–133
45. Lenger K, Bajpai RP, Spielmann M (2013) identification of unknown homeopathic remedies by delayed luminescence. *Cell Biochem Biophys* 2:321–334
46. Mahata CR (2013) Dielectric dispersion studies of some potentiated homeopathic medicines reveal structured vehicle. *Homeopathy* 102:262–267
47. Widakowich J (1997) Microdose therapy: dilution versus potentiation? *Med Hypotheses* 49:437–441
48. Yinnon CA, Yinnon TA (2009) Domains in aqueous solutions: theory and experimental evidence. *Mod Phys Lett B* 23:1959
49. Smith CW (2004) Quanta and coherence effects in water and living systems. *J Altern Complement Med* 10:69–78
50. Marchettini N, Del GE, Voeikov V, Tiezzi E (2010) Water: a medium where dissipative structures are produced by a coherent dynamics. *J Theor Biol* 265:511–516
51. Bellavite P, Marzotto M, Olioso D, Moratti E, Conforti A (2014) High-dilution effects revisited. 1. Physicochemical aspects. *Homeopathy* 103:4–21
52. Calabrese EJ (2010) Hormesis is central to toxicology, pharmacology and risk assessment. *Hum Exp Toxicol* 29:249–261
53. Calabrese EJ, Blain RB (2011) The hormesis database: the occurrence of hormetic dose responses in the toxicological literature. *Regul Toxicol Pharmacol* 61:73–81
54. Van Wijk R, Wiegant FA (2011) Postconditioning hormesis and the similia principle. *Front Biosci (Elite Ed)* 3:1128–1138
55. Wiegant FA, Prins HA, Van WR (2011) Postconditioning hormesis put in perspective: an overview of experimental and clinical studies. *Dose Response* 9:209–224
56. Bell IR, Koithan M (2012) A model for homeopathic remedy effects: low dose nanoparticles, allostatic cross-adaptation, and time-dependent sensitization in a complex adaptive system. *BMC Complement Altern Med* 12:191
57. Bellavite P, Chirumbolo S, Marzotto M (2010) Hormesis and its relationship with homeopathy. *Hum Exp Toxicol (BELLE News)* 16:11–18
58. Bernardini S (2010) Homeopathy: clarifying its relationship to hormesis by EJ Calabrese and WB Jonas. *Hum Exp Toxicol* 29:537–538
59. Calabrese EJ, Jonas WB (2010) Homeopathy: clarifying its relationship to hormesis. *Hum Exp Toxicol* 29:531–536
60. Witt CM, Bluth M, Albrecht H, Weissshuhn TE, Baumgartner S, Willich SN (2007) The in vitro evidence for an effect of high homeopathic potencies—a systematic review of the literature. *Complement Ther Med* 15:128–138
61. Sainte-Laudy J, Belon P (1993) Inhibition of human basophil activation by high dilutions of histamine. *Agent Actions (Inflamm Res)* 38:C245–C247
62. Sainte-Laudy J, Sambucy JL, Belon P (1991) Biological activity of ultra low doses I. Effect of ultra low doses of histamine on human basophil degranulation triggered by *D. pteronissinus* extract. In: Dourempeuich C (ed) *Ultra low doses*. Taylor & Francis, London, pp 127–138
63. Cherruault Y, Guillez A, Sainte-Laudy J, Belon P (1989) E’tude mathematique et statistique des effets de dilutions successives de chlorhydrate d’histamine sur la reactivite des basophiles humains. *Bio-Sciences* 7:63–72
64. Brown V, Ennis M (2001) Flow-cytometric analysis of basophil activation: inhibition by histamine at conventional and homeopathic concentrations. *Inflamm Res* 50(2):S47–S48
65. Lorenz I, Schneider EM, Stolz P, Brack A, Strube J (2003) Sensitive flow cytometric method to test basophil activation influenced by homeopathic histamine dilutions. *Forsch Komplementarmed Klass Naturheilkd* 10:316–324
66. Chirumbolo S, Brizzi M, Ortolani R, Vella A, Bellavite P (2009) Inhibition of CD203c membrane up-regulation in human basophils by high dilutions of histamine: a controlled replication study. *Inflamm Res* 58:755–764
67. Mannaioni PF, Mastroianni R, Mastrangelo D (2010) Adrenaline inhibits the immunological activation of human basophils at pharmacological and ultra-low doses. *Med Sci Monit* 16:BR227–BR232
