

DOES COMPLEMENTARY AND ALTERNATIVE MEDICINE REPRESENT ONLY PLACEBO THERAPIES?

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Complementary and alternative medicine (CAM) is “something you heard about from your hairdresser, who thinks she saw it on *Oprah*—a category that . . . includes acupuncture, homeopathy, healing magnets and assorted herbs and supplements.”¹ This is a quote from Jerry Adler’s editorial in the December 1, 2007, issue of *Newsweek* titled, “A Big Dose of Skepticism.” The editorial represents a strong “shot across the bow” of the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health as well as the tens of thousands of licensed CAM practitioners and millions of their patients who regularly employ what have been termed “CAM therapies.”

Mr Adler states that his 2008 resolution as a medical writer is to “not report on any new treatments for anything, unless they were tested in large, randomized, placebo-controlled, double-blind clinical trials published in high-quality peer-reviewed medical journals.” He takes his lead in this advocacy from the recent book, *Snake Oil Science: The Truth About Complementary and Alternative Medicine* by R. Barker Bausell, PhD.² In essence, Bausell makes a strong case using his background as a former director of research for the University of Maryland’s Center of Complementary and Alternative Medicine that all CAM therapies have an impact on health only by placebo-related effects. He bases his conclusions on the efficacy of CAM therapies on the following 5 criteria:

1. Studies of CAM therapies that show benefit beyond placebo effects have not been done well, whereas studies of CAM therapies that are methodologically sound have not demonstrated benefit beyond placebo.
2. Scientists and clinicians engaged in either the administration or study of CAM therapies have an inherent bias in support of the positive nature of the therapies, and therefore their conclusions are suspect.
3. Scientists and clinicians associated with CAM therapies do not understand methodological issues in the science of clinical trials such as the placebo effect, attrition/drop-out, the natural history of the disease in question, the Hawthorne effect, regression to the mean, or statistical methods of analysis.

4. No scientific mechanism of action for the validity of CAM therapies has been proven beyond that of the known mechanism of action of the placebo effect.
5. There is a lack of understanding of the concept of parsimony (ie, Occam’s razor) that results in unusual and unproven mechanisms beyond placebo effect to be ascribed to CAM therapies.

In support of his contention that these 5 criteria define the limitations of CAM studies, Bausell provides evidence using the Cochrane Collaboration database³⁻⁵ of 98 randomized, controlled CAM studies published in 4 top-tier, peer-reviewed journals: *The New England Journal of Medicine*, *JAMA*, *Archives of Internal Medicine*, and the *Annals of Internal Medicine*. These studies include acupuncture, herbal therapies, chelation therapy, traditional Chinese medicine (TCM), electrical stimulation techniques, hypnotherapy, homeopathy, intercessory prayer, massage, meditation, manipulative therapies, ultrasound, and nutritional supplements such as glucosamine. As he applies his criteria to the validity of these studies he shows that only 5% of the 98 published studies demonstrate positive outcomes beyond that of placebo. It is this analysis that leads to his conclusion that “after initiating [what appears to be a successful CAM] therapy, if you begin to experience some fall-off in its benefits, discuss the situation immediately with your therapist. Most experienced CAM therapists will have a menu of new strategies capable of initiating a new round of placebo effects.”^{2(p294)}

What is wrong with this analysis of the efficacy of CAM therapies? The analysis is based on well-founded concerns from an expert in scientific methodology. It would seem that Bausell has offered a *fait accompli* that wipes away thousands of years of history associated with the purported clinical success of many traditional healing methods with the stroke of one scientific eraser.

