

Complementary and alternative medicine in 2006: optimising the dose of the intervention

If experimental conditions are not optimised, correct interpretation of results is difficult

Many people throughout the world use complementary and alternative medicine (CAM). In the United States, for example, a survey of 31 044 adults aged 18 years or older indicated that 36% had used some form of CAM in the previous 12 months.¹ This widespread use was one reason why, in 1998, the US Congress established the National Center for Complementary and Alternative Medicine (NCCAM) to conduct rigorous research on CAM practices. CAM includes the use of dietary supplements and other natural products; manipulative interventions such as massage; mind–body approaches such as meditation; energy interventions such as acupuncture; and whole medical systems such as traditional Chinese medicine. NCCAM's mission includes disseminating authoritative information to the public and professional communities concerning which CAM practices are safe and effective and which are not.

The use of dietary supplements and natural products is the most widespread CAM practice in the US.¹ Thus, one initial approach taken by NCCAM was to sponsor large trials of supplements using doses representative of those commonly used.² The rationale included the concern that if the common dose is unsafe, it would be important to alert the public. Moreover, these doses were often used in smaller, less well-controlled studies. However, NCCAM found that this is not an optimal research strategy. As NCCAM defines its priorities and strategies for the next few years,³ we recognise that reinvestigation and optimisation of customary procedures, especially dose, is needed if NCCAM is to make informed statements.

Is optimisation of CAM interventions needed?

It is tempting to accept that the widespread use of CAM signifies that these interventions, as customarily used, are beneficial and safe, and the only research needed is a confirmatory study of customary procedures. Over the past few years, we have recognised these assumptions are often incorrect, largely because of the placebo effect, publication bias, and the inherent complexity of clinical interventions.

The placebo effect refers to psychological or physiological changes associated with inert substances or “control” procedures. Placebo effects can be substantial. In an NCCAM-sponsored study on major depression, sertraline (a drug licensed for treatment of depression) was effective in 49% of patients: 25% had full responses and 24% had partial responses. However, placebo was equivalently effective: 43% of patients responded (32% full and 11% partial).⁴ In a non-NCCAM study, arthroscopic surgery for osteoarthritis of the knee (a procedure used before then on 34 000 patients per year in the US) was no more effective than sham surgery.⁵ Given the ubiquity and strength of placebo effects, the effectiveness of some CAM practices, as with some other health treatments, may be, at least partially, due to that effect rather than to specific efficacy of the intervention.

Publication bias results in negative studies appearing less often in the literature, so that reviews in some journals give an overly positive view of CAM effectiveness.

In addition, the literature is unlikely to be conclusive because the manner in which an intervention is commonly used is unlikely to optimise the many factors that together could make an intervention successful. A good example of the difficulty of making correct choices is that of echinacea for the common cold. People could take echinacea for prevention or for treatment of colds; use any of three *Echinacea* species; take an extract of the roots, or the stems, or the flowers, prepared by any of three procedures; and use any of at least three doses. It is very unlikely that public use has identified the correct clinical indication and the correct echinacea formulation without these parameters being systematically evaluated. In this situation, even well-designed large trials⁶ may fail to show efficacy.

Lack of efficacy of a CAM modality in a given study, coupled with uncertainty about optimal experimental conditions in that study, creates a serious problem in interpretation, and this has practical consequences. If the negative results pertain only to the particular study conditions, more work can be done in the expectation that a positive result will eventually emerge. If conditions are optimal and the results pertain to the intervention generally, the efficacy of the intervention could be more justifiably questioned. Early “negative” results present a particular challenge for CAM, given that some people are very sceptical of the field in general, and will seize upon early results of such trials as demonstrating that a CAM treatment is ineffective entirely.

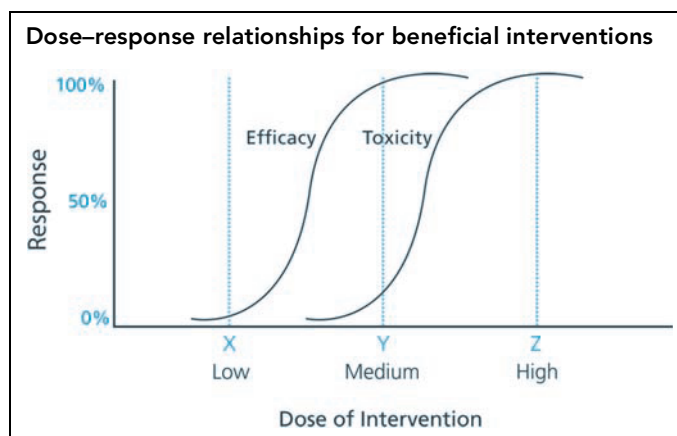
As we became more cognisant of the difficulty in correctly interpreting studies for which conditions were not optimised, we updated NCCAM's website to address one of these issues: dose optimisation.⁷

If there are no data to suggest that the proposed dose is likely to give maximum efficacy, or if there are no data to identify the highest tolerated dose that can be tested, the applicant should evaluate a range of dosages to establish the appropriate dose for the study or clearly explain why the optimal dose cannot be established.

Use of a suboptimal dose that is safe but ineffective does not serve the larger goals of the CAM community. Any given study can only draw conclusions concerning the dose that was tested. If that dose proves ineffective, the community may conclude incorrectly that all doses of the intervention are ineffective, and patients will be denied possible benefit from the intervention.

Dose optimisation: evaluating a range of dosages

An approach to dose optimisation is suggested by the idealised dose–response curves in the Box. The dose of the intervention rises from a low-dose X to a mid-dose Y to a high-dose Z. “Response” can be considered in terms either of efficacy or of



toxicity. In this example, dose X is too low to result in either efficacy or toxicity. Dose Z is so high that toxicity as well as efficacy is seen. Y is an optimal dose, at which high efficacy but only modest toxicity is seen.

These curves should hold for any intervention, not just for biologically active agents. Natural product regimens need to be optimised with respect to dose of material in each pill, the number of pills per day, and the number of days of treatment. Mind-body, manipulative, and other CAM interventions also require optimisation of the dose, frequency, and duration. Meditation, for example, is typically taught in group courses of a given length, with patients told to practise a certain number of times per day. There is little literature on the dose-response relationships between the length of training or the frequency of practice and clinical outcomes. Thus, part of NCCAM's new strategic plan for mind-body research calls for studies to "optimize the timing, components, duration, and level of mind-body interventions to achieve health benefits".⁸

For most interventions, NCCAM considers that the dose that is commonly practised in the community is likely to fall between X and Y and have low to modest specific efficacy. With this assumption, placebo-controlled phase I/II clinical trials of that intervention should start with the customary dose, then increase the dose until high efficacy, a plateau of efficacy, or intolerance in terms of toxicity or patient burden is observed.

CAM practices often involve complex botanical substances in which the active ingredient is very dilute, or other interventions

that can be time-consuming to deliver or practise. For CAM, "intolerance" could be an inability to swallow more product, drink more tea, participate in more classes, or devote more time to certain behaviour such as meditation, rather than the classic systemic toxicity of conventional drugs.

If substantial specific efficacy is seen before intolerance, the conclusion will be that an "optimal" dose of the intervention may have been identified, one that is ready for testing in a larger clinical trial. Only if an optimal dose of the intervention is used can definitive decisions about the effectiveness of an intervention be made.

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