68. Guggisberg AG, Baumgartner SM, Tschopp CM, Heusser P (2005) Replication study concerning the effects of homeopathic dilutions of histamine on human basophil degranulation in vitro. *Complement Ther Med* 13:91–100
69. Bellavite P, Marzotto M, Chirumbolo S, Conforti A (2011) Advances in homeopathy and immunology: a review of clinical research. *Front Biosci (Schol Ed)* 3:1363–1389
70. Kleijnen J, Knipschild P, ter Riet G (1991) Clinical trials of homeopathy. *BMJ* 302:316–323
71. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, Jonas WB (1997) Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 350:834–843
72. Shang A, Huwiler-Müntener K, Nartey L, Jüni P, Dörig S, Sterne JAC, Pewsner D, Egger M (2005) Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet* 366:726–732
73. Peters D (2005) Shang et al. carelessness, collusion, or conspiracy? *J Altern Complement Med* 11:779–780
74. Kiene H, Kienle GS, Schon-Angerer T (2005) Failure to exclude false negative bias: a fundamental flaw in the trial of Shang et al. *J Altern Complement Med* 11:783
75. Walach H, Jonas W, Lewith G (2005) Are the clinical effects of homeopathy placebo effects? *Lancet* 366:2081–2086
76. Bellavite P, Pitari G, Italiano M (2006) Homeopathy and placebo. *Homeopathy* 95:51

77. Rutten L, Stolper E (2006) ‘Proof’ against homeopathy in fact supports Homeopathy. *Homeopathy* 95:57–61
78. Ludtke R, Rutten AL (2008) The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. *J Clin Epidemiol* 61:1197–1204
79. Hahn RG (2013) Homeopathy: meta-analyses of pooled clinical data. *Forsch Komplementmed* 20:376–381
80. El Dib RP, Atallah AN, Andriolo RB (2007) Mapping the Cochrane evidence for decision making in health care. *J Eval Clin Pract* 13:689–692
81. White A, Ernst E (2001) The case for uncontrolled clinical trials: a starting point for the evidence base for CAM. *Complement Ther Med* 9:111–115
82. Muscari-Tomaioli G, Allegri F, Miali E, Pomposelli R, Tubia P, Targhetta A, Castellini M, Bellavite P (2001) Observational study of quality of life in patients with headache, receiving homeopathic treatment. *Brit Hom J* 90:189–197
83. Pomposelli R, Bellavite P (2013) Clinical Roundup: selected treatment options for peripheral neuropathy–homeopathy. *Altern Complement Ther* 19:165–166
84. Pomposelli R, Piasere V, Andreoni C, Costini G, Tonini E, Spalluzzi A, Rossi D, Quarenghi C, Zanolin ME, Bellavite P (2009) Observational study of homeopathic and conventional therapies in patients with diabetic polyneuropathy. *Homeopathy* 98:17–25
85. Walach H, Falkenberg T, Fonnebo V, Lewith G, Jonas WB (2006) Circular instead of hierarchical: methodological principles for the evaluation of complex interventions. *BMC Med Res Methodol* 6:29
86. Witt CM, Luedtke R, Baur R, Willich SN (2005) Homeopathic medical practice: long-term results of a cohort study with 3,981 patients. *BMC Public Health* 5:115
87. Witt CM, Ludtke R, Mengler N, Willich SN (2008) How healthy are chronically ill patients after 8 years of homeopathic treatment?—Results from a long term observational study. *BMC Public Health* 8:413
88. World Health Organization (2001) Legal status of traditional medicine and complementary/alternative medicine: a worldwide review. WHO, Geneva document reference WHO/EDM/TRM/2001.2
89. Wiesener S, Falkenberg T, Hegyi G, Hok J, di Roberti SP, Fonnebo V (2012) Legal status and regulation of complementary and alternative medicine in Europe. *Forsch Komplementmed* 19(Suppl 2):29–36
90. Falkenberg T, Lewith G, di Roberti SP, von Ammon K, Santos-Rey K, Hok J, Frei-Erb M, Vas J, Saller R, Uehleke B (2012) Towards a pan-European definition of complementary and alternative medicine—a realistic ambition? *Forsch Komplementmed* 19(Suppl 2):6–8
