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All Evidence is Equal, but Some Evidence is More Equal than Others: Can Logic Prevail over Emotion in the Homeopathy Debate?

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In his classic political satire *Animal Farm*, George Orwell described a fantasy world in which having total power gradually corrupts and distorts the initially idealized societal commandments articulated by the farm animals who have successfully risen up against a common enemy, i.e., the farmers (people). In the end, the commandment that "all animals are equal" drifts into "all animals are equal, but some animals are more equal than others." Unfortunately, allopathic medicine, i.e., conventional mainstream medicine in its politically dominant position, has reached an analogous juncture in its history of considering evidence. The recent Shang et al. meta-analysis study (Shang 2005), and the accompanying editorials pronouncing the "end of homeopathy" (Lancet. 2005) and the "growth of truth" (Vandenbroucke 2005a) in the prestigious British journal *Lancet* expose an Orwellian selectivity and bias in considering facts, as well as an illogic, under the aegis of "evidence-based medicine." The Shang et al. paper concluded that "the clinical effects of homeopathy are placebo effects" on the basis of 8 unspecified homeopathic studies and 6 unspecified conventional (allopathic) studies out of an original total of 110 studies of each type on the same variety of conventionally-diagnosed conditions.

The editorial stance raises grave concerns about logic, fairness, and rationality in the *Lancet*'s interpretation and use of the evidence, for several reasons:

- The subanalysis on which the main conclusions are based did not specify which 8 papers out of the original 110 homeopathic or 6 papers out of the original 110 allopathic papers were used. This type of lack of reporting transparency and precision is typically not tolerated for allopathic medical reports. For instance, the CONSORT statement requires a full disclosure of outcomes of all initially enrolled patients in a detailed flow chart (Altman et al. 2001); but the lack of comparable details was tolerated for the identity of the small number of actual studies used for the Shang et al. meta-analysis conclusions.
- The Shang et al. paper report is one meta-analysis out of several published meta-analyses (the others have been largely favorable to what they claim is "homeopathy"

(Cucherat et al. 2000; Linde 1997; Reilly et al. 1994)), based on an incomplete and not-up-to-date selection extremely heterogeneous RCTs encompassing multiple different allopathic diagnoses and using interventions that are only sometimes considered homeopathic by homeopaths. That is, isopathy (using a homeopathically-prepared specific agent that triggers specific local symptoms) is not homeopathy by definition (Hahnemann 1843), but it has been included in most meta-analyses of homeopathy. A single remedy chosen on the basis of an allopathic diagnosis without regard to its homeopathic indications is not homeopathy (Hahnemann 1843), but numerous allopathically "high quality" RCT studies that enter meta-analyses such as Shang et al. ignore this major problem in external ecological validity. Furthermore, a remedy only acts homeopathically when it is homeopathic in its pattern of effects on an individualized basis (i.e., similar but not identical to the pattern of global and local disease in the patient as a whole), an issue for population validity.

An incorrectly-chosen remedy for a patient (a not uncommon occurrence in clinical reality) is also not homeopathic and therefore constitutes an inactive "active" intervention that degrades the average outcome of the active/verum group. No RCT studies of homeopathy, and thus no meta-analyses, have as yet accommodated this ecological validity issue in their design other than sometimes to require high homeopath confidence ratings in remedy choice as an inclusion criterion (Bell et al. 2004c). The problem of incorrect remedy selections is an issue for the quality of homeopathy in clinical practice, but the proper scientific response should be to seek ways to improve clinical practice through research, e.g., to seek objective physiological and patient-centered trait predictors of future responsivity (Bell et al. 2004e), rather than to discard the field as a whole.

