Ethical Issues Concerning Research in Complementary and Alternative Medicine

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The use of complementary and alternative medicine (CAM) has grown dramatically in recent years, as has research on the safety and efficacy of CAM treatments. Minimal attention, however, has been devoted to the ethical issues relating to research on CAM. We argue that public health and safety demand rigorous research evaluating CAM therapies, research on CAM should adhere to the same ethical requirements for all clinical research, and randomized, placebo-controlled clinical trials should be used for assessing the efficacy of CAM treatments whenever feasible and ethically justifiable. In addition, we explore the legitimacy of providing CAM and conventional therapies that have been demonstrated to be effective only by virtue of the placebo effect.

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COMPLEMENTARY AND ALTERnative medicine (CAM) encompasses a wide range of popular treatment modalities that are outside conventional practice and generally lack sufficient scientific evidence of their safety and efficacy. These treatments include herbal agents, homeopathic preparations, chiropractic manipulations, massage, acupuncture, meditation, and prayer. Use of CAM in the United States is widespread and growing, as is the recognition that in many developing nations, the dominant form of medical care consists of similar indigenous traditional practices.[1,2] Research on CAM has grown dramatically since 1992, when the Office of Alternative Medicine at the National Institutes of Health (NIH) was established by Congress with an initial budget of $2 million. The National Center for Complementary and Alternative Medicine, created in lieu of this office in 1998, has increased its budget from $50 million in 1999 to an estimated $114.1 million in 2003.[3] Total funding by all the institutes and centers of the NIH for research on CAM and the training of investigators to study CAM will exceed $220 million in 2003, with additional funding being provided by other agencies and philanthropic foundations.

Scant attention has been devoted to the ethics of research studies evaluating CAM treatments. In view of the rapid growth and investments in this field of inquiry, it is timely to address ethical issues relating to research on CAM more formally and substantively. After briefly explicating an ethical framework for clinical research, we apply this framework to 3 controversial ethical issues concerning research evaluating CAM treatments: the value of rigorous research on CAM, the validity of randomized, placebo-controlled clinical trials of CAM treatments, and the justification for placebo-controlled trials of CAM treatments for medical conditions, despite proven effective conventional treatment. Finally, we explore the implications for practice and health care policy of CAM and conventional treatments that are found to be no better than placebo.

Ethical Framework for Clinical Research

An ethical framework for clinical research has 2 objectives: to promote socially valuable clinical investigation and to protect research subjects from exploitation. Emanuel et al[4] proposed a framework consisting of 7 requirements that must be satisfied for ethical clinical research: social value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for enrolled subjects (TABLE). Because these ethical requirements are universal, there are no valid reasons for exempting studies of CAM from any of them.

According to Emanuel et al,[4] the first ethical requirement is social value. All clinical research is conducted to answer 1 or more questions with potential clinical significance. For research lacking value, no basis exists for justifying risks to subjects. Second, clinical research must be designed and conducted with sufficiently rigorous methods so that findings have scientific validity. Proposed studies lacking

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scientific validity are unethical because they expose subjects to risk without the potential to produce generalizable knowledge. Third, clinical research must select subjects fairly in accordance with the scientific objectives of the study and avoid unnecessary involvement of vulnerable groups. Fourth, all clinical research must have a favorable risk-benefit ratio, minimizing risks to subjects and justifying the risks by the potential benefits to subjects and the value of the knowledge to be gained from the research. Fifth, to protect subjects and ensure public accountability, all clinical research studies should receive prospective and ongoing review by a committee composed of individuals independent of the research. Sixth, competent adults should not be enrolled in research unless they have been adequately informed about the study and they have agreed to participate. For research with children and incompetent adults, informed authorization by parents or other surrogate decision makers is required. Seventh, research must be conducted in a way that respects the rights and protects the well-being of enrolled subjects.

