Can homeopathy withstand scientific testing?

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Introduction

What is the importance of homeopathy in veterinary practice? The television appearance of E.L. Ellinger (DVM) during the Foot and Mouth (FMD) crisis in 2001 gave an insight into the views held by veterinarians practicing homeopathy. And we can be confident these views were representative because Ellinger is not just anybody; she is an active member of the Group of Homeopathic-practicing Veterinarians of the Royal Dutch Veterinary Society, the Dutch representative for the International Association for Veterinary Homeopathy (IAVH) and, in 2001, she was a guest lecturer at the Faculty of Veterinary Medicine in Utrecht[1].

It was 4 April 2001 when she was interviewed on the RTL5 television programme '5 in het land'. The FMD crisis was at its peak and there was considerable debate about whether the large-scale slaughter of animals could be prevented by vaccinating those that were susceptible in risk areas. Despite widespread support among Dutch people for this approach, it would have had a devastating effect on the meat export industry and was therefore not an option. Ellinger, however, was offering an alternative: she had prepared a homeopathic remedy that would protect against FMD without the production of antibodies, thus allowing exports to continue. Although she advised this 'homeopathic protection' be given to all animals within a 15 km radius of contaminated areas, her suggestion was not taken up, undoubtedly because of the complete lack of evidence that her remedy protected against FMD.

There are other areas of veterinary medicine in which homeopathy is applied as though it were an accepted form of treatment. But what are the arguments for supporting this? Is there evidence that homeopathy really does work in these cases? To answer these questions, we must first consider the background of homeopathy as well as the commonly accepted methods of argumentation in medical science in general.

Scientific testing of homeopathy

To answer the question whether there is scientific proof that homeopathy is effective, both the basic principles of homeopathy and the practical application of these principles in veterinary practice need to be tested. The principles of homeopathy comprise two elements: the similia principle (*similia similibus curentur*) and potentiation. For the practical application of the similia principle, the so-called 'drug picture' is essential. This consists of a medical impression based on observations made of a patient that can then be compared, according to scientific norms, with comparable observations in a control group. This point is discussed below.

Potentiation, the second principle of homeopathy, involves the stepwise dilution of the active ingredient in an excess of solvent. According to homeopathy, this increases the curative power of the material. According to science, by contrast, such an extreme degree of dilution is reached that no molecules of the original material remain and thus the solution cannot be effective[2]. Scientific investigation can be used to show whether such a dilute solution brings about effects other than those of the diluent alone and will be discussed later.

The application of the principles in veterinary practice is a subject particularly suitable for testing. Those veterinarians practicing homeopathy do not differ from their 'regular' colleagues as much as one might expect: they, too, make a diagnosis, apply treatment based on their diagnosis and claim the patient is thereby cured. The presence or absence of treatment thus furnishes a measurable difference. I will return to this, but first would like to discuss the basic principles of homeopathy.

The drug picture

Drug pictures form the basis of homeopathy. They are set down in thick tomes, of which the Materia Medica of Hahnemann and the Materia Medica of Kent are the best known, though there are others, such as Clarke's three volume Dictionary of Practical Materia Medica, the Complete Materia Medica of

Boericke and Pathak and Tyler's Homeopathic Drug Pictures. The drug pictures described in these books are based on 'provings', but how is a proving derived? In the Materia Medica, Hahnemann gave an example in which he, his family and friends consumed more than 100 substances and carefully recorded the effects they observed[3]. Their descriptions are very detailed, such as 'wanting a snack', 'needing to use more tobacco than usual', 'a child's wish to be picked up by the mother' and 'amorous dreams'. However, we should remember Hahnemann lived in another era, when the romantic was at its high point and Goethe wrote about the suffering of the young Werther. However it is presented, the drug picture remains a collection of observations that can be tested scientifically. But how, with our present knowledge of statistics, should this be done? The observations that form the drug picture must satisfy three criteria: they must be 1) measurable, 2) reproducible, and 3) not based on chance. But, if we apply these criteria to the drug pictures, not much remains standing. Many of the described symptoms are subjective and cannot be quantified; exactly how much more is an increased need for tobacco? The reproducibility of the observations is also indeterminable. Furthermore, it will always remain uncertain whether these subjective observations can be extrapolated to animals. But it is statistical testing with regard to 'chance' that shows the weakest point in the drug picture. It should be remembered, of course, that in Hahnemann's time no one had heard of double-blind controlled studies, but the situation is different now. To determine whether an observed effect is 'real' or the result of chance, a statistical test is applied and the result is generally specified with regard to its 'significance'. A significant abnormality means that the probability the observed effect is based on chance is smaller than a predetermined limit. This is also called the alpha value and is generally set at 5%. But before the significance can be calculated, we must be certain that we have made sufficient observations to confirm a significant effect. The number of observations required depends on the value of the variable to be measured and on the magnitude of the expected deviation. The greater the value of the variable and the greater the difference between the experimental group (receiving the drug in question) and the control group (receiving the placebo), the smaller the number of observations required. But I can tell you from personal experience that within the accepted margins large groups of patients are usually necessary. The margin is known as the beta value and is usually set at 20%. It indicates the probability that an effect will actually be found, assuming that there is one. If the predetermined alpha and beta criteria are not met, no effect whatever is observed. And that is the situation that applies at present to the drug pictures.