- The Shang et al. paper is methodologically flawed even within the allopathic framework (see Aickin in this issue). Therefore, logically, the Shang et al. paper is not the final word on the entire research literature on homeopathy. In other areas of

medical research, the notion that any paper, especially one meta-analysis of selected clinical studies, offers the final word on a topic is usually treated as scientifically risky, if not unfair, illogical, and irrational (Jonas 2001). As outlined below, there are many studies in the basic science, preclinical, and clinical literatures suggesting that homeopathically prepared remedies are not inert and that homeopathic care as an intervention is safe and effective for many patients. Apparently, the *Lancet*'s view is that the conservative interpretation of a single review of only some of the "evidence" is unnecessary when the topic is homeopathic research.

- Meta-analyses, even good ones, rely on quality ratings of internal validity of randomized controlled trials designed to test conventional drugs with specific effects on specific disease mechanisms (Concato 2004b). No quality ratings of the homeopathy used in each study were employed in the Shang et al. meta-analysis (Was homeopathic treatment provided in a clinically typical methodology? Was the fate of homeopathy in the study based on the prescribing skills of a single homeopath or of multiple well-qualified homeopaths? Were the homeopaths highly confident of their remedy selections? Were typical global and multiple local homeopathic outcomes systematically assessed in the study?, i.e., ecological validity. That is, "high quality" studies were judged solely in terms of their conventional strengths in testing a given intervention, i.e., homeopathy, as though it were a biomedical drug with a disease-specific action.

PLAYING BY THE RULES: WHOSE RULES?

In terms of external validity, the fundamental principles of homeopathy are that the treatment addresses the patient's entire pattern of problems at once in a patient-specific, but not disease-specific, manner (Vithoulkas 1980). Homeopathic outcomes are different from those in conventional medicine; homeopaths report global and hierarchically-organized multiple, multidimensional changes at local (body part) levels (Bell et al. 2002; Vithoulkas, 1980). Thus,

the very nature of homeopathy, similar to another complex whole system of CAM, acupuncture (Gould 2001; Paterson et al. 2003; Paterson 2005; Schulman 2004), is inherently non-specific. Non-specific does not mean biologically inert, i.e., non-specificity is more than a simple "placebo" effect (Walach 2001). Shang et al. stated in their methods section that they randomly chose only one outcome from each study for their analysis, if multiple outcomes were reported. By itself, this methodological error weakens the fairness of the comparisons between the homeopathic and allopathic studies. To infer from the data that homeopathic remedies do not exert disease-specific effects, i.e., that they are not allopathic drugs, is consistent with the claims of homeopathic clinicians and the conceptual principles of the field, but such a conclusion only highlights the need to design clinical studies of homeopathy that reflect the philosophical underpinnings and clinical practices of homeopathy rather than those of allopathy.

An analogy for a conventional drug would be to test the effects of penicillin for all patients with symptoms and signs of an apparent infection. The design quality of the studies would otherwise be excellent. However, penicillin will not work for patients with viral infections or bacterial infections resistant to its effects or for persons with fevers from other, non-infectious causes - and it thus might show benefit only for a subset of patients with symptoms of infections, i.e., the ones with true penicillin-sensitive infections. How would penicillin fare in a meta-analysis of studies averaging all patients together, evaluating only internal but not external ecological or population validity, and ignoring the intrinsic nature of penicillin in benefiting certain patients? Variable luck of the investigators in recruiting patients with penicillin-sensitive infections in a given study as well as publication bias in medicine generally to favor publication of positive rather than negative results would likely lead to current scenario from the Shang et al. paper – that is, the publication of a small number of "high quality" positive studies, but the rejection of penicillin for treatment of infections in general on the basis of meta-analysis. Proponents would insist that penicillin is nonetheless very helpful for certain patients with the "right" infections, and skeptics would scoff at the argument. But the proponents would be correct

– penicillin is very helpful, but only for patients in a target population whose problem matches the capacity of the drug to act for them (Caspi et al. 2004; Caspi 2004). So goes the situation for homeopathy.

In short, conventional mainstream medicine has defined the game, the rules, and the interpretation. At a practical level, the antipathy toward homeopathy in the clinical research funding world and the historical focus of homeopaths on clinical care have combined to leave homeopathic research without a sufficient number of funded investigators and with a research approach in only the earliest stages of development (Bell 2003a). Those researchers who have done homeopathic clinical studies have consciously or unwittingly agreed to evaluate their field by allopathic rather than homeopathic rules.

