

The Evidence Base for Homeopathy

Abbreviations:

AVMA: American Veterinary Medical Association

CAVM: Complementary and Alternative Veterinary Medicine

RCT: Randomized clinical trial

SAPEH: Score for Assessment of Physical Experiments in Homeopathy

JAAHA: Journal of the American Animal Hospital Association

PEK: Program of Evaluation of Complementary Medicine

CAM: Complementary and Alternative Medicine

AVH: Academy of Veterinary Homeopathy

EBM: Evidence based medicine

Introduction

The AVMA has recognized CAVM as a category of practice meriting separate guidelines. Veterinary homeopathy falls under the AVMA's definition of CAVM. The guidelines apply the same standards to all practices of veterinary medicine: "The AVMA believes that all veterinary medicine, including CAVM, should be held to the same standards."¹

While stating the ultimate goal of evidence-based medicine, that "Claims for safety and effectiveness ultimately should be proven by the scientific method," the guidelines also recognize that most therapies and procedures used in *all* of veterinary medicine have not been thoroughly studied via clinical trials and replications of clinical trials, but rather are largely based on extrapolation and clinical expertise, the latter being an important arm of evidence-based medicine. The AVMA guidelines state, "Circumstances commonly require that veterinarians extrapolate information when formulating a course of therapy. Veterinarians should exercise caution in such circumstances. Practices and philosophies that are ineffective or unsafe should be discarded."¹

Veterinary homeopathy differs from mainstream conventional medicine in two important regards. First, the medicines used in homeopathic practice are often administered in highly diluted form in either water or on lactose pellets. It is hypothesized that their mode of action differs from those of substances given in pharmacologic doses and having direct agent-dependent effects on the body.²

Second, its method of testing predates the emergence of RCT as the gold-standard of experimentation, instead employing the pathogenetic trial, or "proving,"ⁱ in its testing of medicines. Homeopathy has been in practice for 200 years, but it is only recently that the RCT has been applied to confirm the principle of "like cures like" as

ⁱ In the homeopathic proving, the human test subjects are given small doses of substances and asked to record the symptoms they develop. These symptoms are subsequently collated and categorized. The results identify the toxicological properties of the substance for later medicinal applications. Samuel Hahnemann, the founder of homeopathy, proved 106 remedies in his lifetime. These remedies are still used today, although representing only a small portion of the more than 2000 remedies in clinical use.

well as to fine-tune such elements of homeopathy as the pathogenetic trial and remedy selection.

In spite of these two important differences from mainstream veterinary medicine, the large number of cases documented in the historic homeopathic medical literature as well as the clinical experience of current human and veterinary homeopaths have shown that homeopathy offers the potential for veterinarians to expand the realm of therapy for patients. With the reemergence in the past 20 years of veterinary homeopathy in the United States and Canada, and with the growth of veterinary homeopathy in South and Central America, Europe, Asia, Australia, New Zealand, Africa and the Middle East, a highly trained and experienced crop of veterinary homeopaths is emerging. It is hoped that in time academic institutions will employ qualified professionals trained in veterinary homeopathy. With these fundamental prerequisites achieved, the evidence pyramid for veterinary homeopathy can begin to grow.

The Science

Science is the state of knowing. The acquisition of knowledge is an ongoing *process* that includes trial and error, disappointments, successes, discoveries, modifications, and most importantly, building upon all prior experiences and understanding. Science is a process that has no end. Conclusions are not forgone. Assumptions are easily overturned. Paradigms are constantly up for reconsideration.

The concept that “a dramatically new understanding of physics, chemistry, and biology which overturns the very foundations of modern biomedical science would be necessary” or that “a revolution in basic science would need to take place” for the proposed mechanisms of homeopathy to be valid is simplistic, partly based on outdated science, and partly based on a lack of knowledge of established science.³

The background for such statements is based on the dogma that persists from work performed in the late 19th and early 20th centuries. This work derived Avogadro’s constant, approximately 6.022×10^{23} , the *theoretical* dilution beyond which no material substance should exist. Since many (but not all) homeopathic remedies are employed at dilutions beyond this theoretical constant, the chief argument against homeopathy appeared as one of plausibility: “because of the presumptive lack of sufficient bulk-form source material to exert a ‘usual’ pharmacological dose-response effect,” proponents of this now-outdated view argued that homeopathic remedies could not work. Further, they argued that according to principles of typical clinical pharmacology, lower bulk-form “doses” should exert lesser effects, until no biological effects occurred.²

However, current well-accepted science in the field of nanopharmacology has shown the presence of nanoparticles of the original bulk-source material as well as remedy-modified silica nanostructures in these high dilutions. These remain stable whether in liquid form or on lactose pellets when prepared according to the homeopathic principles of triturationⁱⁱ and succussionⁱⁱⁱ. Detection of these particles

ⁱⁱ The process by which the starting solid material is ground with milk sugar in the initial steps of remedy preparation.

has been enabled by the use of high resolution imaging techniques such as atomic force microscopy, scanning electron microscopy and transmission electron microscopy.^{4,5,6,7} The process by which these nanoparticles are transferred during the preparation of homeopathic remedies has been documented with high speed videography.⁷ An overwhelming preponderance of these studies has been published in peer-reviewed mainstream scientific journals.