But there is much more to the story than that which is told. First of all, he has seemingly lumped all of what is considered non-traditional medical intervention under the rubric of CAM. He has selectively chosen issues in the history of science to support his hypothesis that there is no basis of a clinical benefit for any CAM therapy (which many readers might interpret as “non-pharmacological therapies”) beyond that of placebo. The implication of Bausell’s argument is that the success that was witnessed with the development in the 1930s of antibiotic therapy ushered in the era of successful, non-placebo therapies⁶ that, unlike CAM therapies, had demonstrable effects beyond that of placebo. With regard to the



necessity of conducting large randomized clinical trials to determine non-placebo effects of a specific therapy, it is interesting to note that many accepted surgical procedures have not been tested by randomized, placebo-controlled trials. They are, however, considered standards of care based on agreement among trained medical professionals that they are efficacious.⁷

Also interesting is Bausell's contention that it is essential to know the mechanism of action of a specific therapeutic intervention when it is well known that many of the pharmaceutical preparations approved for use by the US Food and Drug Administration do not have known mechanisms of action.⁸ The definitive criteria that establish the safety and efficacy of any therapy may be a little more complicated than Bausell's analysis implies.

There is another important limitation of using the randomized, placebo-controlled trial as the only criterion for determining the non-placebo value of a therapy. The randomized, placebo-controlled clinical trial favors the evaluation of an intervention that can be easily blinded and placebo-controlled. As such, it is an excellent methodology to evaluate the effect of 1 pill tested against 1 clinical endpoint—for example a new-to-nature angiotensin-converting enzyme inhibitor for systolic and diastolic blood pressure compared to an identical-looking placebo. This methodology, however, is not as easily applied when one wants to study the effect of a CAM therapy involving specific diet or lifestyle intervention on blood pressure. Diet and lifestyle interventions are impossible to completely blind and therefore are more susceptible to issues related to the Hawthorne effect, compliance, dropout, or the placebo effect.

The issue of the limitations of control of dietary intervention trials was discussed in a recent review describing the inter-individual variation of response that occurs in dietary studies and the need for managing genetic heterogeneity with large study groups and specific dietary subgroup analysis.⁹ This criticism can be applied to important studies such as the Dietary Approach to Stopping Hypertension (DASH). These studies demonstrated clinical validity of the effect diet and lifestyle have on hypertension but did not fulfill Bausell's criteria of an acceptable, randomized, placebo-controlled trial.^{10,11} In the end, the well-designed study of a pharmaceutical product for hypertension has far fewer methodological issues confounding its results than do the diet-and-lifestyle intervention studies.^{12,13}

Beyond the obvious methodological challenge of how to blind and develop appropriate placebos for CAM intervention trials is another thorny issue. How long does it take to demonstrate true improved patient outcome in a clinical study? Most clinical intervention trials evaluating the effect of a new therapeutic agent for the management of a chronic health problem will be of a year's duration at most. It is assumed that at the end of this period of time the safety and effectiveness of the agent has been "proven." But what if this agent is applied in clinical practice for a much longer duration than the 1 year it was studied? Many patients with a chronic disease have their therapies applied indefinitely, as is the case with type 2 diabetes, osteoarthritis pain and disability, chronic digestive problems such as esophageal reflux disease, chronic

depression, benign prostatic hypertrophy, hyperlipidemias, and hypertension.^{14,15} In these cases the true safety and effectiveness of the therapy that had been proven through the administration of a successful short-term randomized, placebo-controlled trial might in the longer term prove to either not improve outcome or even cause serious adverse effects. An example is the recent voluntary recall of the selective COX-2 inhibitor Rofecoxib by Merck & Co (Whitehouse Station, New Jersey) due to the number of adverse drug reactions that occurred after patients had been taking the drug for an extended period of time.^{16,17} It wasn't that the drug had not been proven to be safe and effective through multiple randomized, placebo-controlled trials—rather, the adverse drug reactions occurred when patients took the drug for a period of time that was longer than the duration of the clinical trials.

