

supply,¹ for the combination of 25 mg B₆, 0.4 mg B₁₂, and 2.5 mg folic acid, the estimated treatment effect on risk of ischemic stroke, coronary heart disease, or death was a 3% decrease (95% CI, -16% to 12%). Thus, although no statistically significant effect was evident, we could not rule out a modest effect in this population.

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1. Amendment of standards of identity for enriched grain products to require addition of folic acid: clarification, 61 *Federal Register* 173 (1996).

Ethical Issues in Research in Complementary and Alternative Medicine

To the Editor: In their Special Communication, Dr Miller and colleagues¹ stressed the need for studies that can identify whether complementary and alternative medicine (CAM) treatments produce clinically valuable placebo effects. They argued that such studies should control for the natural progression of disease, and should use objective rather than subjective outcomes.

We disagree with the authors, however, that trial designs must include both placebo-control and no-treatment arms to demonstrate placebo effects. Rather, we propose a simpler design, comprising 2 parallel, blinded trials with different proportions of participants randomized to active-treatment and placebo groups in each of the 2 trials. Participants would be informed of these proportions during informed consent, and thus those in the trial with a higher likelihood of receiving treatment would have higher expectations regarding their probable outcomes. If CAM has placebo effects, participants randomized to active-treatment and placebo groups in the trial in which a higher proportion are treated would be expected to manifest better outcomes than those randomized to active-treatment and placebo groups, respectively, in the trial in which a lower proportion receive active treatment. The magnitude of the placebo effect may be calculated by estimating the rate at which outcomes improve with the proportion treated and by contrasting projected outcomes in 2 hypothetical trials: 1 with zero participants treated and 1 with all participants treated.

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1. Miller FG, Emanuel EJ, Rosenstein DL, Strauss SE. Ethical issues concerning research in complementary and alternative medicine. *JAMA*. 2004;291:599-604.

To the Editor: While we concur with Dr Miller and colleagues¹ that the evidence for making practice and public health decisions in CAM should come from large, double-blind, randomized controlled trials (RCTs), we believe there are 2 key ethical issues in CAM research that the authors should have addressed. First, who determines the “social value” of CAM research? Second, use of the terms “placebo” and “non-specific” ignores the complexity of clinical responses found when delivering therapies in a rich and meaningful context.

The widespread use of CAM is a public health issue. Consequently, the public should have a role in determining its research focus and priorities. The ethical need for a systematic process to obtain input and priorities by the public and CAM practitioners has been extensively discussed elsewhere.²⁻⁴ These discussions call for an expanded vision of research quality that answer questions beyond those of “efficacy.” In other words, CAM research requires the highest standards of rigor, including meeting the quality criteria of “model validity.”⁵

Ethical and methodological complexities of CAM research interact in complex ways. For example, one treatment may be contextually rich in ritual and meaning but deliver only a small benefit from its hypothesized “specific” effect. In contrast, a second treatment may be contextually simple but provide a larger hypothesized specific effect. If the RCT is the only standard of “social value,” then the second treatment would appear superior. For CAM therapies with minimal risk and a caring component, however, patients may actually prefer the first. By holding to a hierarchy of evidence with the RCT on top, and by having researchers independently decide what hypotheses will be used to determine when an effect is “nonspecific,” an artificially constructed environment with limited public input then determines the “social value” of medical research. In doing so, scientists usurp their ethical obligation to the public—those who stand to benefit or come to harm from the use of CAM.

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To the Editor: We agree with Dr Miller and colleagues¹ that any therapy should be evaluated by the most rigorous and feasible methods possible. We do not entirely agree, however, with their assertion that therapies might be considered legitimate entirely by virtue of their placebo effect. The authors argued that the basis of using placebo controls has to do with demonstrating risk-benefit ratio. In fact, the primary reason for using placebo controls has to do with establishing a specific causal relationship between a therapy and outcome; ie, whether an intervention has scientific veracity. Placebo controls account for other factors that influence outcomes.

It remains unclear exactly which factors contribute to a placebo effect² or even whether placebos have any significant clinical effects.³ With more evidence, it might be ethically appropriate to combine any identifiable placeboogenic factors with already proven specific therapies. This would mean using factors that promote nonspecific healing to enhance specific curative treatment instead of adopting placebo therapies separately. Condoning pure ritual without specific effects (aside from the ethical and compassionate norms of the patient-physician relationship) within evidence-based medicine may undercut medicine's scientific and ethical foundations. Patients could seek their rituals elsewhere. It is possible that the outcome of such healing rituals may actually be enhanced in the nonscientific environment in which most alternative therapies are delivered.⁴

Also, the authors claimed that mechanistically investigating proven therapies is more likely to rapidly advance science than is investigation of placebo effects. We are not as sure. They cited the example of the recent discovery of a possible connection between polymorphisms in the serotonin transporter gene and susceptibility to depression. In fact, this polymorphism may also be associated with placebo responses.⁵ Learning how to enhance medical outcomes via placebo research could have a critical positive impact on health care and scientific knowledge. Including fictive interventions might not be as beneficial.

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1. Miller FG, Emanuel EJ, Rosenstein DL, Strauss SE. Ethical issues concerning research in complementary and alternative medicine. *JAMA*. 2004;291:599-604.
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To the Editor: Dr Miller and colleagues¹ concluded that CAM has no scientifically proven effects and thus argued that it cannot be used as a placebo treatment. I would go a step further

and suggest that placebo should not be used to treat patients in any form. The use of placebo always requires some form of lying to the patients, which is both ethically and logistically problematic.

Furthermore, placebo response may not be predictable in individual patients, and thus there is little rational basis on which to prescribe it in general.