Value of Rigorous Research on CAM

It is estimated that between 29% and 42% of adults in the United States use 1 or more CAM treatments during a year.[1,2] A national survey estimated that total expenditures for CAM treatments were $27 billion in 1997.[2] Individuals choose CAM treatment for a variety of reasons, including dissatisfaction with the inability of conventional medicine to cure or relieve all ailments, the adverse effects and expense of conventional treatments, and the belief that conventional medicine is too impersonal and technologic. CAM is attractive because it is perceived as "natural" and therefore safe, it promotes wellness and not just treatment of illness, and it is provided by practitioners who give individualized attention to their patients.[5] The widespread use of CAM underscores the social value of rigorous research to verify whether the assumptions of its safety and efficacy are valid.

The first investigations of CAM practices have already raised concerns about the claims surrounding some of the practices. Contrary to popular beliefs, natural products marketed as dietary supplements can be unsafe and interfere with the actions of conventional life-saving drugs.[6] Dietary supplements are not standardized, resulting in high variability from one lot of a product to another, and they may be adulterated with drugs or contaminated with heavy metals.[6,7] Although many CAM treatments supposedly have been established as elements of long-standing healing practices, serious scrutiny has cast doubt about whether they are all safe and effective.

Promotion of the safety and health of the public requires reliable scientific knowledge about the risk-benefit ratio of various CAM treatments. Re-

Table. Principles of Ethical Research and Specification for Placebo-Controlled Trials*

Principle	Definition	Specification for Placebo-Controlled Trials
Social value	Clinical research must generate generalizable knowledge that can improve human health.	By enhancing scientific validity, the use of placebo increases the potential value of the research to society.
Scientific validity	Clinical research must be designed and conducted with rigorous methodology to generate reliable and valid data.	A placebo control must be required to optimize the chance of achieving a valid test of treatment efficacy.
Fair subject selection	Clinical research must not enroll preferentially vulnerable patients into risky studies or privileged patients into studies with high likelihood of benefits. Enrollment should aim primarily to achieve the scientific objectives of the research and secondarily to minimize risks, to enhance value, and to be conducted efficiently.	Children and incompetent adults should not be enrolled unless scientifically necessary and authorized by an appropriate surrogate decision maker.
Favorable risk-benefit ratio	Clinical research should be designed to minimize risks and ensure that the risks are proportional to the potential benefits to the individual subjects and the expected knowledge gained for society.	Assignment to the placebo for the duration of the study cannot pose undue risks of serious harm or discomfort, and the risks of the placebo are minimized and justified by the value of the knowledge gained.
Independent review	Independent review ensures that clinical research fulfills ethical requirements to protect subjects and ensure public accountability.	Independent review verifies the investigator's claim that the placebo is scientifically necessary and poses no undue risks.
Informed consent	Information relevant to the clinical research must be disclosed to subjects so they can understand and voluntarily consent to participate in the research.	Information disclosed must explain the use of placebo and the risks of being assigned to it.
Respect for enrolled subjects	Clinical research must respect subjects by (1) permitting withdrawal; (2) protecting privacy through confidentiality; (3) informing subjects of newly discovered risks or benefits; (4) informing subjects of the results of the research; and (5) protecting subject welfare.	Adequate procedures for monitoring subjects must be instituted to permit early termination of a study arm or substitution of standard intervention when symptoms and signs progress significantly.

*Adapted from Emanuel et al.[4]

search identifying effective and ineffective CAM treatments contributes to evidence-based medicine and can improve medical care. It can guide physicians in deciding whether to support, encourage, or counsel against CAM use by their patients. Perhaps more important, given the ready availability of many CAM products in the marketplace, compelling research findings will help consumers make more informed personal health choices. In addition, only through research will the mechanisms of action of effective alternative therapies be revealed, with the potential to enhance the understanding and treatment of disease. Finally, research on CAM can lead to discovery of new classes of drugs, as evidenced by the recent invention of a new class of antimalarial drugs from compounds found in the ancient Chinese herb *Artemisia annua*, used for treatment of chronic fevers.[8]