Further, biological activity of the material remaining in these highly diluted solutions is entirely plausible. The quantity of remaining particles (in picograms) is well within the range for other bioactive substances like hormones and viruses.⁸ Nanoparticles have enhanced bioavailability and heightened reactivity, lending them the ability to signal specific information in living organisms (via chemical, optical, electromagnetic, magnetic, thermal and/or quantum properties) and to stimulate immunological and/or inflammatory reactivity and modulate specific genomic expression patterns.^{2,6,9} The processes by which nanoparticles mediate changes in the body are not pharmacological but rather physiological, and appear to follow the widely accepted principles of hormesis^{iv}.^{2,10} The presence of these particles as well as the proven potential for biological activity in nano-concentrations invalidate the old view that homeopathic agents have no effective substance and therefore cannot have physiologic effects.

Advances in fields of science, such as toxicology, neurobiology, neuropharmacology, psychiatry, immunology and physiology have resulted in an interdisciplinary convergence in understanding of how homeopathic remedies may work in the body. Metaplasticity, time-dependent sensitization, and cross-sensitization are all responses that occur in the host as a result of exposure to the correct homeopathic remedy.² This emerging model for the effects of remedies in complex living systems also is congruent with and verifies basic tenets of homeopathy, such as the law of similars,^v the importance of modalities^{vi}, the homeopathic aggravation^{vii}, and

iii The shaking of the glass container that contains the solution with the homeopathic remedy.

iv Hormesis is a term used by toxicologists to refer to a biphasic dose response to an environmental agent characterized by a low dose stimulation or beneficial effect and a high dose inhibitory or toxic effect. For example, at low doses, (0.5-1mg/kg) erythromycin enhances gastric motility and emptying, but at higher doses, (10-20mg/kg) it may cause emesis. (Erythromycin in *Plumb's Veterinary Drug Handbook*. Seventh Ed.) In the fields of biology and medicine, hormesis is defined as an adaptive response of cells and organisms to a moderate (usually intermittent) stress.

v *Similia similibus curentor*, "Let likes cure like." The underlying principle which forms the basis for selection of homeopathic remedies for patients. The remedy is matched to the patient's unique set of symptoms based on the known symptoms that the remedy can cause when given to healthy people in the homeopathic provings. (See footnote i.)

vi The term "modality" in the homeopathic context refers to the specific sensitivities of the patient to conditions such as heat, cold, weather conditions, movement, etc. In selecting a homeopathic remedy, of great importance are the modalities that make the patient's condition better or worse.

vii A transient worsening of symptoms which precedes the curative response

Hering's direction of cure^{viii,11,12} Nearly all of these studies supporting this new understanding have been published in peer-reviewed mainstream medical journals.

Research in basic science, on the cellular level as well as that of the whole organism, has demonstrated the activity of homeopathic remedies as well as efficacy of remedies. Witt *et al* performed a systematic review of 67 *in vitro* experiments gleaned from 75 journals. All studies involved stepwise agitated dilutions with substances in $<10^{-23}$ concentrations. Of note is that thirty-three percent were replications. Quality was assessed by the modified SAPEH score.^{ix} Seventy-three percent showed an effect with ultramolecular dilutions, including 68% of eighteen studies showing a SAPEH score ≥ 6 . The authors concluded that even experiments with a high methodological standard could demonstrate an effect of high potencies.¹³

Endler *et al* performed a bibliometric study to provide an overview of fundamental biochemical and biological studies that used high homeopathic potencies, and that were subjected to laboratory-internal, multicenter, or independent repetition trials. They found 24 experimental models in basic research on high homeopathic potencies which were repeatedly investigated. Twenty-two models were reproduced with comparable results, six models with different results, and repetition showed no results for fifteen models. Seven models were independently reproduced with either comparable or different results. They comment that:

This relation is fairly well reflected by multicenter studies, i.e. studies that were centrally organized, but carried out by various researchers in different laboratories, namely 66% comparable, 17% different and 17% no effects. Thus multicenter studies seem to be an adequate tool to investigate basic high potency models.¹⁴

^{viii} According to "Hering's Direction of Cure," over time the patient's healing occurs from above downward, from more important to less important organs, and in reverse order in time of symptom appearance.