91. von Ammon K, Frei-Erb M, Cardini F, Daig U, Dragan S, Hegyi G, di Roberti SP, Sorensen J, Lewith G (2012) Complementary and alternative medicine provision in Europe—first results approaching reality in an unclear field of practices. *Forsch Komplementmed* 19(Suppl 2):37–43
92. Menniti-Ippolito F, Gargiulo L, Bologna E, Forcella E, Raschetti R (2002) Use of unconventional medicine in Italy: a nationwide survey. *Eur J Clin Pharmacol* 58:61–64
93. Bornhofs G, Wolf U, Ammon K, Righetti M, Maxion-Bergemann S, Baumgartner S, Thurneysen AE, Matthiessen PF (2006) Effectiveness, safety and cost-effectiveness of homeopathy in general practice—summarized health technology assessment. *Forsch Komplementarmed* 13(Suppl 2):19–29
94. Trichard M, Chaufferin G, Nicoloyannis N (2005) Pharmacoeconomic comparison between homeopathic and antibiotic treatment strategies in recurrent acute rhinopharyngitis in children. *Homeopathy* 94:3–9
95. Witt C, Keil T, Selim D, Roll S, Vance W, Wegscheider K, Willich SN (2005) Outcome and costs of homeopathic and conventional treatment strategies: a comparative cohort study in patients with chronic disorders. *Complement Ther Med* 13:79–86
96. Rossi E, Crudeli L, Endrizzi C, Garibaldi D (2009) Cost-benefit evaluation of homeopathic versus conventional therapy in respiratory diseases. *Homeopathy* 98:2–10
97. Frenkel M, Mishra BM, Sen S, Yang P, Pawlus A, Vence L, Leblanc A, Cohen L, Banerji P, Banerji P (2010) Cytotoxic effects of ultra-diluted remedies on breast cancer cells. *Int J Oncol* 36:395–403
98. Banerji P, Campbell DR, Banerji P (2008) Cancer patients treated with the Banerji protocols utilising homeopathic medicine: a best case series program of the National Cancer Institute USA. *Oncol Rep* 20:69–74
99. Johannessen H, von Bornemann HJ, Pasquarelli E, Fiorentini G, Di CF, Miccinesi G (2008) Prevalence in the use of complementary medicine among cancer patients in Tuscany, Italy. *Tumori* 94:406–410
100. Rossi E, Baccetti S, Firenzuoli F, Belvedere K (2008) Homeopathy and complementary medicine in Tuscany, Italy: integration in the public health system. *Homeopathy* 97:70–75
101. Plasschaert AI, Rovers MM, Schilder AG, Verheij TJ, Hak E (2006) Trends in doctor consultations, antibiotic prescription, and specialist referrals for otitis media in children: 1995–2003. *Pediatrics* 117:1879–1886
102. Fixsen A (2013) Should homeopathy be considered as part of a treatment strategy for otitis media with effusion in children? *Homeopathy* 102:145–150
103. Eizayaga JE, Eizayaga JI (2012) Prospective observational study of 42 patients with atopic dermatitis treated with homeopathic medicines. *Homeopathy* 101:21–27
104. Witt CM, Brinkhaus B, Pach D, Reinhold T, Wruck K, Roll S, Jackel T, Staab D, Wegscheider K, Willich SN (2009) Homeopathic versus conventional therapy for atopic eczema in children: medical and economic results. *Dermatology* 219:329–340
105. Smith R (2001) Restoring the soul of medicine (Editorial). *BMJ* 322:117
106. Fayeton S, Van Wassenhoven M (2001) Clinical verification of symptom pictures of homeopathic medicines. *Br Homeopath J* 90:29–32
107. Van Wassenhoven M (2004) Towards an evidence-based repertory: clinical evaluation of *Veratrum album*. *Homeopathy* 93:71–77
108. Rutten AL, Stolper CF (2009) Diagnostic test evaluation by patient-outcome study in homeopathy: balancing of feasibility and validity. *J Eval Clin Pract* 15:1230–1235
109. Rutten AL, Stolper CF, Lugten RF, Barthels RW (2009) Statistical analysis of six repertory rubrics after prospective assessment applying Bayes’ theorem. *Homeopathy* 98:26–34
110. Kotaska A (2004) Inappropriate use of randomised trials to evaluate complex phenomena: case study of vaginal breech delivery. *BMJ* 329:1039–1042
111. Kiene H (1996) A critique of the double-blind clinical trial. *Altern Ther* 2:59–64
112. Kiene H, Kienle GS, Schon-Angerer T (2006) Bias in meta-analysis. *Homeopathy* 95:54