What if allopathic drugs were held to the non disease-specific outcome standards routinely reported in homeopathy? Would allopathically-treated patients, like homeopathically-treated patients, report better overall well-being, greater energy, and improvement in multiple symptoms, some of which they had forgotten to mention, with shifts in multiple mental, emotional, and physical problems toward recovery from a single agent with minimal side effects and low cost? Does allopathy mobilize the same patterns of patient-wide, whole system changes that homeopaths report (Bell et al. 2003c)? Future studies comparing homeopathy with allopathy need to level the playing field by evaluating for outcomes from both an allopathic and a whole systems (Ritenbaugh et al. 2003; Verhoef et al. 2004), homeopathic point of view (Bell 2003a).

THE EVIDENCE BEYOND SHANG ET AL.

The *Lancet* editorial (2005) expresses the usual opinion of skeptics that homeopathy is "absurd" because of the dilution factor of some of its medicines (remedies) beyond Avogadro's number, i.e., it must follow that remedies are biologically inert in living organisms. This is an opinion without supporting evidence. *Lancet* ignores the fact that homeopathic remedies are prepared not only with dilution, but also with vigorous shaking or succussion. The basic science data suggest that it is the succussion that makes a key difference between an active versus an

inactive agent in homeopathy. The actual replicated basic science systematic evidence from different, independent laboratories is that homeopathically-prepared remedies beyond Avogadro's number differ from remedy-free solvent controls in their measurable properties, including calorimetry (Elia 2004; Elia 1999), thermoluminescence (Rey 2003), and optical emission characteristics (Bell 2003b). The findings challenge the assumptions of high school chemistry, but not those of modern materials science (Roy 2005). Prior research suggests that homeopathic basic science studies are prone to contaminants and confounds for which careful rigorous controls are needed (Becker-Witt 2003), but not that the remedies are inert.

Moreover, the preclinical evidence from multiple different, independent laboratories is that homeopathically-prepared remedies have biologically measurable effects in in vitro and in vivo animal studies (Bellavite 2002; Bertani et al. 1999; Endler 1994; Schulte 1998). For example, the famous controversial Benveniste paper in *Nature* showing ultradilutions of immunoglobulin E antiserum modulated basophil histamine release (Davenas et al. 1988) was promptly attacked via evaluation by a "quackbuster" magician and his colleagues. A recently-published European multi-site study with improved objective technology has now demonstrated that ultradilutions of histamine do modulate basophil activation (Belon 2004). The *Lancet* editorial and Vandenbroucke commentary made no mention of this fact.

In addition, laboratories in many different countries have demonstrated that homeopathically-prepared remedies exert measurable effects in animals (Endler 1994; Schulte 1998). In isopathic research, animals experimentally poisoned with arsenic show ameliorating effects on biological toxicity under treatment with homeopathically-prepared (diluted and succussed) arsenic than with placebo controls (Datta et al. 1999; Kundu et al. 2000; Mallick et al. 2003; Mitra et al. 1999). Homeopathically-prepared glutamate has protective effects for rat neurons in cell culture when used isopathically for experimental glutamate toxicity (Jonas et al. 2001). Sleep electroencephalographic patterns of animals differ from controls after ingestion of one of two different homeopathically-prepared remedies, i.e., coffea cruda (Ruiz-Vega et al.

2000) and nux vomica (Ruiz 1997; Sukul et al. 1999), that are reported to exert effects on human sleep in clinical settings. Cataleptic effects of haloperidol increase as a function of concomitant treatment with ultra dilutions of various homeopathically-prepared remedies in animals (Sukul 1986). Ultradilute acetylsalicylic acid produces significant differences from controls in a laser-induced thrombus formation model system (Belougne-Malfatti et al. 1998; Doutremepuich et al. 1994). In vitro and in vivo animal study effects do not necessarily translate into clinical efficacy, but they do indicate that homeopathic remedies are active agents.