^{ix}Score for Assessment of Physical Experiments on Homeopathy. SAPEH had been developed to assess the quality of physical research in homeopathy. (Becker-Witt C, Weissshuhn TE, Ludtke R, Willich SN. Quality assessment of physical research in homeopathy. *J Alt Compl Med* 2003;9:113-32.) It is based on three quality constructs - methodology, experiment standardization, presentation - that divide into eight items, checking for ten criteria. Each item scores one point for an affirmative answer, except controls and experiment standardization with two points each.

The methodology items check that the experimental design uses techniques to control factors that may cause bias (e.g. systematic or random errors).

The modified SAPEH should be read at item level to assess an experiment. The total SAPEH score and its subscores support only rough global impressions and should always be accompanied by score details. For the purposes of the present study, six or seven points with controls of equal contamination would indicate a reasonable control for bias, and more than seven points including two for controls would strengthen this.

Independent laboratory confirmation of results was found to be high, and within expected values for positive findings in multi-centered repetitions. Indeed, studies such as physiologic effects of thyroxin in frogs and degranulation of basophils exposed to ultradiluted and succussed substances have been replicated (and published in mainstream medical journals) and shown positive results.^{15,16,17,18,19,20} Since the publication of two review articles demonstrating the efficacy of these SSD solutions, more research continues to be published that expands our knowledge base in this area.^{21,22,23,24}

The largest area of documentation of efficacy of homeopathic remedies comes from case reports and case series, generated since the beginning of homeopathy as documented in books and journals of homeopathy, and extending to today with more formalized case reports. Although the bulk of these have been for humans, more recent case reports include conditions such as canine epilepsy, babesiosis, feline eosinophilic granuloma complex, and atrial paroxysmal tachycardia.^{25,26,27,28} JAAHA published its first homeopathy case report in the November/December 2011 issue. This was a successful treatment of nasal aspergillosis, documented at a veterinary teaching hospital.²⁹

An expanding number of clinical trials in humans are being conducted and published (including in mainstream medical journals). Benefits of homeopathic treatment are being shown for many conditions, including but not limited to childhood diarrhea, mild traumatic brain injury, fibromyalgia, and respiratory disease.^{30,31,32,33,34,35,36,37,38} Many of these clinical trials already involve replications for certain conditions, confirming the efficacy of homeopathy.³⁹ Additionally, emerging clinical trials are confirming the proving symptoms from previously-proven remedies and revealing findings that can be implemented to fine-tune the accuracy of the provings.^{40,41,42,43}

Clinical trials in the veterinary field have been performed. Mathie et al recently published a bibliometric study of RCTs for a systematic review in veterinary homeopathy. They found 38 studies of 27 different species-specific medical conditions in seven species that satisfied the acceptance criteria: substantive report of a clinical treatment or prophylaxis trial in veterinary homeopathic medicine randomized and controlled and published in a peer-reviewed journal.⁴⁴ Clinical trials showing evidence in favor of veterinary homeopathy have been published in areas such as handling stress in calves, neonatal piglet diarrhea, Foot-and-Mouth Disease in cattle, and weight gain in broiler chickens.^{45,46,47,48} In 2011, JAAHA published its first clinical trial of a combination product for canine osteoarthritis prepared by serial dilution and succussion.⁴⁹

Design and execution of clinical trials in homeopathy require additional considerations from those of conventional medicine. Likewise, evaluation of clinical trials on study design as it applies to clinical trials for conventional drugs may relegate a study to the “better design” category when in fact the study design does not adhere to homeopathic principles such as individualization of remedies and the use of single remedies. Additionally, failure to predetermine the correct remedy for an individual could increase the risk that an ineffective medicine is being administered to the subject in the verum group. Fortunately, as studies in the relatively new field of research in homeopathy progress, so do improvements in

study design which take into account unique considerations for clinical trials in homeopathy.^{50,51}

More recent properly designed meta-analyses and systematic reviews have shown that homeopathy cannot be explained by the placebo effect and/or that homeopathy is effective.^{32,36,52,53} The most recent general meta-analysis, included in the Connecticut Veterinary Medical Association's accompanying white paper and presented as evidence against the efficacy of homeopathy, was highly publicized and widely criticized for failing to adhere to the standards of properly-constructed meta-analyses.⁵⁴ The criticism was most notable in that one of its sponsors, the International Review Board of the PEK of the Swiss Federal government, stated, "There is a consensus among the review board members that the final PEK process deviated from what would have been expected by conventional standards."⁵⁵