Validity of Placebo-Controlled Trials for Evaluating CAM

As a scientifically based practice, medicine depends on the premise that treatments should be known to be effective for preventing, curing, or relieving the symptoms of disease. The observation that patients improve after receiving treatment understandably produces the belief that the improvement was caused by the treatment. This belief, however, exemplifies the fallacy of *post hoc ergo propter hoc* (after this, therefore because of this). Improvement may be due to several factors other than treatment efficacy, including the self-limited course of a disease, waxing and waning symptoms, spontaneous remission, and the placebo effect. The randomized, double-blind, placebo-controlled trial is the most rigorous method of discriminating true treatment effects, making it the design of choice, where applicable, for evaluating the efficacy of treatments. Nevertheless, practical and ethical constraints make it impossible in some cases to use placebo controls and double-blind techniques.

Some commentators have argued that the placebo-controlled trial is not a valid or fair method for evaluating CAM treatments.[9-11] Specifically, it is claimed that the scientific techniques of treatment protocols, randomization, double-blind conditions, and use of placebo controls distort the "holistic" therapeutic milieu of CAM, which values extensive personal attention, individualized treatment selection, and the use of healing rituals. Placebo-controlled trials test the specific effects of isolated treatments. This "reductionistic" method abstracts treatment interventions from the therapeutic milieu that is integral to CAM. Accordingly, some CAM advocates have declared that placebo-controlled trials bias the evaluation of CAM, leading to the conclusion that CAM treatments are worthless because they have not been demonstrated to be superior to placebo in rigorous randomized trials.

In assessing the appropriateness of placebo-controlled trials for evaluating CAM from an ethical perspective, it is important to recognize the diversity of CAM treatments, which, like the diversity of conventional treatments, ranges from those that are readily subjected to placebo-controlled investigation to those that are not. For example, if herbal treatments have specific therapeutic efficacy, it is because of their biochemical properties. Furthermore, herbal treatments are often obtained over the counter without any consultation with a CAM practitioner,[2,12] which to a large extent obviates the concern that randomized clinical trials (RCTs) of herbal treatments would distort the therapeutic milieu of CAM. Consequently, there is no reason why the standards of evaluation appropriate for drugs should not also apply to herbal treatments. The public interest served by demonstrating that drugs are safe and effective before they are marketed applies equally to evaluation of herbal treatments, even though the current laws under which herbal products and other dietary supplements are regulated and marketed in the United States do not require proof of safety or efficacy.[13]

Conventional medicine, just as CAM does, provides treatments within a symbolic healing context by using "nonspecific" therapeutic attention and expectations.[14] This method does not preclude the value of rigorous testing of specific conventional treatment interventions, casting doubt on the thesis that such testing is inherently biased in the case of CAM treatments. It is true that RCTs that require standardized treatment for all research subjects may not be appropriate for evaluating some highly individualized CAM treatments. In these cases, CAM treatments investigated in placebo-controlled trials can be provided according to the diagnostic and therapeutic methods typical of CAM practitioners.[15,16]

Although the use of randomization, placebo controls, and informed consent for trial participation alters typical CAM practice, these same research procedures modify the treatment practice in RCTs of conventional medical therapies. There are some CAM treatments, such as spinal manipulation and hypnosis, for which blinding of patients or subjects and controls that adequately mimic the CAM treatment may not be feasible. For example, a randomized trial of hypnosis in the treatment of functional dyspepsia compared hypnosis with supportive psychotherapy plus pill placebo and with standard medical treatment (ranitidine).[17] The report of study results noted that "the supportive treatment controlled for the time spent with the patient during HT [hypnotherapy]." It does not control, however, for potentially enhanced expectations for improvement from receiving hypnosis. This difficulty in constructing adequate controls for hypnosis is not unique to this CAM intervention; it applies to most clinical trials of psychotherapy, for example.

When randomized trials cannot provide adequately masked administration of CAM therapies, careful attention must be devoted to trial design to minimize bias in outcome assessment. Use of a no-treatment control and a priori specification of a clinically significant target difference in the primary outcome can indicate whether a

CAM treatment produces genuine benefit, even if the possibility cannot be excluded that such an outcome difference is due to a placebo effect. An example of an RCT so designed compared a standard chiropractic manipulation, a technique of physical therapy, and an educational booklet for management of lower back pain.[18] Chiropractic and physical therapies were found to be only modestly superior to the booklet, which served as a reasonable proxy for a no-treatment control.

