

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CENTER FOR COMPLEMENTARY
AND ALTERNATIVE MEDICINE**

**NATIONAL ADVISORY COUNCIL FOR COMPLEMENTARY
AND ALTERNATIVE MEDICINE
MINUTES OF THE FORTY-FOURTH MEETING
February 3, 2012**

NACCAM Members Present

Dr. Brian Berman, Baltimore, MD
Dr. Adam Burke, San Francisco, CA
Dr. Catherine Bushnell, Montreal, Quebec, Canada
Dr. Daniel Cherkin, Seattle, WA
Dr. Gary Curhan, Boston, MA
Dr. Steven DeKosky, Charlottesville, VA
Dr. Susan Folkman, San Francisco, CA
Dr. Jane Guiltinan, Seattle, WA
Dr. Scott Haldeman, Santa Ana, CA
Dr. Frances Henderson, Jackson, MS
Dr. Janet Kahn, Burlington, VT
Dr. David Kingston, Blacksburg, VA
Dr. John Licciardone, Fort Worth, TX
*Dr. Philippa Marrack, Denver, CO
Dr. Lloyd Michener, Durham, NC
Dr. Linda Powell, Chicago, IL

*Teleconference

NACCAM Members Not Present

Dr. Stephen Ezeji-Okoye, Palo Alto, CA
Dr. Richard Niemtzwow, Clinton, MD
Dr. Katherine Shear, New York, NY
Dr. Xiaoming Tian, Bethesda, MD

NIH Staff Present

Robyn Bent, NCI, NIH
Biao Liao, CSR, NIH
Barbara Sorkin, ODS, NIH
Karyl Swartz, CSR, NIH

Dan Xi, OCCAM, NCI, NIH
Members of the Public

Marguerite Clarkson
Steven Dentali
Cathleen Kearns
Trey Lundgren
Cynthia Jardine McLister
Alison Soffer
Taylor Walsh

I. Closed Session

The first portion of the forty-fourth meeting of the National Advisory Council for Complementary and Alternative Medicine (NACCAM) was closed to the public, in accordance with the provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

A total of 172 applications were assigned to NCCAM. Of these, 56 were reviewed by NCCAM, 116 by Center for Scientific Review. Applications that were noncompetitive, not discussed, or were not recommended for further consideration by the scientific review groups were not considered by Council.

Council agreed with staff recommendations on 96 applications, requesting \$24,524,584 in total costs.

II. Open Session—Call to Order

The open session of the NACCAM meeting convened at 10:15 a.m. Dr. Martin Goldrosen, NACCAM Executive Secretary, called the meeting to order.

The minutes of the October 14, 2011, NACCAM meeting were approved unanimously.

III. Report From the Director

NCCAM Director Dr. Josephine Briggs welcomed the six new NACCAM members: Drs. Catherine Bushnell, Jane Guiltinan, Scott Haldeman, Frances Henderson, John Licciardone, and Lynda Powell.

Congress has approved the creation of the National Center for Advancing Translational Sciences (NCATS), which will consolidate resources from a variety of programs across the National Institutes of Health (NIH), including the Clinical and Translational Science Awards (CTSAs). Dr. Briggs is serving as the Acting Director of NCATS' Division of Clinical Innovation. Although Dr. Briggs' involvement will be temporary, she expects her role to be valuable to

NCCAM's research because the CTAs have great potential to examine changes in health care and to strengthen capacities for clinical research.

Chris Thomsen, Director of NCCAM's Office of Communications and Public Liaison (OCPL) since its founding, has retired. Following a vigorous national search, Alyssa Cotler, formerly Deputy Director of OCPL/NCCAM has been appointed Director. Camille Hoover, Executive Officer of NCCAM since its founding, has been recruited to be Executive Officer of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). A national search is underway to identify Ms. Hoover's successor. In addition, a national search for a scientific director to lead an NCCAM's new intramural pain research program is nearing completion. Kim Nesbitt has joined NCCAM as a health program specialist.

NCCAM is mentioned in two bills proposed in the U.S. House of Representatives.

The final enacted budget for Fiscal Year (FY) 2012 is similar to NCCAM's FY 2010 appropriation and slightly higher than that for FY 2011. However, funds available for competing awards are substantially smaller than they were last year.

NCCAM is enhancing oversight activities to ensure that the research it funds is conducted in the most scientifically valid, safe, and efficient manner possible. A contract for the NCCAM Clinical Studies Monitoring Service has been awarded, and site visits for recently funded NCCAM studies began in January 2012.

The clinical trial of silymarin for chronic hepatitis C has been completed. Preliminary results were presented at the November 2011 meeting of the American Association for the Study of Liver Diseases, and the primary results paper has been submitted for publication.

Clinical (human subjects) research represents more than half of NCCAM's research portfolio, and NCCAM has been taking leadership roles in trans-NIH human subjects research efforts, including the Patient Reported Outcomes Measurement Information System (PROMIS[®]) and the Health Care Systems Research Collaboratory, both projects of the NIH Common Fund.