Previously, a 2006 Health Technology Assessment report on effectiveness, cost-effectiveness, and appropriateness of homeopathy was compiled on behalf of the PEK of the Swiss Federal Office for Public Health. Their results showed many high quality investigations of pre-clinical research of homeopathic high potencies inducing regulative and specific changes in cells or living organisms. In addition, 20 of 22 systematic reviews detected at least a trend in favor of homeopathy. In their estimation, five studies yielded results indicating clear evidence for homeopathic therapy. Their evaluation of 29 studies in the category of "Upper Respiratory Tract Infections/Allergic Reactions" showed a positive overall result in favor of homeopathy. Six out of seven controlled studies were at least equivalent to conventional medical interventions. Eight out of sixteen placebo-controlled studies were significant in favor of homeopathy.⁵⁶

Effectiveness and Cost-Effectiveness

When integrated into national health care systems, homeopathy has been shown to be effective as well as cost-effective.^{57,58} In the United Kingdom, each of the homeopathic hospitals on the National Health Service (NHS) reported clinical outcomes for a wide range of medical complaints. Positive outcomes were approximately 70% at each hospital.^{58,59,60,61,62} A twelve-month outcome survey from the Liverpool Department of Homeopathic Medicine found that of 1100 patients surveyed, 76.6% reported an improvement in their condition with 60.3% reporting a major improvement; and 52% of 814 patients who were taking conventional medication were able to reduce or stop these medications.⁶³

A cost-effectiveness study of recurrent acute rhinopharyngitis in 499 children showed that the homeopathic approach yielded significantly better results than antibiotic treatment in terms of effectiveness, number of complications, and quality of life, with lower direct medical costs covered by the French Social Security system. Parents of the patients incurred less sick leave as well.⁶⁴ A cohort study of 493 patients with chronic diagnoses in Germany showed greater improvement in patients' assessments after homeopathic versus conventional treatment, as well as more favorable physician assessments for children who had received homeopathic treatment.⁶⁵ A study in Switzerland of cost-effectiveness of CAM v. conventional medical therapies from 1999-2005 showed 15.4% lower costs for homeopathy versus conventional medicine. Fewer adverse effects were reported for CAM

therapies.⁶⁶ In a multicenter cohort study in Germany, 83 elderly patients receiving homeopathic treatment for the first time were monitored over a two-year period. The severity of their complaints decreased significantly over this time.⁶⁷ A retrospective observational study of patients with respiratory diseases (asthma, allergic complaints, Acute Recurrent Respiratory Infections) in Italy found that homeopathic treatment was associated with a significant reduction in the use and costs of conventional drugs, and that costs for homeopathic therapy were significantly lower than those for conventional pharmacological therapy.⁶⁸ An eight-year study of chronically ill patients receiving homeopathic treatment for the first time in Germany and Switzerland showed that disease severity decreased significantly, while physical and mental quality of life scores also increased considerably.⁶⁹

Safety

Homeopathic remedies are more prudently administered by veterinarians trained in veterinary homeopathy. The AVH offers a certification in veterinary homeopathy which is granted after completion of a minimum of 125 hours of approved homeopathic education. The applicant must demonstrate proficiency and knowledge in homeopathic prescribing by a written exam and submission of case reports. The trained veterinary homeopath is able to perform a thorough patient examination and evaluation; select the appropriate remedy including its potency, dose, and individualized repetition; evaluate the response to the remedy which includes recognizing any homeopathic aggravation; and manage the case which may include judicious dose adjustments or withdrawal of conventional medications.

AVH does not advocate that clients medicate their own animals without veterinary supervision. The trained veterinary homeopath is able to evaluate all medical records, order further diagnostic testing, recognize zoonotic diseases, and recommend a change in treatment modality when indicated.

The trained veterinary homeopath is educated to follow ethical practice. Veterinary homeopaths are legally obligated to make sure that the client has been informed of any conventional treatments that may exist for the patient's condition. Informed clients opt for professional homeopathic care for many reasons, including concerns about safety and side-effects of conventional therapies, the absence of any safe or effective conventional alternative, cost, and personal preferences which may include their prior use of homeopathic remedies.^{70,71} EBM recognizes personal preferences in tailoring a treatment plan for the patient. Although only a few studies exist directly comparing the efficacy of homeopathic treatment to conventional therapies in veterinary medicine, clinician expertise, another basic tenet of EBM, also plays an important role in counseling clients on their treatment options.^{49,72,73}

Besides the clinician-driven safety of homeopathy, the constituents and method of preparation of remedies are regulated in the United States by the Food and Drug Administration. A systematic review of English language papers of adverse effects of homeopathic remedies found that effects were slightly higher than those of placebo but minor, transient and comparable to those of placebo. Case reports in

conventional medical journals pointed more to adverse effects of mislabeled “homeopathic products” (using various herbal and mineral components) than to true homeopathic remedies.⁷⁴ The one sample of contamination that the authors of the white paper cite occurred in remedies marketed in Croatia.⁷⁵