Another concern raised about evaluating CAM therapies in RCTs is the ability with this research design to evaluate the effectiveness of modalities as they are used in routine practice. Patients committed to CAM may decline to volunteer for blinded RCTs because they are unwilling to be assigned a conventional treatment comparator or a placebo. Similarly, patients who believe strongly in conventional treatments may be unwilling to submit themselves to CAM approaches. As a consequence, some CAM therapies may not be practicably subjected to placebo-controlled investigation, whereas studies that are effectively conducted may have limited generalizability. This problem of "external validity" is a generic issue for randomized trials, which is not unique to evaluating CAM. Retrospective or even prospective observational studies of routine CAM practices may provide useful data with respect to outcomes such as patient satisfaction and help to develop hypotheses for subsequent more rigorous assessment, but they do not permit valid inferences about treatment effectiveness.

Thus, strong methodologic reasons support and encourage the use of placebo-controlled trials in evaluating CAM treatments to produce the most valid and compelling efficacy data. CAM treatments mainly are used for chronic conditions, such as pain, fatigue, headache, allergies, insomnia, digestive complaints, depression, and anxiety, for which there are, at best, only partially effective conventional treatments available.[19] These conditions typically are characterized by fluctuating symptoms and high rates of placebo response observed in placebo-controlled trials. CAM (and conventional) treatments for these conditions offer symptomatic relief that usually can be measured only by subjective patient assessment. Without the use of placebo controls, clinical trials evaluating many CAM treatments will lack scientific validity, making them difficult or impossible to interpret.[20]

The knowledge derived from rigorous research that CAM treatments are better or no better than placebo or conventional treatments provides valuable information for CAM practitioners who are interested in evidence-based medicine and for their patients who desire optimal health outcomes and who typically pay the entire cost of CAM therapies because few of these practices are reimbursed by health insurance.

Ethical Requirements for Placebo-Controlled Trials of CAM

Placebo-controlled trials evoke ethical concerns when they are used to evaluate treatments for conditions with proven effective treatment.[21] Patients randomized to placebo receive neither the treatment under investigation nor a standard treatment of proven efficacy. Placebo-controlled trials despite proven effective treatment can be ethically justified if they satisfy the ethical requirements for clinical research. When specified for the context of these trials, the key ethical requirements are the following (Table): (1) scientific validity: placebo controls must be scientifically necessary to produce a valid test of treatment efficacy; (2) favorable risk-benefit ratio: assignment to placebo for the defined study duration does not pose undue risks of serious harm or discomfort, and the risks of placebo are minimized and justified by the value of the knowledge to be gained from the trial; (3) informed consent: information provided to subjects and consent documents adequately disclose the rationale for placebo and the risks of placebo assignment; and (4) respect for enrolled subjects: adequate procedures for monitoring of subjects are instituted, including explicit criteria for early trial termination and standard treatment in case of severe symptomatic worsening.[22]

Despite the existence of proven effective conventional therapies, many placebo-controlled trials of CAM treatments can satisfy these requirements. With respect to the requirement of scientific validity, a recent placebo-controlled trial of St John's wort in major depression of moderate severity is instructive.[23] Although this herbal treatment appeared to be effective in the treatment of depression of mild to moderate severity in earlier, smaller, and less well-designed trials,[24] no data suggested that it would be superior to a standard treatment in an active-controlled trial. A 2-arm active-controlled equivalence or "noninferiority" trial would have lacked assay sensitivity because it would be impossible from the results of the trial to determine whether the absence of a statistically significant difference between St John's wort and a standard antidepressant was due to the efficacy of both treatments or the ineffectiveness of both.[20] In fact, in this 3-arm trial of 340 depressed patients, neither St John's wort nor the comparator sertraline was superior to placebo on the primary outcome measure. An active-controlled equivalence trial of St John's wort without a placebo control would be ethically suspect because it would have doubtful scientific validity.