Potentiation

Potentiation of the substance to be used in a homeopathic treatment is carried out by serial dilution combined with vigorous shaking. The dilution is usually taken to such an extreme that the chance there are any molecules of the original material still present in the solvent at the end of the procedure is nil. According to scientific veterinary medicine, no effect whatever can then be expected, but homeopathy assumes that during potentiation spiritual healing power of the original material is transferred to the solvent. This effect is even supposed to increase in proportion to the increasing dilution. The notion that something that is no longer present can still exert an effect is at odds with the concepts of the natural sciences. Hence science demands cast iron evidence for this claim, or as James Randi expressed it: 'unusual claims require unusually good proof'. In 1988, it seemed that something might even come of this. The renowned French asthma researcher Jacques Benveniste submitted an extraordinary manuscript to the journal 'Nature', describing an experiment of his in which basophile granulocytes responded to a homeopathic dilution of an allergen. He attributed this to the transfer of a property of the allergen to the solvent and named this 'the memory of water'. Nature's chief editor, John Maddox, did not believe in this but realised the manuscript could unleash a scientific revolution. He accepted the article but with a precondition: identical results had to be attained when the experiment was repeated in Benveniste's laboratory under the observation of a delegation drawn up by Maddox. Benveniste accepted the challenge. The group of observers that came to his lab had an unexpected composition, however. In addition to Maddox himself, the team consisted of Walter Stewart (a respected investigator and adversary of scientific fraud) and James Randi, a 'professional magician' better known as the '*The Amazing Randi*'. Maddox's choice of Randi caused some amazement, but he had built up a reputation for exposing those claiming to have paranormal gifts. His role in the team was to ensure that the blinding of the experiment was not violated before all the measurements were carried out. For this purpose he had the windows of the laboratory blacked out with newspaper and the code of the test and control tubes placed in a sealed envelope taped to the ceiling. When the experiment was repeated the activation of basophile granulocytes in tubes treated with 'homeopathic diluted antigen' did not differ from that in the control tubes, which were only treated with the solvent. Later it became clear that the laboratory technicians in the original experiment knew which tubes were treated with 'homeopathic allergen' so that in the interpretation of the results they

had let themselves be led astray by their belief in the outcome.

The publication of the results of this repetition of Benveniste's experiment in Nature spelled the end of his reputation as a respected investigator. But Randi went a step further: he offered a reward of one million dollars for anyone providing experimental evidence that homeopathy works. The English science television programme Horizon took up the challenge and gathered a team of investigators to repeat, under controlled conditions, an experiment previously performed by Dr. Madeleine Ennis. The experiment strongly resembled that of Benveniste, but this time the basophile granulocytes were stimulated with homeopathic diluted histamine in place of an allergen. The control was in the hands of two persons: James Randi and Professor John Enderby, vice-president of the Royal Society. Again pains were taken for very stringent blinding of the experiment. When the codes were broken at the end of the experiment, no difference was found between the effects of the homeopathic diluted histamine and the solvent. Once again the evidence for *'the memory of water'* was negated. The reward put up by Randi is still on offer, but no new candidates have applied.

Efficacy

There are various ways in which the working or effect of a treatment can be tested: 1) the opinion of experts, 2) retrospective clinical research, 3) prospective randomised double-blind clinical research, and 4) meta-analysis of clinical research. The first method has little evidential value. It is sometimes claimed that the so-called consensus meeting of specialists mainly serves to confirm that about which they disagree. Retrospective clinical research was much used in the past but it is no longer accepted by any scientific journal. Prospective randomised double-blind clinical research is now considered to be the golden standard. But it can also be coloured by such factors as ethnic or cultural differences or an invalid analysis of the results. It can also happen that the results of studies with comparable objectives and design do not agree. In order that the findings can still be interpreted, the investigations are compared in a meta-analysis. It is especially the methodological aspects of the different investigations that are critically analyzed in this analysis. If we wish to draw conclusions about the effectiveness of homeopathy, it is especially the last of these approaches that is important. By now a great deal of clinical research has already been carried out on the effectiveness of homeopathy and this research has been carefully analyzed in several meta-analyses, although they only concern homeopathy in humans and not in animals. The results of these meta-analyses are summarised below.

Jos Kleijnen from Maastricht published the first meta-analysis of clinical research on the effects of homeopathy in 1991. The research concerned 96 publications in which 107 clinical investigations were described. Kleijnen and co-workers concluded that there were indeed indications that homeopathy works, but '*At the moment the evidence of clinical trials is positive but not sufficient to draw definitive conclusions because most trials are of low methodological quality and because of the unknown role of publication bias'* [4]. By 'publication bias' the author meant that research in which an effect was shown was more likely to be published than that in which no effect was observed. This distorts the picture in favour of an effect. An important technical shortcoming was that the patients were not asked which group they thought they had been placed in. This control of the blinding was not applied in any of the analyzed studies, while the breaking of the code by the patient is sufficient to explain the small positive effects in favour of homeopathy [1].