In November 2011, Dr. Sean Mackey of the Stanford University School of Medicine and the Stanford Systems Neuroscience and Pain Lab presented the Stephen E. Straus Distinguished Lecture in the Science of Complementary and Alternative Medicine. His lecture was titled "Opening Windows to the Brain: Lessons Learned From the Neuroimaging of Pain." In cooperation with the Samueli Institute, NCCAM Deputy Director Dr. Jack Killen took a leadership role in organizing a January 2012 conference on the placebo effect in health care. Upcoming events include a Spring 2012 roundtable on herb-drug interactions, as well as participation by some staff in the International Research Congress on Integrative Medicine and Health, to be held in May 2012.

A number of NCCAM-funded publications appearing between October 2011 and January 2012 all received substantial attention from the news media. Among these were clinical trials showing that yoga or stretching was more helpful than a self-care book for low-back pain; that soy protein supplements did not reduce the progression of atherosclerosis; and that, for neck pain, spinal manipulation was more helpful than medication—as was home exercise with advice. NCCAM

also received media attention in a series of articles in the *Chicago Tribune*. In other media coverage, Dr. Briggs was interviewed on CNN; a former NACCAM member, Dr. Ted Kaptchuk, was interviewed for an article on the placebo effect in *The New Yorker*; and a series of *Wall Street Journal* articles on neuroimaging and pain included comments from Dr. Briggs.

IV. Council Operating Procedures

Dr. Goldrosen reviewed Council operating procedures, including processes for NCCAM reports to Council, secondary review of grant applications, approval of concepts for research initiatives, and handling of appeals from applicants. Council unanimously passed a motion approving the operating procedures as presented.

V. Improving the Assessment of Patient-Reported Health Using NIH PROMIS Instruments

Dr. Kevin P. Weinfurt, Professor in Psychiatry and Behavioral Sciences, Duke University School of Medicine, presented an overview of PROMIS and how it can be used in clinical research.

Typically, clinical trials have evaluated benefits in terms of biological and physiological measures that describe an effect on the body. However, effects on patients' lives—e.g., symptom status, functional status, general health, and quality of life—also are important. These types of outcomes are measured through systematic assessments of patients' perspectives, called patient reported outcomes (PROs). Measurement of PROs is crucial for burden-of-disease studies, comparative effectiveness research, and outcomes research. It has faced challenges, however, because many measures of the same concepts exist, and the quality of these measures varies widely, making it difficult to combine data across studies or conditions.

To develop better ways to measure PROs, NIH sponsored the development of PROMIS, which includes a set of validated measures of PROs; a body of science on PRO measurement; and software to make tools for PRO assessment available. Questions in PROMIS item banks measure a variety of aspects of physical, mental, and social health, such as fatigue, mobility, and depression. A given item bank can be used across diseases and for different severities, enhancing comparability of study results. PROMIS items are tested for validity, reviewed for translatability, and field tested in individuals with low literacy. Ready-made questionnaires and computerized adaptive tests are both available through the PROMIS Assessment Center.

PROMIS is a work in progress, but it has already had a substantial impact, with 111 studies collecting data using the Assessment Center and others using PROMIS measures with their own software. At least 44 grants submitted to NIH are either using PROMIS measures as outcomes or proposing to develop new PROMIS measures. PROMIS is being used in national population health surveys and in field testing in preparation for the 2013 release of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Inquiries have been received about the potential use of PROMIS in clinical care. PROMIS is also receiving international attention, with requests for translation into 33 languages.

Discussion. In response to questions, Dr. Weinfurt clarified that the intent of NIH was to make PROMIS as freely available as possible. Dr. Weinfurt also explained that reliability tests have

been performed for most PROMIS measures. Greater precision can be achieved by using multiple questions to assess the same metric. Council members pointed out that the use of the population mean as a benchmark is not always desirable because the mean may not represent the optimum condition. They also noted that language translation is only one of multiple challenges in applying metrics to different countries and cultures. A barrier to the adoption of PROMIS is the current use of other measures in specific clinical communities. Clinical trials need to use outcome measures that are accepted and standard in clinical practice. Council members discussed opportunities to add PROMIS measures to clinical trials to allow for comparison with currently used measures. Members also expressed interest in the possibility of using PROMIS measures to assess positive aspects of health (i.e., thriving or excelling rather than just functioning), as well as the impact of disease.

VI. Update on NCCAM's Strategic Plan

The afternoon session was devoted to updates on the implementation of NCCAM's third strategic plan, which was released a year ago.

NCCAM Communications Program

Alyssa Cotler, Director of the Office of Communications and Public Liaison, summarized developments in NCCAM's communications program under the strategic plan. She explained that NCCAM's goals, as outlined in the plan, are to advance the science of symptom management; develop effective, practical, personalized strategies for promoting health and well-being; and enable better evidence-based decisionmaking. The strategic plan helped NCCAM articulate its strategies within communications, focusing on decision making by the public and health care providers, and enabling informed dialogue. The strategic plan is consistent with NIH's overall communications platform.