The 2006 Swiss PEK report cited previously found that not only could the effectiveness of homeopathy be supported by clinical evidence, but when applied properly, homeopathy has few side-effects and the use of high potencies is free of toxic effects.⁵⁶

Conclusions

The Connecticut Veterinary Medical Association Resolution entitled, “Homeopathy has been identified as an ineffective practice and its use is discouraged” and accompanying “White Paper: The Case Against Homeopathy” contain many unsubstantiated allegations and subtle, subversive and unfounded assertions about veterinary homeopathy. These documents hold homeopathy to a higher standard of “evidence” than that adhered to by most conventional therapies. The paper emphasizes the need to use only therapies that have undergone the highest quality clinical trials, while dismissing clinical experience and client preferences, basic tenets of EBM. In fact, if one were to expand the authors’ proposed resolution to include all of veterinary medicine, then as practitioners of conventional medicine, we would find ourselves working with a significantly limited selection of therapeutic options. The authors make outdated and inaccurate statements about the presence and quality of studies in homeopathy, and where studies show a favorable outcome, they allege, often inaccurately, that such studies have only been published in homeopathy journals. Further, in spite of well-documented publication bias favoring areas of “hot” research for publication in a handful of high-visibility journals, the authors insinuate that publication in a journal dedicated to one field, but only if that subject is homeopathy or CAM, is somehow biased.⁷⁶

As stated in the White Paper, all medicine involves balancing risks against benefits. In the case of homeopathy, the risks are negligible in the hands of trained veterinary homeopaths, and the benefits in even some of the most severe cases can be strong.

Submitted by the Academy of Veterinary Homeopathy
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- ¹ AVMA Guidelines for Complementary and Alternative Veterinary Medicine. <https://www.avma.org/KB/Policies/Pages/AVMA-Guidelines-for-Complementary-and-Alternative-Veterinary-Medicine.aspx>.
- ² Bell I, Koithan M. 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* 2012;12:191
- ³ Anonymous. White paper: the case against homeopathy. *Addendum #1 to CVMA Proposed AVMA Resolution: "Homeopathy has been identified as an ineffective practice and its use is discouraged."*
- ⁴ Chikramane PS, Suresh AK, Bellare JR, Kane SG. Extreme homeopathic dilutions retain starting materials: A nanoparticulate perspective. *Homeopathy* 2010; 99(4):231-42.
- ⁵ Upadhyay RP, Nayak C. Homeopathy emerging as nanomedicine. *Int J High Dilution Res* 2011;10(37):299-310.
- ⁶ Das S, Das J, Samadder A, Bhattacharyya SS, Das D, Khuda-Bukhsh AR. Biosynthesized silver nanoparticles by ethanolic extracts of *Phytolacca decandra*, *Gelsemium sempervirens*, *Hydrastis canadensis* and *Thuja occidentalis* induce differential cytotoxicity through G2/M arrest in A375 cells. *Colloids Surf B Biointerfaces* 2012;325-36.
- ⁷ Chikramane PS, Kalita D, Surech AK, Kane SG, Bellare JR. Why extreme dilutions reach non-zero asymptotes: a nanoparticulate hypothesis based on froth flotation. *Langmuir* 2012;28(45):15864-75.
- ⁸ Lewin SR, Ribeiro RM, Walters T, Lau GK, Bowden S, Locarnini S, Perelson AS. Analysis of hepatitis B viral load decline under potent therapy: complex decay profiles observed. *Hepatology* 2001;34(5):1012-20.
- ⁹ Montagnier L, Aissa J, Ferris S, Montagnier J-L, Lavallee C. Electromagnetic signals are produced by aqueous nanostructures derived from bacterial DNA sequences. *Interdisciplinary Sci Comput Life Sci* 2009;1:81-90.
- ¹⁰ Mattson MP. Hormesis defined. *Ageing res rev* 2008;7(1):1-7.
- ¹¹ Wiegant F, Van Wijk R. The similia principle: results obtained in a cellular model system. *Homeopathy* 2010;99(1):3-14.
- ¹² Van Wijk R, Wiegant FA: Postconditioning hormesis and the homeopathic Similia principle: molecular aspects. *Hum Exp Toxicol* 2010;29(7):561-5.
- ¹³ Witt, CM, Bluth, M, et al. The *in vitro* evidence for an effect of high homeopathic potencies- A systematic review of the literature. *Complement Ther Med*. 2007;15(2): 128-38.
- ¹⁴ Endler PC, Thieves K, Matthiessen P, Bonamin L, Scherr C, Baumgartner S. . Repetitions of fundamental research models for homeopathically prepared dilutions beyond 10⁻²³: a bibliometric study. *Homeopathy* 2010;99(1):25-36.
- ¹⁵ Endler PC, Pongratz W, van Wijk R, Kastberger G, Haidvogel M. Effects of highly diluted succussed thyroxin on metamorphosis of highland frogs. *Berlin J Res Hom* 1991;1:151-60.
- ¹⁶ Endler PC, Pongratz W, Kastberger G, Wiegant FAC, Haidvogel M. Climbing activity in frogs and the effect of highly diluted succussed thyroxine. *Br Homeopath J* 1991; 80:194-200.
- ¹⁷ Endler PC, Pongratz W, Smith CW, Schulte J. Non-molecular information transfer from thyroxin to frogs with regard to 'homoeopathic' toxicology. *Vet Hum Toxicol* 1995;37(3): 259-60.