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1. Miller FG, Emanuel EJ, Rosenstein DL, Straus SE. Ethical issues concerning research in complementary and alternative medicine. *JAMA*. 2004;291:599-604.

To the Editor: Dr Miller and colleagues¹ categorized the acupuncture study by Smith et al² as "negative" because the difference between sham and active acupuncture treatments was not statistically significant. Lewith and Vincent,³ however, argued that sham acupuncture is a weak active treatment, as suggested in this case by the lag in anti-nausea effect between the sham and the 2 active treatments. Women receiving the highest dose of acupuncture (ie, the traditional acupuncture group) reported significantly less nausea throughout the trial. Women receiving the next highest dose of acupuncture reported significantly less nausea from the second week in the trial, while women receiving the lowest dose of acupuncture (ie, sham acupuncture) reported significantly less nausea from the third week in the trial.

Although the authors could have cited high-quality RCTs with positive results,⁴ they reported that most trials have negative results. Linde and Willich⁵ point out that different systematic reviews have reached different conclusions about the efficacy of CAM.

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1. Miller FG, Emanuel EJ, Rosenstein DL, Straus SE. Ethical issues concerning research in complementary and alternative medicine. *JAMA*. 2004;291:599-604.
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In Reply: Drs Cantor and Malani claim that placebo effects can be demonstrated by comparing a pair of 2-arm trials of active treatment vs placebo that have different proportions of participants randomized to receive active treatment. This is an interesting speculation; however, we are unaware of any data to support this claim or to indicate that this design is just as able, or more able, to discriminate placebo effects than would be a

3-arm trial comparing active treatment, placebo, and no treatment. Their alternative design may suggest placebo effects but still leaves open the critical question of whether either the active treatment or placebo-control is better than no treatment.

Dr Jonas and colleagues question who determines the social value of CAM research and advocate for public input. For biomedical research in general, the public's position on an approach is expressed through participation on institutional review boards, data and safety monitoring boards, and certainly in their willingness to serve as research participants. In the case of government agencies, such as the National Center for Complementary and Alternative Medicine, the research mission and budget is accountable to elected representatives of the public. Moreover, their research priorities are set with the approval of their chartered national advisory councils, whose members are appointed by the Secretary of the Department of Health and Human Services and include representatives of diverse stakeholder groups including patient advocates.

We argued for placebo-controlled trials of CAM treatments, when they are feasible, but did not argue that this is the only valid research design. Active-controlled superiority trials evaluating 2 CAM therapies or a CAM therapy vs a conventional treatment would also provide valuable and valid data. An adequately powered, randomized, active-controlled trial would demonstrate the superiority of their proposed first treatment over their second.

The legitimacy of recommending low-risk therapies that benefit patients solely or mainly by virtue of the placebo effect is controversial but deserves further inquiry and debate. We agree with Drs Kaptchuk and Lembo that well-designed research is needed to assess the potential clinical benefits of placebo treatments and better understand the mechanisms that account for placebo effects.

We disagree with Dr Marusic that it is necessary to lie to patients when recommending a treatment that is believed to work by virtue of a placebo effect. If solid evidence exists to support the efficacy of a placebo, the clinician can truthfully communicate to the patient that the treatment has been found to be superior to no treatment in relieving symptoms.

We disagree with Dr Millea that we misinterpreted the findings of the study by Smith et al regarding acupuncture to treat nausea and vomiting in early pregnancy.¹ His claim that we over-reported negative studies of CAM misses the point of our article, which was to examine ethical issues relating to rigorous research on CAM. We selected specific studies to illustrate methodological and ethical issues; we were not attempting a systematic review or meta-analysis of the evidence for the therapeutic value of specific CAM treatments.

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RESEARCH LETTER

Nutritional Content of Hospital Diets

To the Editor: Hospitalized elderly patients have a relatively high risk for malnutrition.¹ While some of this problem may be related to factors such as preexisting malnutrition, lack of appetite, or inability to eat, it is not known to what degree clinically indicated restricted diets contribute to such deficiencies.

Methods. We analyzed commonly prescribed diets served in 2 US hospitals. One was a large private not-for-profit academic research-oriented medical center serviced by a well-known commercially contracted hospital food service and the other was a large metropolitan Veterans Affairs medical center with an in-house dietary department. Amounts of ingredients for recipes for every item served in the 7 prescribed meal plans in both hospitals were recorded in a comprehensive database that allowed precise nutritional analyses by weight of food serving. The data included ingredients used in literally thousands of recipes; for instance, 1 hospital had more than 50 different recipes for green beans. Nutritional information supplied by the manufacturer of prepackaged foods was used when available.

To analyze these meals, we weighed each item with an electronic scale accurate to the nearest 0.1 g. Two weeks of breakfast, lunch, and dinner meals made up of standardized portion sizes for each prescribed diet were analyzed for daily nutrient content using the United States Department of Agriculture Database, 1997. The Nutritionist V nutrition analysis software package (First Databank Inc, San Bruno, Calif) was used for data analysis.

Results. The FIGURE displays the amount of nutrients supplied each day by the different diets in relation to published age-specific minimum daily intake requirements. Although most diets supply adequate energy, protein, and vitamin A, they are generally deficient in terms of a number of additional vitamins and minerals.

Conclusion. Hospital-prescribed diets, especially the restricted diets, may often lack important nutrients. Nutrient deficits in hospital meals could have serious consequences for elderly patients, especially those hospitalized for extended periods. Older patients frequently present with advanced nutritional deficiencies and, when hospitalized, rarely eat everything they are served. Moreover, age-, disease-, or treatment-related changes

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