Even the highly-touted "negative" clinical study of dust mite prepared as a homeopathic remedy but prescribed isopathically, not homeopathically (i.e., not in accord with actual homeopathic practice) to adult asthmatics demonstrated different dynamical patterns of global disease, lung function, and mood responses to the verum remedy as compared with the placebo (Lewith et al. 2002). Homeopathically-prepared dust mite, prescribed isopathically in the latter study, did not act in the same manner as did the placebo (Hyland 2002). Skeptics can rush to judgment that the net lack of clinical benefit in the study justifies rejection of the field of "homeopathy" (actually, by logic, it may support rejection of the clinical intervention of isopathy with dust mite in adult asthma, but offers no data on the field of homeopathic treatment per se) or open-minded scientists can look at the nonlinear dynamical findings from the remedy and wonder why (Bellavite 2003). Moreover, our own laboratory has shown that verum individualized homeopathic remedies in fibromyalgia patients produce electroencephalographic pattern changes not seen with placebo under double-blind conditions (Bell et al. 2004a; Bell et al. 2004d). In short, the evidence is that homeopathically-prepared remedies exert nonlinear dynamical effects on organisms different from those of conventional drugs. *Lancet* is willing to end homeopathy on the basis of the conclusions of a single flawed meta-analysis paper that concludes a publication bias within a highly selected subset of the clinical literature, but overlooks the far larger body of scientific evidence suggesting that homeopathic remedies exert effects different from those of placebo.

The clinical evidence from numerous observational studies on hundreds to thousands of patients in different countries has consistently demonstrated that homeopathy benefits the majority of patients who receive it for a wide range of conditions and shows an excellent safety record (Anelli et al. 2002; Frenkel et al. 2002; Goldstein 1998; Guthlin 2004; Mathie 2003; Riley et al. 2001; Schlappack 2004; Thompson et al. 2002; Van Wassenhoven et al. 2004; Walach et al. 2000; Witt et al. 2005). In some studies (Frenkel et al. 2002; Van Wassenhoven et al. 2004), though not all (Witt et al. 2005), homeopathy also generates significant cost savings via reduction in reliance on conventional symptomatic drugs. When conventional medical researchers discuss conventional drugs, they now argue that well-done observational studies have validity in the world of evidence, e.g,. in journals as prestigious as the New England Journal of Medicine (Concato 2004a; Concato 2004b; Concato et al. 2000). A central point is that observational data in conventional medicine are often more relevant to effectiveness in everyday clinical practice (external ecological validity) than are the RCT efficacy studies, which focus on idealized replicable drug testing in uncomplicated patients (internal validity). However, in view of the fact that the observational data on homeopathy are consistently favorable to the field, mainstream skeptics would dismiss the body of observational findings in homeopathy as an inferior and unimportant form of data.

The Shang et al. paper also made no comparison of safety issues. In the allopathic world, the evidence shows that even correctly prescribed conventional medications cause extensive morbidity and mortality (Lazarou 1998) (although the extent of the latter findings also have been challenged as a flawed meta-analysis (Kvasz 2000)). In the face of such data, it is inaccurate, and potentially harmful to patients seeking options, to conclude that allopathic medicine has been demonstrated to be superior to other forms of care (Vandenbroucke 2005b), especially those complex systems with long historical traditions of benefit and safety.

INDIVIDUAL DIFFERENCE FACTORS IN CLINICAL OUTCOMES RESEARCH

Is homeopathy some sort of panacea for all patients with all types of problems? Of course not. The evidence suggests that certain individuals are more inclined to use homeopathy (and other systems of CAM)(Honda et al. 2005). Initial data also indicate that some individuals with particular electroencephalographic responses to the first test dose of a remedy may be more likely to benefit (Bell et al. 2004e). The individual differences may stem more from the nature of the person such as genetically-based personality traits (Bell et al. 2004b) and accuracy of the pattern matching between the remedy and the unique symptomatology of the patient (Vithoulkas 1980), than the nature of the allopathic disease label. Patient recruitment in homeopathy studies following the conventional design model for drug RCTs draws from the general pool of patients with a given disease label without regard to the target population of patients with a preference for and a capacity to respond to homeopathy. No RCT of homeopathy to date has recruited and then randomized the subset of potential responder patients (Caspi and Bell 2004a; Caspi and Bell 2004b) to active versus placebo groups. Potential responders might be prescreened, for example, by both personality tests (Bell et al. 2004b) and electrophysiological testing (Bell et al. 2004e) before randomized treatment.