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- ¹⁸ Davenas, F, Beauvais, J, et al. Human basophil degranulation triggered by very dilute antiserum against IgE. *Nature*. 1988;333(6176):816-8.
- ¹⁹ Chirumbolo S, Brizzi M, et al. Inhibition of CD203c membrane up-regulation in human basophils by high dilutions of histamine: a controlled replication study. *Inflamm Res*. 2009;58(11):755-64.
- ²⁰ Belon P, Cumps J, et al. Histamine dilutions modulate basophil activation. *Inflamm Res*. 2004;53(5): 181-8.
- ²¹ Bellavite P, Magnani P, Zanolin E, Conforti A. Homeopathic doses of Gelsemium sempervirens improve the behavior of mice in response to novel environments. *Evid Based Complement Alternat Med* 2011;2011:362517.
- ²² Mohammadi R, Amini K, Charehsaz S. Homeopathic treatment for peripheral nerve regeneration: an experimental study in a rat sciatic nerve transection model. *Homeopathy* 2012;101:141-6.
- ²³ Das J, Das S, Samadder A, Bhadra K, Khuda-Bukhsh AR. Poly (lactide-co-glycolide) encapsulated extract of *Phytolacca decandra* demonstrates better intervention against induced lung adenocarcinoma in mice and on A549 cells. *Eur J Pharm Sci* 2012;47(2):313-24.
- ²⁴ Frenkel M, Mishra BM, Sen S, Yang P, Pawlus A, Vence L, Leblanc A, Cohen L, Banerji P, Banerji P. Cytotoxic effects of ultra-diluted remedies on breast cancer cells. *Int J Oncol* 2010;36(2):395-403.
- ²⁵ Varshney JP. Clinical management of idiopathic epilepsy in dogs with homeopathic belladonna 200C: a case series. *Homeopathy*. 2007;96(1):46-8.
- ²⁶ Chaudhuri S and Varshney JP. Clinical management of babesiosis in dogs with homeopathic *Crotalus horridus* 200C. *Homeopathy* 2007;96:90-4.
- ²⁷ Aboutboul R. Snake remedies and eosinophilic granuloma complex in cats. *Homeopathy* 2005;95:15-9.
- ²⁸ Varshney JP, Chaudhuri S. Atrial paroxysmal tachycardia in dogs and its management with homeopathic digitalis—two case reports. *Homeopathy* 2007;96:270-2.
- ²⁹ Epstein S, Hardy R. Clinical resolution of nasal aspergillosis following therapy with a homeopathic remedy in a dog. *J Am Anim Hosp Assoc* 2011;47(6):e110-5.
- ³⁰ Jacobs J, Jimenez LM, Gloye SS, Gale JL, Crothers D. treatment of acute childhood diarrhea with homeopathic medicine: a randomized clinical trial in Nicaragua. *Pediatrics* 1994;93(5):719-25
- ³¹ Chapman EH, Weintraub RJ, Milburn MA, Pirozzi TO, Woo E. Homeopathic treatment of mild traumatic brain injury: A randomized, double-blind, placebo-controlled clinical trial. *J Head Trauma Rehabil* 1999;14(6):521-42.
- ³² Terry R, Perry R, Ernst E. An overview of systematic reviews of complementary and alternative medicine for fibromyalgia. *Clin Rheumatol* 2012;31(1):55-6.
- ³³ Bell IR, Lewis DA 2nd, Schwartz GE, Lewis SE, Caspi O, Scott A, Brooks AJ, Baldwin CM. Electroencephalographic cordance patterns distinguish exceptional clinical responders with fibromyalgia to individualized homeopathic medicines. *J Altern Complement Med* 2004; 10(2):285-99.
- ³⁴ Bell IR, Lewis DA 2nd, Brooks AJ, Schwartz GE, Lewis SE, Caspi O, Cunningham V, Baldwin CM. Individual differences in response to randomly assigned active individualized homeopathic and placebo treatment in fibromyalgia: implications of a double-blinded optional crossover design. *J Altern Complement Med* 2004;10(2):269-83.

