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## Investigating CAM

John Hoffer invokes homeopathy as an example of how medical scientists set a higher bar for proof of efficacy for complementary or alternative medicine (CAM).[1] Rather than describing this as a "complication," it might be better understood as an entirely appropriate response to extraordinary claims of any sort. "Evidence" of effectiveness can be found for any treatment, no matter how arcane. The question is how good the evidence is, in light of well-established scientific principles. In the case of homeopathy, we must ask whether chance and poor experimental design can explain positive results obtained in randomized controlled trials (RCTs) of homeopathy or whether RCTs with negative results (usually done by non-advocates of this type of therapy) but accompanied by a vast and well-established body of scientific evidence are in fact in error.

Hoffer also mentions St. John's wort and glucosamine as therapies of established efficacy. However, although positive RCTs of St. John's wort exist, the most rigorous studies (placebo-controlled and randomized, with proper case definitions and a treatment-responsive population) indicate no benefit.[2-6] Glucosamine enjoys the support of over 14 RCTs,[7] but critical reviewers will be concerned about the fact that almost all of these were conducted with funding from purveyors of this compound. Publication bias therefore appears to play a role.

Hoffer's call for funding to be directed to case reports and series on CAM therapies as a way of "grooming" them as candidates for RCTs may simply result in a situation in which nothing new is learned. Why? Because uncontrolled and nonrandomized trials are poorly suited for investigating the subjective or "soft" outcomes that CAM therapies so often promise to deliver. Randomization, placebo control and blinding limit the effect of precisely those biases that are likely to explain the "effects" of CAM therapies.

A brief glance through PubMed reveals a plethora of clinical CAM trials. The fact that so many have been done (over 2000 in the case of acupuncture) without producing any clear examples of valid new therapies not only indicates that research money is available but also that it might be better directed.

Why the evaluation of scientifically implausible therapies should be a priority of any magnitude remains an open question. One could argue that some funds should be spent to ensure that prevalent therapies be investigated for safety and drug interactions. Yet research funds are scarce as it is, and the public would be poorly served if money were deliberately funnelled into treatments already recognized as implausible.

**Lloyd B. Oppel**
Physician
University of British Columbia Hospital
Vancouver, BC

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**[The author responds:]**

I applaud Lloyd Oppel's objection to wasting money testing highly implausible therapies, but it seems to me that he is missing the bigger picture. Important new ideas often seem implausible at their inception. The goal of therapeutic research should be to generate important, novel (and hence, at the outset, implausible) ideas, find out which of them may actually be correct, and then gather definitive evidence one way or the other. My article[1] outlined a practical, low-cost strategy for determining which complementary and alternative medicine (CAM) approaches are plausible enough to justify a thorough and fair evaluation.

Government and nongovernment funding agencies have taken the position that CAM merits evaluation. Furthermore, CAM may infuse important new ideas into medicine at a time when much of our mainstream therapeutic research agenda serves the pharmaceutical industry.

Glucosamine sulfate is a safe, inexpensive and potentially useful therapy for osteoarthritis[2] that is especially interesting because it is clinically plausible but biologically implausible. We recently proposed that sulfate, rather than glucosamine, could mediate its beneficial effects.[3]

Oppel cites 2 negative RCTs of St. John's wort in depression. The first was restricted to patients with severe, chronic depression, and its authors suggested that people with milder and less chronic disease might have done better.[4] In the second trial, also restricted to patients with major depression, St. John's wort fared no worse than the established treatment, sertraline.[5] One might conclude that severely depressed patients — especially those referred to specialty units and in whom standard antidepressants fail — are unlikely to respond to St. John's wort.

Oppel misunderstands my point about the role of plausibility in setting standards of evidence. If is often said that there is no difference between

CAM and conventional therapies; rather, there are only therapies that either work or don't work. The reality is that scientifically oriented physicians accept a lower standard of evidence for adopting a therapy they consider scientifically plausible.

**L. John Hoffer**
Sir Mortimer B. Davis – Jewish General Hospital
Montréal, Que.

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## *CMAJ* on the Web

The article on diagnosing and treating diabetic ketoacidosis and the hyperglycemic hyperosmolar state[1] was very informative. I especially appreciate the fact that neither a subscription nor membership in the Canadian Medical Association is required to download articles from the *CMAJ* Web site. This is helpful to those of us who are unable to subscribe to the journal.

**Antonio P. Ligot**
General Surgeon and Hospital Director
Good News Clinic & Hospital
Banaue, Ifugao
The Philippines

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## Should cost-effectiveness take the blame?

Amiram Gafni and Stephen Birch,[1] in their excellent article on the importance of opportunity costs, posit that the uncontrolled growth in expenditures of the Ontario Drug Benefits Program (ODBP) is attributable to the use of the incremental cost-effectiveness ratio (ICER) of interventions, without consideration of opportunity costs, in the development of policy recommendations. The program's failure to control expenditures leads the authors to conclude that "simple tools such as the ICER represent a departure from the economics discipline and hence they fail to address the decision-makers' problems."

While cost-effectiveness is indeed frequently misused, this particular conclusion does not seem justified. The real cause of the "uncontrolled growth in expenditures" of the ODBP is surely the belief of its administrators that their resources will, in fact, not be limited. That they are justified in this belief is evidenced by the fact that the government allows the program's expenditures to grow by 10% to 15%, year after year, as reported by Laupacis.[2] Only if resources were limited and the program's budget fixed would it be necessary to consider opportunity costs. As long as administrators of the program are allowed to increase expenditures, it is entirely appropriate that they should try to get the best value for those resources by considering the ICER of each potential addition to the program. Indeed, it is the continuing failure of governments and their electors to forgo any health technology capable of bringing any benefit that is the real cause of the uncontrolled growth in expenditures.

**Maurice McGregor**
Professor Emeritus
Department of Medicine
McGill University
Montréal, Que.

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**[The authors respond:]**

We disagree with Maurice McGregor's suggestion that the real cause of the uncontrolled growth in expenditures of the Ontario Drug Benefits Program (ODBP) is the belief on the part of the program's administrators that their resources will not be limited. McGregor's letter indicates confusion between the case of unlimited resources and the case in which resources are allowed to grow. In a world with unlimited resources, there is no scarcity and thus choices need not be made between different programs (i.e., there are no opportunity costs). In this situation, maximizing total health improvements requires only information on effectiveness; no information about costs is needed. In contrast, in the situation where program resources (such as those for the ODBP), even if scarce, are allowed to increase, choices will be needed: the additional resources must be taken from elsewhere, and those resources are insufficient to support all new interventions. Contrary to McGregor's claim, the information provided by the incremental cost-effectiveness ratio (ICER) is insufficient to identify the efficient use of additional resources (see Appendix 1 to our commentary[1]). Only by considering opportunity costs can the "best value for those resources" be determined.

McGregor's assessment that ODBP administrators believe that resources "will, in fact, not be limited" is not supported by evidence. In his description of the decision-making process of the ODBP, Laupacis stated, "Given that resources for health care are limited, it seems sensible . . . that cost-effectiveness is the main criterion used to determine which drugs are reimbursed from the public purse."[2] Administrators were led to believe that selecting programs on the basis of ICER values would maximize total health improvements from whatever resources were made available. Decision-