Are Treatments Worthless If They Are No Better Than Placebo?

In evidence-based medicine the RCT is considered the gold standard for assessing the value of therapies. Experimental treatments that are safe and proven effective in placebo-controlled RCTs are introduced into medical practice, new treatments that are demonstrated to be superior to a standard treatment in active-controlled trials supplant that standard treatment, and experimental or established treatments that are shown to be no better than placebo are abandoned. The reason for taking superiority to placebo as a test of

treatment value is that a treatment that is no better than placebo has no distinctive therapeutic efficacy that can outweigh the risks of physical harm or discomfort that it causes. In other words, the treatment lacks a favorable risk-benefit ratio.

The question remains whether treatments that are benign or of low risk may have clinical value despite not showing superiority to placebo, especially in conditions with no effective treatments, with conventional treatments that are only partially effective for some patients, or when conventional treatment has significant or distressing adverse effects. If the placebo effect can produce therapeutic benefit, why should it be denied to patients who have no better alternatives? Some commentators have speculated that CAM treatments produce enhanced placebo effects because of healing rituals and extensive personal attention of CAM therapists.[19,25] Kaptchuk[19] poses the question, "Should a person with chronic neck pain who cannot take diazepam because of unacceptable side effects be denied acupuncture that may have an 'enhanced placebo effect' because such an effect is 'bogus'?"

As this question suggests, the answer depends, in part, on whether the placebo effect is real. The placebo response rate in RCTs is often erroneously assumed to represent therapeutic benefit produced by the placebo intervention.[26] The fallacy of *post hoc ergo propter hoc* needs to be considered with respect to putative placebo effects of CAM or conventional treatments. The observed improvement of patients randomized to placebo in RCTs ("the placebo response") may be attributed to factors independent of the placebo intervention or the therapeutic milieu, such as natural fluctuations in symptoms of the condition, spontaneous remission, and biased subjective reports by trial participants.[27] RCTs comparing a treatment with a placebo control and a no-treatment group can help discriminate true placebo effects.[27,28] A recent meta-analysis of 114 such trials casts doubt on the reality or therapeutic power of the placebo effect across a wide range of medical conditions.[29] However, evidence of therapeutic placebo effects was indicated for studies evaluating treatments of pain and for studies with continuous subjective outcomes. Several of the included trials evaluated CAM therapies, but these were not analyzed separately.

The most compelling evidence that the effects of CAM or conventional treatments are a direct result of placebo effects would derive from RCTs with 3 or more arms showing that patients randomized to a treatment have superior outcomes to those randomized to no treatment, even though the treatment is no better than placebo. For example, a single-blind placebo-controlled trial randomized 593 pregnant women with symptoms of nausea and vomiting to individualized acupuncture needling according to the principles of traditional Chinese medicine, acupuncture at only the Pericardium 6 point, sham acupuncture, and a no-acupuncture control group.[30] At the end of the 4-week study period, the acupuncture and sham acupuncture groups had statistically better outcomes in terms of nausea and dry retching compared with the no-acupuncture control group, but there were no significant differences between the acupuncture and sham acupuncture groups. A similar pattern of results was observed in a randomized trial of traditional acupuncture, sham acupuncture, and no acupuncture for patients with chronic lower back pain.[31]

These results indicate, but do not conclusively demonstrate, a therapeutic placebo effect of acupuncture. The inclusion of the no-treatment group in the study controls for the natural history of the condition under investigation but not for the possibility of biased outcome ratings.[27] The patients randomized to a no-treatment control group in such studies necessarily will know that they did not receive the treatment under investigation. Those receiving real or sham acupuncture may have reported less nausea and dry retching (or less pain) to "please" the investigators or because they believed that they should have improved as a result of acupuncture; those in the no-acupuncture control group may have negatively biased their report of symptoms because of disappointment in not receiving this treatment. Accordingly, randomized trials showing that a CAM or conventional treatment is superior to a no-treatment control group, though no better than a placebo, suggest but do not prove that these treatments have efficacy as placebo therapies. On the other hand, if the patients in the no-treatment groups do just as well as individuals randomized to the real or placebo treatments, then the evidence indicates that the CAM or conventional treatment lacks therapeutic value.