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- ³⁵ Bell IR, Lewis DA 2nd, Brooks AJ, Schwartz GE, Lewis SE, Walsh BT, Baldwin CM. Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. *Rheumatology* 2004;43(5):577-82.
- ³⁶ Bellavite P, Marzotto M, Chirumbolo S, Conforti A. Advances in homeopathy and immunology: a review of clinical research. *Front Biosci (Schol Ed)* 2011;3:1363-89.
- ³⁷ Haidvogel M, Riley DS, Heger M, Brien S, Jong M, Fischer M, Lewith GT, Jansen G, Thurneysen AE. Homeopathic and conventional treatment for acute respiratory and ear complaints: a comparative study on outcome in the primary care setting. *BMC Complement Altern Med* 2007;7:7.
- ³⁸ Frass M, Dielacher C, Linkesch M, Endler C, Muchitsch I, Schuster E, Kaye A. Influence of potassium dichromate on tracheal secretions in critically ill patients. *Chest* 2005;127:936-41.
- ³⁹ Shafei HF, AbdelDayem SM, Nagwa HM. Individualized homeopathy in a group of Egyptian asthmatic children. *Homeopathy* 2012;101:224-30.
- ⁴⁰ Walach H, Sherr J, et al. Homeopathic proving symptoms: result of a local, non-local, or placebo process? A blinded, placebo-controlled pilot study. *Homeopathy* 2004;93:179-85.
- ⁴¹ Dominici G, Bellavite P, et al. Double-blind, placebo-controlled homeopathic pathogenetic trials: Symptom collection and analysis. *Homeopathy* 2006;95:1230.
- ⁴² Goodyear K, Lewith G, Low JL. Randomized double-blind placebo-controlled trial of homeopathic 'proving' for Belladonna C30. *Journal of the Royal Society of Medicine*. 1998;91(11):579-82.
- ⁴³ Fisher P, Dantas F. Homeopathic pathogenetic trials of Acidum malicum and Acidum ascorbicum. *British Journal of Homeopathy*. 2001;90:118-25.
- ⁴⁴ Mathie RT, Hacke D, and Clausen J. Randomised controlled trials of veterinary homeopathy: Characterising the peer-reviewed research literature for systematic review. *Homeopathy* 2012;101:196-203
- ⁴⁵ Reis LS, Pardo PE, Oba E, Kronka Sdo N, Frazatti-Gallina NM. Matricaria chamomilla CH12 decreases handling stress in Nelore calves. *J Vet Sci* 2006;7(2):189-92.
- ⁴⁶ Hektoen L, Larsen S, Odegaard SA, Loken T. Comparison of homeopathy, placebo and antibiotic treatment of clinical mastitis in dairy cows-methodological issues and results from a randomized-clinical trial. *J Vet Med A Physiol Pathol Clin Med* 2004;51(9-10):439-46.
- ⁴⁷ Lotfollahzadeh S, Alizadeh MR, Mohri M, Mokhber Dezfouli MR. The therapeutic effect of Tarentula cubensis extract (Theranekron) in foot-and-mouth disease in cattle: a randomized trial in an endemic setting. *Homeopathy* 2012;101(3):159-64.
- ⁴⁸ Barbour EK, Sagherian V, Talhouk S, Talhouk R, Farran MT, Sleiman FT, Harakeh S. Evaluation of homeopathy in broiler chickens exposed to live viral vaccines and administered Calendula officinalis extract. *Med Sci Monit* 2004 Aug;10(8):BR281-5.
- ⁴⁹ Neumann S, Stolt P, Braun G, Hellmann K, Reinhart E. Effectiveness of the homeopathic preparation Zeel compared with carprofen in dogs with osteoarthritis. *J Am Anim Hosp Assoc* 2011;47(1):12-20.
- ⁵⁰ Jacobs J, Williams A-L, Girard C, Njike VY, Katz D. Homeopathy for attention-deficit/hyperactivity disorder: a pilot randomized-controlled trial. *Journal of Alternative and Complementary Medicine* 2005;11:799-806.
- ⁵¹ Frei H, Evert R, et al. Randomised controlled trials of homeopathy in hyperactive children: treatment procedure leads to an unconventional study design. Experience

with open-label homeopathic treatment preceding the Swiss ADHD placebo controlled, randomized, double-blind cross-over trial. *Homeopathy* 2007; 96(1):35-41.

⁵² Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D. Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. *Pediatr Infect Dis J* 2003;22(3):229-34.

⁵³ Davidson JR, Crawford C, Ives JA, Jonas WB. Homeopathic treatments in psychiatry: a systematic review of randomized placebo-controlled studies. *J Clin Psychiatry* 2011;72(6):795-805.

⁵⁴ Shang A, Huwiler-Müntener K, Nartey L, Juni P, Dorig S, Sterne JA, et al. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet* 2005;366:726-32.

