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National Center for Complementary and Alternative Medicine
National Institutes of Health
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- 1. What are the greatest opportunities for research in the next few years?**
- 2. What are the greatest challenges to conducting CAM research?**
- 3. What impact is CAM research having on trends in integrative medicine?**

The Council for Responsible Nutrition (CRN)¹ appreciates the opportunity to provide NCCAM with comments regarding the above three questions posed as part of its Stakeholder Dialogue held on June 20, 2007. CRN believes that integrative medicine – combining the best of complementary and alternative medicine (CAM) and modern medicine – should continue to play an expanding role in the future healthcare of Americans. Two of the most widely discussed, but poorly quantified aspects of healthcare prevention of disease and the preservation of good health. As the population ages, the portion over age 65 grows at a rapid rate and healthcare costs soar to all-time highs, the prevention of chronic disease is becoming more and more of a practical necessity, not only to preserve the quality of life of America’s citizens, but also to contain healthcare costs and their effect on the overall economy. Yet, well-documented approaches to disease prevention, including the integration of many dietary supplements into a healthy lifestyle, are still viewed by many in the medical community as unsubstantiated.

Research into the Role of Prevention

¹ Council for Responsible Nutrition is the leading trade association representing dietary supplement manufacturers and ingredient suppliers. CRN companies produce a large portion of the dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug store and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. Our 65+ manufacturer and supplier members agree to adhere to voluntary guidelines for manufacturing, labeling and marketing and CRN’s Code of Ethics.

The opportunities for CAM research vis-à-vis prevention remain relatively unexplored. The main functions of dietary supplements, considered to be a form of CAM, are to help maintain health and reduce the risk of disease. Indeed, from both a regulatory and commercial standpoint, the maintenance of “normal” health and the reduction of disease risks are the only health-related claims that can be made in marketing and labeling of these products, as the law views any claim for treatment, mitigation or cure of a disease to be solely the purview of pharmaceuticals or “drugs.”² Herbs, botanical extracts, antioxidants and other bioactives can play an important role in health maintenance and reduction of chronic disease risk. As NCCAM develops its research and funding priorities, it is critical that the Center appreciate the commercial marketplace impacts (or lack thereof) as well as the potential public health benefits for research focused solely on treatments and cures.

CRN urges NCCAM to place more resources towards the study of so called “at risk” populations, consisting of individuals who may be predisposed to or show early signs of chronic disease, but who have not yet been formally diagnosed and who are not already utilizing treatment medications. These include individuals who are, for example, exhibiting signs of insulin resistance, but are not yet diabetic; those who display “borderline” hypertension, hypertriglyceridemia, hyperhomocysteinemia but have not yet been diagnosed with cardiovascular disease; those who display early signs of dementia, but have not yet been diagnosed with Alzheimer’s; and those who experience knee pain but have not yet been diagnosed with osteoarthritis.

The outcomes of such research have several potentially significant benefits. Most importantly, the results could provide clear strategies for prevention of some of the major chronic diseases facing Americans. Moreover, those particularly at risk for these diseases will gain valuable information as to whether these preventive “treatments” work. More finely tuning the study populations will provide clearer directions for future research as well. In the context of the randomized, controlled trial (RCT) utilizing at risk populations rather than the generally healthy population to assess disease risk reduction is both more practically and financially

² As an example of the lack of utility for much of the research conducted on nutrients, consider that FDA typically refuses to consider studies involving dietary supplements or nutrients conducted in diseased populations as a basis for approving health claims for those products related to reducing the risk of disease. FDA has stated that studies in diseased populations are not indicative of the effects in a healthy population and therefore maintain that this data has little relevance for demonstrating the reduction of risk of disease versus treatment of a diseased population.

feasible, with reduced sample sizes, trial duration and monetary costs associated with conducting the research. The outcomes of such research will have more direct application to real world utilization of these products.

Suitable Endpoints for Prevention

However, reliance on at risk populations alone may not be sufficient to properly assess the effects of dietary supplements on disease risk reduction. Reliable and scientifically validated surrogate endpoints of disease and biomarkers are absolutely essential for studying disease prevention/risk reduction. Chronic disease takes decades to manifest itself, and if disease itself is left as the sole outcome measure for assessing risk reduction in RCTs, such trials would be cost prohibitive. The paucity of reliable and acceptable surrogate endpoints and biomarkers for chronic disease is perhaps the single greatest obstacle to conducting more much needed research on prevention. At present, serum lipids (including triglycerides and forms of cholesterol), colon polyps, bone mineral density, elevated blood pressure and elevated blood sugar represent a disappointingly short list of “validated” markers of chronic disease. CRN strongly recommends that NCCAM engage in the ongoing discussions within NIH and other agencies regarding establishment of more surrogate endpoints and biomarkers for disease than are currently relied on.