Thus, the evidence indicates that the subject selection procedures of allopathically-designed RCTs of homeopathy are a potentially inaccurate reflection of the real world clinical population of persons who end up in homeopathic treatment. The proper question is not a broad public health policy question that an RCT can answer (Jonas 2001), i.e., does homeopathy work for everyone with a specific allopathic diagnosis *on average*? Rather, the proper question is patient-centered at *an individual* level, i.e., is homeopathic treatment more effective than placebo in a specific patient who has the testable, prescreened potential to respond?

As consumer interest in complementary and alternative medicine continues to grow (Barnes et al. 2004), mainstream medicine has demanded that CAM researchers provide evidence for specific efficacy (where conventional drugs shine), with a secondary emphasis on safety, cost,

or effectiveness data (where CAM may have its greatest advantages). At face value, evidence-based medicine is a reasonable and desirable goal for practice. Basing clinical care solely upon "expert" opinion and bias is fraught with potential risk of using ineffective or dangerous therapies for the patient.

The problem with evidence-based medicine derives not from the ideal definition and intent, but rather, from the actual application of the concept. Evidence-based medicine is defined as "the judicious use of the best current evidence in making decisions about the care of the individual patient. Evidence-based medicine (EBM) is meant to integrate clinical expertise with the best available research evidence and patient values" (http://www.medterms.com/script/main/art.asp?articlekey=33300, accessed 9/9/05). A large, convergent body of research literature suggests that mainstream clinical practice itself does not live up to expectations in terms of RCT-derived, "evidence-based" efficacy standards (Avorn et al. 1982; Bates et al. 2003; Chren et al. 1994; Fisher 2003; Freeman et al. 2001; Green et al. 2005; Kravitz et al. 1995; Rosenbloom et al. 2005; Wazana 2000).

Research has shown that conventional physicians in practice or in training often cannot and do not follow "evidence-based" practice recommendations in the real world. Physicians report that they cannot determine from reading studies on large groups of uncomplicated patients when and how the average findings from an idealized efficacy study on a single drug might apply to the specific, typically complicated individual patient who is consulting them. Logistical issues, dosage adjustments for side-effects, co-morbid conditions, potential drug-drug interactions in polypharmacy, patient preferences and cultural beliefs, pharmaceutical company influences on patients and physicians, economic considerations, patient access and adherence, patient-provider relationships, and numerous other factors converge to determine the effectiveness of a treatment in real-world practice. The practical test of the value of an intervention for an individual patient is in its effectiveness as practiced in full context, not in efficacy-based RCT studies.

CONCLUSIONS

Overall, as several investigators have commented, conventional medicine itself needs a much more extensive research literature on individualized treatment planning and on individual differences in response to treatment, in order to fill out a more usable and rational evidence base to guide patient care (August et al. 2004). Homeopathy, as a complex intervention, has important lessons to teach clinicians and researchers with regard to issues in individualized treatment, patterns of outcomes, and even the nonlinear dynamical processes of healing in the patient as a whole system (Bell et al. 2002; Hyland 2003). The body of scientific evidence on homeopathy extends far beyond the limitations of the Shang et al. (2005) study. The data in the literature show that a number of curious - and sometimes clinically beneficial - phenomena can occur during homeopathic treatment (Bell et al. 2003c). It behooves the medical and scientific community to reassess its biases and look in a far more balanced and thoughtful way at all of the evidence (Barber 1961; Jonas 2001).

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