⁵⁵ Walach H, Linde K, Eichenberger R, Stalder H, Kristensen FB, Kleijnen J. Summary Consensus Statement of the PEK Review Board regarding the PEK process and the PEK products. 2005. 27th September 2005.

⁵⁶ Bornhoft G, Wolf U, von Ammon K, Righetti M, Maxion-Bergemann S, Baumgartner S, Thurneysen AE, Matthiessen PF. Effectiveness, safety and cost-effectiveness of homeopathy in general practice- summarized health technology assessment. *Forsch Komplementmed* 2006;13 Suppl 2:19-29.

⁵⁷ Spence D S, Thompson E A, Barron S J. Homeopathic treatment for chronic disease: a 6-year university-hospital outpatient observational study. *Journal of Alternative and Complementary Medicine* 2005;11:793-8.

⁵⁸ Sharples F, van Haselen R, Fisher P. NHS patients' perspective on complementary medicine: a survey. *Complementary Therapies in Medicine* 2003;11:243-8.

⁵⁹ Spence D, Thompson E A, Barron S J. Homeopathic treatment for chronic disease: a 6-year university-hospital outpatient observational study. *J Altern Complement Med* 2005;5:793-8.

⁶⁰ Clover A. Patient benefit survey: Tunbridge Wells Homeopathic Hospital. *Br Homeopath J* 2000;89:68-72.

⁶¹ Richardson W R. Patient benefit survey: Liverpool Regional Department of Homeopathic Medicine. *Br Homeopath J* 2001;90:158-62.

⁶² Reilly D, Mercer S W, Bikker A P, Harrison T. Outcome related to impact on daily living: preliminary validation of the ORIDL instrument. *BMC Health Serv Res* 2007;7:139.

⁶³ Richardson W R. Patient benefit survey: Liverpool Regional Department of Homeopathic medicine. *British Homeopathic Journal* 2001;90:158-62.

⁶⁴ Trichard m, Chaufferin G, Nicoloyannis N. Pharmacoeconomic comparison between homeopathic and antibiotic treatment strategies in recurrent acute rhinopharyngitis in children. *Homeopathy* 2005;94(1):3-9.

⁶⁵ Witt C, Keil T, Selim D, et al. Outcome and costs of homeopathic and conventional treatment strategies; a comparative cohort study in patients with chronic disorders. *Complement Ther Med* 2005;13(2):79-86.

⁶⁶ Studer HP, Busato A. Comparison of Swiss basic health insurance costs of complementary and conventional medicine. *Forsch Komplementmed* 2011;18(6):315-20.

⁶⁷ Teut M, Ludtke R, Schnabel K, Willich SN, Witt CM. Homeopathic treatment of elderly patients—a prospective observational study with follow-up over a two year period. *BMC Geriatr* 2010;10:10.

-
- ⁶⁸ Rossi E, Crudeli L, Endrizzi C, Garibaldi D. Cost-benefit evaluation of homeopathic versus conventional therapy in respiratory diseases. *Homeopathy* 2009;98(1):2-10.
- ⁶⁹ Witt CM, Ludtke R, Mengler N, Willich SN. How healthy are chronically ill patients after eight years of homeopathic treatment?--Results from a long term observational study. *BMC Public Health* 2008;8:413.
- ⁷⁰ Kooreman P, Baars EW. Patients whose GP knows complementary medicine tend to have lower costs and live longer. *Eur J Health Econ* 2012;(13)769-76.
- ⁷¹ Leckridge B: *Homeopathy in Primary Care*. New York, NY: Churchill Livingstone Books; 1997.
- ⁷² Werner C, Sobiraj A, Sundrum A. Efficacy of homeopathic and antibiotic treatment strategies in cases of mild and moderate bovine clinical mastitis. *J Dairy Res* 2012;77(4):460-7.
- ⁷³ Klocke P, Ivmeyer S, Butler G, Maeschli A, Heil F. A randomized controlled trial to compare the use of homeopathy and internal Teat Sealers for the prevention of mastitis in organically farmed dairy cows during the dry period and 100 days post-calving. *Homeopathy* 2010;99(2):90-8.
- ⁷⁴ Dantas F, Rampes H. Do homeopathic medicines provoke adverse effects? A systematic review. *Br Homeopath J* 2000;89, Suppl1, S35-8.
- ⁷⁵ Tumir H, Bosnir J, Vedrinar-Dragojević I, Dragun Z, Tomić S, Puntarić D. Preliminary investigation of metal and metalloid contamination of homeopathic products marketed in Croatia. *Homeopathy* 2010;99(3):183-8.
- ⁷⁶ Young MA, Ioannidis, JPA, Al-Ubaydli O. Why current publication practices may distort science. *PLoS Med* 2008;5(10):e201