Is there a legitimate role within evidence-based medicine for low-risk CAM approaches, such as acupuncture, or conventional treatments that have therapeutic benefit caused primarily if not entirely by a positive placebo effect, as indicated by rigorous RCTs? Arguably, such treatments are effective according to evidence-based standards when they have been demonstrated to be superior to no-treatment controls in randomized trials. They may be considered to offer a favorable risk-benefit ratio for patients, provided that there are no better standard therapeutic options or they refuse standard conventional treatment of proven efficacy. Whether validated placebo treatments would warrant insurance coverage is a further but separate issue.[32]

Analysis and discussion are needed to examine whether some CAM and conventional treatments produce genuine, clinically valuable placebo effects. Critical to this inquiry is consideration of study designs and techniques of outcome measurement that can eliminate or minimize the potential for bias in randomized trials with placebo and no-treatment arms aimed at elucidating the placebo efficacy of treatments. In addition, research is needed to study the placebo effect and to test the hypothesis that some treatments produce enhanced placebo effects. Such

studies have now begun through a targeted placebo research initiative implemented collaboratively by multiple NIH institutes.[33] A better understanding of the placebo effect has the potential to improve medical care.

The prospect of validating some CAM and conventional treatments as placebo therapies should not be understood as diminishing the importance of evaluating whether they are superior to placebo. Treatments with specific efficacy have greater clinical value than those that produce therapeutic benefit solely by means of the placebo effect. Moreover, enhanced scientific value is likely to accrue from identifying treatments that produce superior outcomes to placebo. For example, RCTs demonstrating that antidepressant medications are superior to placebo have stimulated extensive research on the role of neurotransmitters in the pathophysiology of mood and anxiety disorders and the mechanism of action of these treatments.[34] They have also been instrumental in prompting investigations of whether polymorphisms in the serotonin transporter gene are associated with susceptibility to depression.[35] As with conventional treatments, the identification of CAM treatments that have specific efficacy holds similar promise for advancing the understanding and treatment of disease.

Conclusion

Growing use of CAM treatments in the United States and increased appreciation of the role of traditional, indigenous healing practices in developing nations necessitate rigorous, ethically sound clinical research to assess their therapeutic value. The standards of evidence-based medicine, developed over the years to understand and evaluate conventional medical therapies, apply equally to CAM. The arguments that placebo-controlled RCTs are not appropriate for evaluating most CAM treatments lack merit. Although the use of placebo-controlled trials raises ethical concerns when proven effective treatment exists for the condition under investigation, they are ethically justified, provided that stringent criteria for protecting research subjects are satisfied. Conceptual and empirical research should focus on whether CAM and conventional treatments that are demonstrated to be no better than placebo may still have therapeutic value, provided that their risks are minor and their benefit can be reliably attributed to the placebo effect.

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REFERENCES

1. Ni H, Simile C, Hardy AM. Utilization of complementary and alternative medicine by United States adults: results from the 1999 National Health Interview Survey. *Med Care.* 2002;40:353-358.

2. Eisenberg D, Davis RG, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA.* 1998;280:1569-1575.

3. National Center for Complementary and Alternative Medicine. Available at: http://www.nccam.nih.gov. Accessed December 9, 2003.

4. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA.* 2000;283:2701-2711.

5. Astin JA. Why patients use alternative medicine: results of a national study. *JAMA.* 1998;279:1548-1553.

6. De Smet PAGM. Herbal remedies. *N Engl J Med.* 2002;347:2046-2056.

7. Ernst E, Thompson Coon J. Heavy metals in traditional Chinese medicines: a systematic review. *Clin Pharmacol Ther.* 2001;70:497-504.

8. Marshall E. Reinventing an ancient cure for malaria. *Science.* 2000;290:437-439.

9. Walach H. The efficacy paradox in randomized controlled trials of CAM and elsewhere: beware of the placebo trap. *J Altern Complement Med.* 2001;7:213-218.