A CAM treatment often is based on a much longer historical perspective of safe use in indigenous cultures.^{18,19} It may not "measure up" in terms of outcome from a short-term placebo-controlled trial, but it may actually provide for both a safer and more effective outcome in the longer term. No long-term, head-to-head outcome studies have been done to compare the safety and effectiveness of specific CAM therapies to those of pharmaceutically based therapies.^{20,21} However, population studies of various diet and lifestyle CAM therapies have shown significant improvements in health outcomes when compared to populations that have not adopted these habits.^{22,23} The recent HALE (Healthy Aging Longitudinal Study in Europe) project, a 10-year study of health outcomes in individuals aged 70 to 90 years who elected to consume a Mediterranean diet compared to an age- and gender-matched control group in the same countries who consumed their traditional European diet, illustrates this concept.²⁴ The study reported that "among individuals aged 70 to 90 years, adherence to a Mediterranean diet and healthful lifestyle is associated with a more than 50% lower rate of all-cause mortality and cause-specific mortality."^{24(p1433)} Although this study doesn't fulfill the Bausell criteria of a randomized, placebo-controlled trial, it was published in a peer-reviewed, tier-one journal, and the results have potentially significant implications on health outcomes of an aging population. As Ivan Ilich said in his landmark book *Medical Nemesis*²⁵ and as suggested by the HALE study, the big breakthroughs in health have not occurred through agents developed by the application of the randomized controlled clinical trial to develop new medicines but rather through the effective application of nutrition, sanitation, and hygiene, all of which were considered "CAM therapies" in their time.

The question that emerges from Bausell's interpretation of CAM therapies is whether the randomized clinical trial is the appropriate methodology to address the most important questions concerning our health where chronic disease is the dominant form of disease in the developed world.²⁶ What is emerging is a different model for evaluating a therapy's safety and effectiveness that is born out of the developing algorithms of systems biology.^{27,28} It uses multivariate, non-parametric statistical methods of analysis of complex data sets. Rather than constructing the experiment to hold all variables constant except the clinical endpoint that is to be

studied, this model allows the study participants to engage in real-world activities of daily living and then determines how the captured complex data set clusters into patterns of significant outcome.^{29,30} Bausell's questioning of the non-placebo validity of all CAM therapies is built on an old model of statistics. It is through the computing power of the 21st century and new technology that pattern recognition and cluster analysis of complex data sets can be routinely accomplished.

Work that is being done on the analysis of complex biological systems at places such as the Institute for Systems Biology in Seattle, Washington, has presented an opportunity for new experimental methodologies to be employed in clinical studies.³¹ These new methods of analysis don't suffer the "one agent for one outcome" bias of the randomized, placebo-controlled clinical trial. The systems biology approach to medicine is now being seriously discussed as part of the development of an integrated biological approach to healthcare.³² The Institute for Functional Medicine recently published the *Textbook of Functional Medicine*, which describes a clinical approach to applying systems biology to the management of chronic disease.³³ The clinical model described in the textbook is built on a foundation of evidence from not only randomized, controlled clinical trials but also studies published from epidemiology, meta-analyses, case-controlled studies, basic science discoveries, and complex data set analyses. The functional medicine approach to chronic disease represents a new paradigm in healthcare that moves beyond the limitations of CAM described by Bausell.

We are witnessing a new era in which it might be said that we are "moving back to the future." The move back is to explore what makes the greatest impact on improving health outcomes in a society burdened with the rising incidence of chronic disease from a historical perspective. The future holds the development of new experimental methods of designing studies that can better address complexity within human populations and the computing and statistical methodologies to bring clarity from confusion.^{34,35}

It is certainly true that all interventions are "tainted" by methodological issues such as the placebo effect. Some therapies have a much greater likelihood of a strong placebo effect than others, such as those for chronic pain. It is also true that some therapies are much more difficult to separate methodologically from that of the placebo effect. This is the case with a number of CAM therapies in that it may be virtually impossible to completely blind the participants or the practitioners or provide a suitable placebo. Using the new experimental methods that are based on complexity theory and systems biology and the statistical methods that support them, we will be better able to address the long-term safety and efficacy of many CAM therapies. It is through this work that studies will help answer the question of which CAM therapies work via placebo effect and which therapies will aid us in fighting chronic disease and infirmity.³⁶

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