For calcium, pick milk over marketing

Dr. Walter P. Bobechko ("Calcium supplementation for the nation," *Can Med Assoc J* 1997;156: 1269) suggests that calcium be added to juices and beverages to prevent osteoporosis, as is done in the US. To those of us who have studied the dietary trends in the US for a long time, and tend to view them with a great deal of suspicion, this idea appears to be little more than a marketing gimmick, like the food industry's "no cholesterol" scam, which frightened millions of consumers away from fresh (low-profit) farm foods and convinced them that manufactured (high-profit) replacements, particularly "fortified" products, are actually healthier.

Adding calcium to a product that does not normally contain it, or very much of it, does not necessarily increase the product's overall nutritional value. Calcium is best obtained from whole milk and other full-fat dairy foods. These foods provide the companion nutrients (vitamins and fatty acids) needed for the calcium to be absorbed, retained and fully utilized. Low-fat and fat-free dairy products are not "healthier" than unaltered products; many are worthless.

The defatted products tend to be lacking in taste as well; hence the massive increase in soft drink sales as milk consumption has plummeted in recent years. Dental health surveys in our schools are already finding more cavities (which predicts an even greater increase in osteoporosis in the future), not because there is no calcium in our orange juice, but because there is no fat in our milk.

Should our federal government be striving to harmonize health policies with those of the US, where half of the population is obese, where coronary artery disease is still the number-one killer, where diabetes is called an epidemic, and where cancer rates are the highest in the world and still climbing? I think not.

Thomas Anderson, PhD
Summerland, BC

Questioning tests for AMI

In the touching article "Death by coronary" (*Can Med Assoc J* 1997;156:1733-4), by Dr. David Rapoport, I was surprised to read that his friend, who had just suffered acute myocardial infarction, was "stress-tested and thallium-scanned" as soon as she was admitted to the coronary care unit. I challenge the wisdom of subjecting a patient in the acute stage of myocardial infarction to such procedures; they were not only unnecessary but also hazardous.

I note that this article was peer reviewed, but the reviewer did not spot this error in judgement.

Tsung O. Cheng, MD
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[The editor-in-chief responds:]

Dr. Cheng seems to have missed the forest but found a tree. The author of the article was not writing a treatise on the management of coronary disease; he was simply writing about the loss of a friend and his own experience of bypass surgery. In choosing peer reviewers, we pick those with expertise and interest in the subject matter of the manuscript. I doubt that even an astute cardiologist would have been able, from the clinical information provided in the paper, to make the judgement that the treatment was "unnecessary [and] . . . hazardous."

John Hoey, MD
Editor-in-Chief
CMAJ

The placebo effect

I was glad to note that the authors of the article "Bioethics for clinicians: 10. Research ethics" (*Can Med Assoc J* 1997;156:1153-7) mention the special circumstances involved when incompetent patients are recruited into clinical studies. In the population of cognitively impaired frail elderly people, this is a critical issue. If we exclude these patients en masse from all clinical trials, how can we turn around and generalize studies to this special population?

I find the ethics of placebo-controlled studies difficult to deal with. The authors state that, when studying a condition for which standard treatment exists, "it is unethical (since placebo is an inferior 'treatment') to expose patients to the risk of 'treatment' with placebo alone." Although the concept of clinical equipoise is powerful and easily understood, I wonder what the precise role of placebo-controlled studies is. As new drugs are developed and marched through phase I and II studies, it is not difficult to find circumstances in which they should be compared with placebo to show their efficacy. We cannot justify large, phase III clinical trials that are placebo-controlled when standard therapy exists, but what about earlier-stage studies? When developing drugs, one cannot always compare them with standard therapy at the outset. And yet, without placebo-controlled trials, can we ever bring new drugs that are superior to standard therapy into clinical use?

Shabbir M.H. Alibhai
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Received via email

[One of the authors responds:]

Dr. Alibhai asks a good question: When are placebo controls ethically acceptable and scientifically

necessary in clinical research? At the start of a clinical trial, a state of clinical equipoise must exist; that is, there must be genuine disagreement among expert practitioners as to the preferred treatment.[1] A nonvalidated treatment may be compared with a placebo control if (1) no standard therapy exists, (2) standard therapy exists but it has been shown to be no better than placebo, (3) standard therapy is placebo, (4) standard therapy is toxic and of marginal benefit, or (5) validated treatment exists but is not available because of cost or limited supplies.[2] Two special circumstances deserve to be made explicit. Placebo controls are appropriately used when the new, nonvalidated treatment is an "add-on" to standard therapy (so that the comparison is standard therapy plus new drug versus standard therapy plus placebo) or when the study population is restricted to persons whose disease has not responded to standard treatment and for whom no second-line standard treatment exists.[3]

The ethical issue is no different for phase 1 and phase II clinical trials. In my experience, the use of placebo controls is unusual in such trials. These studies enrol small numbers of patients and thus comparison with a control, placebo or otherwise, is unlikely to have sufficient statistical power. Phase I trials evaluate the toxicity and pharmacodynamics of new drugs and most often involve healthy subjects. In such cases, the risks to the subjects are justified by the importance of the knowledge likely to be gained, even though no therapeutic benefit is expected.[4] Because of the toxicity of anticancer agents, phase I cancer studies typically involve patients for whom no effective therapy exists. In either case, and assuming the design of the study required the use of a control, a placebo control would be ethically unproblematic. Phase II trials seek to establish whether a nonvalidated treatment is efficacious for a particular condition, so actual patients are enrolled. The use of a placebo control (again, assuming that the study design necessitates a control) would have to meet the conditions laid out in the first paragraph.

All too often clinical trials performed as part of the drug-approval process in Canada subject research participants to placebos despite the existence of effective treatment. Not only is this practice unethical, but it exposes researchers and institutions to legal liability.[5] Researchers, research ethics boards, pharmaceutical companies and the Health Protection Branch of Health Canada must work together to ensure that new-drug research meets the highest ethical and scientific standards.

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