Prevention Research Beyond the RCT

In addition, the assessment of the preventive and disease risk reduction benefits of CAM need not solely rest on the outcomes of RCTs. NCCAM has the opportunity to help shape the evolving paradigm for healthcare research so that it properly accommodates treatments that lie outside the practice of traditional, allopathic medicine in this country. The Center should use the development of funding criteria and research priorities to assure that all rigorous and scientifically defensible research is given equal consideration and that the results of those studies will be made available for healthcare practitioners to evaluate and act upon. Repeatedly, there are calls in some circles to recognize RCTs as the *only* gold standard for evaluating healthcare practices. Indeed, the bias for RCTs within FDA in this regard is demonstrated in its recently issued *Draft Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims* (2007), which characterizes observational studies as solely “hypothesis

generating” studies, while RCTs are considered “confirmatory”. Is the RCT really the only appropriate tool for demonstrating the benefits of nutrients, including dietary supplements? Or are there other, equally valid ways to demonstrate health benefits from these products?

One prominent researcher in the field of nutrition recently wrote, “The randomized controlled trial (RCT), which has become the gold standard for establishing the efficacy of pharmacologic agents, is poorly suited to the evaluation of nutritional effects” (Heaney, 2006). That paper correctly surmises that nutrients, unlike drugs, are present in the body at background levels and the body responds to targeted drugs very differently than it does to nutrients, which affect multiple organ systems within the body. The classic drug-based RCT model, when used to test the effects of nutrients, requires comparison of a “replete” or “supplemented” group vs. a “deficient” group presenting both ethical and practical dilemmas that often times cannot be resolved (e.g. the Women’s Health Initiative) (Jackson et al., 2006). While these limitations should not lessen the importance of the RCT in establishing causality, they should be recognized and acknowledged. And likewise, the value of rigorous observational studies should not be discounted, and may be equally illuminative as RCTs.

CRN recognizes the scientific rigor of RCTs, and they are certainly an important piece of the research puzzle. But we cannot ignore all the other research—case-control and cohort studies, and other epidemiological data—as these studies often point us in the direction indicating where further research should be focused and may be just as rigorous for proving hypotheses as well as developing them. If observational studies demonstrate a benefit which is not confirmed by a clinical trial, that does not discount the importance of the initial studies. The totality of the evidence should not be dismissed. Often times the two different study types attempt to answer different questions; or perhaps the RDT or the meta-analysis based on a series of RCTs was studying a different population, or seeking to validate a treatment rather than prevention, or wasn’t studying the proper dose to begin with. Ironically, two of the most widely accepted calls for health-related behavior changes in the United States today: the call for people to quit -- or not begin -- smoking cigarettes, and the call for a diet rich in whole fruits and vegetables, are both based almost entirely on observational data, not RCTs.

Therefore, in instances where effects of nutrients are being assessed, we recommend that NCCAM also consider placing more emphasis (and research dollars) on appropriately designed and rigorously conducted observational studies as potential sources of data. In addition to being

less cost prohibitive, observational studies more accurately reflect real life conditions and are not prone to the same ethical and practical dilemmas as RCTs. Such limitations may or may not be as significant when assessing the effects of botanicals or other bioactives that the human body is not normally exposed to or does not possess background levels. In these cases, depending on the availability of data, RCTs may be the most appropriate approach to assess the effects in humans.

Conclusions

We are not suggesting that one approach to developing the evidence base is clearly superior to another, or that only one approach should be used to study prevention. Rather, our recommendation to NCCAM is to adapt its focus and priorities to include more research on prevention, to carefully evaluate study designs that will accurately analyze prevention therapies using dietary supplements, and to consider other means of assessing the effects of these substances beyond the classic RCT.

Once again, CRN appreciates the opportunity to provide comments to NCCAM on these important issues. We hope the Center finds these comments both supportive and constructive and that they will be given ample consideration in developing future research policy.

Sincerely,



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