There was little further interest in this topic until in 1996 the Geneesmiddelenbulletin (Dutch bulletin of drugs and therapeutics) gave attention to homeopathy. The study of van Kleijnen was discussed and extended with a meta-analysis of 11 clinical studies, which 'more or less' fulfilled the criteria for prospective randomized clinical research. The Geneesmiddelenbulletin concluded that *'not one homeopathic remedy has been shown to have a specific effect in double-blind randomized and placebo-controlled research'* [2].

In 1997, Klaus Linde (an epidemiologist sympathetic to homeopathy) published a meta-analysis of 98 clinical studies in the Lancet [3]. At first glance his conclusion appears favourable to homeopathy: *'The results of our meta-analysis are not compatible with the hypothesis that the clinical effects of homeopathy are completely due to placebo'*, but Linde immediately qualified this by remarking: *'However, we found insufficient evidence from these studies that homeopathy is clearly efficacious for any single clinical condition'*. Linde continued working and a year later published a second meta-analysis of 32 clinical studies of homeopathy [4]. The conclusion of this analysis closely resembled that in 1997: *'The results of the available randomized trials suggest that individualized homeopathy has an effect over placebo'*. Once again the conclusion was immediately qualified, because methodological shortcomings put a spoke in the wheel: *'The evidence, however, is not convincing because of methodological shortcomings and inconsistencies. When the analysis was restricted to*

methodologically best trials no significant effect was seen'. Because technical aspects of experiments evidently have a great influence on the results of clinical research in homeopathy, Linde directed his attention especially to this point. In 1999 he published a study of the effects of the quality of clinical research in homeopathy on the results [5]. As the starting point he used the same 89 publications that he had analyzed in the Lancet in 1997. He applied three techniques to these investigations: 1) analysis of the components, 2) a minimum score analysis, and 3) a cumulative meta-analysis. For the component analysis, two groups of investigations were compared with regard to a single criterion (e.g. whether or nor there was an explicit statement about randomization, whether or not there was double-blinding, whether or not there was a complete follow-up). For the minimum score analysis, points were awarded to each investigation on the basis of methodological aspects. Then a limiting value was determined and investigations scoring above and below this were compared with each other. In the cumulative meta-analysis, the individual investigations were added stepwise on the basis of the previously applied quality score. Linde's investigation revealed that especially double-blinding and randomization influenced the results of the examined publications: *'Studies that were explicitly randomized and were double-blind [...] yielded significantly less positive results than studies not meeting the criteria'*. In addition, Linde pointed out the previously mentioned publication bias. These observations led him to qualify the conclusions he had made in 1997: '*The evidence of bias weakens our original meta-analysis [from 1997], which overestimated the effects of homeopathic treatments'.*

The most recent meta-analysis dates from 2002 and was published by Ezard Ernst, who works in the Department of Complementary Medicine at the University of Exeter in England. Ernst's examination was concerned not with individual investigations but rather with 17 meta-analyses of the effectiveness of homeopathy [6]. Six of these 17 articles were repeat analyses of frequently cited meta-analyses; the other 11 were described as independent systematic analyses. Ernst concluded: '*There was no condition which responds convincingly better to homeopathic treatment than to placebo or other control interventions. [...] There was no homeopathic remedy that was demonstrated to yield clinical effects that are convincingly different from placebo'*.

In summary, it can be concluded that there has been a great deal of research on the effectiveness of homeopathy. Much of this research is methodologically weak and justifies no conclusion about the effectiveness of homeopathy. But there has also been good research, from which it is apparent that the effect of homeopathy is no greater than that of placebo.

Conclusion

The test of science is hard and merciless. Many conditions must be satisfied in order to demonstrate therapeutic effectiveness. The golden standard is the prospective randomized double-blind clinical trial. For medicine this is a formidable enough challenge; for homeopathy it appears to be insurmountable. After seven years of investigation costing more than $100 million per year [7], there is still no evidence whatever that extremely diluted solutions of homeopathic substances have any effect. The actual existence of drug pictures has not been confirmed and the application of homeopathic therapy has no more effect than a placebo. With regard to the title of this article, there is but one possible conclusion: homeopathy has not withstood the test of science.

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The author presented the paper on 12 January 2004 at the invitation of the Executive Board of the Royal Dutch Veterinary Society during discussions of the continuation of the group 'Homeopathic-practicing Veterinarians' within the Society.

English translation: B.E. Belshaw

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7. National Council for Alternative and Complementary Medicine (USA).

[1] Ellinger participated in the elective course 'alternative medicine'. This elective course has since been discontinued; Ellinger is no longer a guest lecturer at the Faculty

[2] Avogadro's constant (N = 6 x 1023) represents the number of atoms or molecules in one mole of any substance. The probability that any molecules remain following dilution beyond this number is negligible

[3] Among these are plants such as chamomile and deadly nightshade and inorganic materials (e.g., sulphur), but there are also materials used less often, such as pulverised honeybees, ground oyster shell, and toasted sea sponge