10. Thorne S, Best A, Balon J, Kelner M, Rickhi B. Ethical dimensions in the borderland between conventional and complementary/alternative medicine. *J Altern Complement Med.* 2002;8:907-915.

11. Fabrega H. Medical validity in eastern and western traditions. *Perspect Biol Med.* 2002;45:395-415.

12. Mills S. Herbal medicine. In: Lewith G, Jonas WB, Walach H, eds. *Clinical Research in Complementary Therapies.* Edinburgh, Scotland: Churchill Livingstone; 2002:211-227.

13. *Dietary Supplement Health and Education Act of 1994*. Washington, DC: US Government Printing Office; 1994. Publication 03-417.

14. Moerman DE, Jonas WB. Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med.* 2002;136:471-476.

15. Levin JS, Glass TA, Kushi LH, Schuck JR, Steele L, Jonas WB. Quantitative methods in research on complementary and alternative medicine. *Med Care.* 1997;35:1079-1094.

16. Bonne O, Shermer Y, Gorali Y, Katz M, Shalev AY. A randomized, double-blind, placebo-controlled study of classical homeopathy in generalized anxiety disorder. *J Clin Psychiatry.* 2003;64:282-287.

17. Calvert EL, Houghton IA, Cooper P, Morris J, Whorwell PJ. Long-term improvement in functional dyspepsia using hypnotherapy. *Gastroenterology.* 2002;123:1778-1785.

18. Cherkin DC, Deyo RA, Battie M, Street J, Barlow W. A comparison of physical therapy, chiropractic manipulation and provision of an educational booklet for the treatment of patients with low back pain. *N Engl J Med*. 1998;339:1021-1029.

19. Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of healing ritual have clinical significance? *Ann Intern Med.* 2002;136:817-825.

20. Temple R, Ellenberg SE. Placebo-controlled trials and active-control trials in the evaluation of new treatments: part 1: ethical and scientific issues. *Ann Intern Med.* 2000;133:455-463.

21. Rothman KJ, Michels B. The continuing unethical use of placebo controls. *N Engl J Med.* 1994;331:394-398.

22. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials: a middle ground. *N Engl J Med.* 2001;345:915-919.

23. Hypericum Depression Trial Study Group. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA.* 2002;287:1807-1814.

24. Whiskey E, Werneke U, Taylor D. A systematic review and meta-analysis of *Hypericum perforatum* in depression: a comprehensive clinical review. *Int Clin Psychopharmacol.* 2001;16:239-252.

25. Brody H. *The Placebo Response*. New York, NY: Cliff Street Books; 2000:143-150.

26. Hrobjartsson A. What are the main methodological problems in the estimation of placebo effects? *J Clin Epidemiol.* 2002;55:430-435.

27. Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? *J Clin Epidemiol.* 1997;12:1311-1318.

28. Ernst E, Resch Kl. Concept of true and perceived placebo effects. *BMJ.* 1995;311:551-553.

29. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? an analysis of clinical trials comparing placebo with no treatment. *N Engl J Med.* 2001;344:1594-1602.

30. Smith C, Crowther C, Beilby J. Acupuncture to treat nausea and vomiting in early pregnancy: a randomized controlled trial. *Birth.* 2002;29:1-9.

31. Leibing E, Leonhardt U, Koster G, et al. Acupuncture treatment of chronic low-back pain: a randomized, blinded placebo-controlled trial with a 9-month follow-up. *Pain.* 2002;96:189-196.

32. Boozsang KM. Is the alternative medicine? managed care apparently thinks so. *Conn Law Rev.* 2000;32:567-613.

33. Department of Health and Human Services. Elucidation of the underlying mechanisms of placebo effect [National Institutes of Health Web site]. Available at: http://grants1.nih.gov/grants/guide/rfa-files/RFA-AT-02-002.html. Accessed December 9, 2003.

34. Insel TR, Charney DS. Research on major depression: strategies and priorities. *JAMA.* 2003;289:3167-3168.

35. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003;301:386-389.