NCCAM's focus is on research that may help people live better lives by managing pain and other symptoms, encouraging healthy behavior, and ensuring safety. NCCAM's communications priorities include explaining the importance of the research process and providing credible, evidence-based information so people can make the most informed decisions. Almost 40 percent of the American public uses some form of complementary health approach, spending \$34 billion a year out-of-pocket. They need NIH research, which has the best, most rigorous standards in the world, and they need scientifically sound information available in ways that fit their lifestyles. To ensure that their needs are met, NCCAM is assessing its communications efforts on two primary fronts: messages and vehicles.

NCCAM is talking to thought leaders in major research organizations, provider associations, and patient advocacy groups about what they know about and think of NIH's research investment in complementary health practices. Also, NCCAM is planning a set of focus groups with consumers to learn more about what information is most useful to them in making decisions.

NCCAM is continually assessing the reach and effectiveness of its communications vehicles. Its Web site is a major vehicle, with 2.4 million visitors a year, about 12.5 percent of whom access it from mobile devices. Based on user feedback, NCCAM has been able to more effectively

provide the information users need to make health decisions. The new portal on safety is an example.

NCCAM has more than 6,000 “likes” on Facebook and almost 8,000 followers on Twitter. It has held its first Twitter chat, in which questions about complementary health were answered in real time. Soon, it will be possible to read NCCAM’s *Herbs at a Glance* booklet on a tablet, smartphone, or e-book reader.

At the same time, NCCAM is not forgetting the many people who still call toll-free numbers to get health information. NCCAM’s clearinghouse answers more than 200 calls each month and sends out e-mail or paper-based information and literature. NCCAM also continues to reach out to traditional media outlets, which remain highly influential. Last fall, Dr. Briggs met with reporters and editors at *The New York Times* and *The Wall Street Journal*, and meetings of this type will continue to be scheduled. Making these connections is key to ensuring that information about NCCAM is presented accurately.

Ms. Cotler concluded her presentation by inviting Council members to act as NCCAM’s eyes, ears, and voices beyond the NIH campus, both to share what they hear and to help NCCAM continue to ensure that the public and health professionals have the information they need to make sound decisions.

Discussion. In response to questions, Ms. Cotler explained that distinguishing individuals’ posts on NCCAM’s Facebook page from information provided by NCCAM has not been a problem; that OCPL could work with Council members to develop talking points on various topics; and that NCCAM is reaching out to health care providers through its *Clinical Digest* and health care provider portal. Council members commented that journal review articles could be a valuable way to share NCCAM messages with the research community and that more of the medical grand rounds that Dr. Briggs initiated several years ago would be welcome. Dr. Briggs noted that NCCAM interacts with health policy makers in some of its activities, but this is not as high a priority for NIH as for some other Federal agencies.

NCCAM High Priority Research Programs

Dr. Emmeline Edwards, Director of NCCAM’s Division of Extramural Research (DER), introduced a session in which DER program officers gave examples of current NCCAM-sponsored research in four areas emphasized in the strategic plan. Dr. Edwards explained that NCCAM currently has 324 active grants, including 98 R01 grants, a substantial increase in R01s in comparison with previous years.

NCCAM Pain Research Program

For the symptoms management priority area, NCCAM Program Officer Dr. Partap Khalsa summarized NCCAM’s pain research program. The use of complementary health practices for pain by the American public is high, which is one of NCCAM’s motivations for funding studies on promising interventions for pain. Pain research continues to account for a large proportion of NCCAM’s extramural research program. Research results show that some complementary health practices, particularly mind and body practices, appear to provide clinical benefits. Scientific challenges remain, however, including determining the mechanisms by which these practices

work, difficulty in masking practitioners and participants in clinical trials, the individualized or complex nature of some complementary interventions, the lack of good biomarkers for measurement of impacts on biological processes, and the unavailability of sham or placebo controls for some interventions.

Dr. Khalsa described two recent NCCAM-funded studies—one on tai chi for fibromyalgia and another on spinal manipulation for chronic headache—that had promising results but important limitations. He also presented a study of acupuncture for low-back pain that overcame some of the usual limitations by providing a credible sham intervention, devising ways to mask participants and assessors to group assignment, and incorporating long-term followup into the study plan. He gave an example of mechanistic research in this area: a study that found that clinical improvement following spinal manipulation for low-back pain is associated with increased size of the abdominal and lumbar-multifidus muscles.

Discussion. In response to a question, Dr. Khalsa explained that changes in the size of the multifidus muscle could occur over a very short time because they reflect contractile state (as opposed to hypertrophy). Dr. Briggs explained that potential partnerships for low-back-pain studies exist with other NIH institutes and centers, such as the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Drug Abuse, and that Drs. Killen and Khalsa are leading a trans-NIH working group on back pain. The lack of availability of placebo/sham controls for some therapies is a limitation, but research can nevertheless continue on a variety of fronts, with different types of studies informing each other.

NCCAM's Support of Healthy Lifestyle Behaviors and Behavior Change Research

For the lifestyle priority area, NCCAM Program Officer Dr. Wendy Weber described NCCAM's support of research on how complementary health practices might be used to promote healthy lifestyles and desirable behavior changes. Complementary health approaches are being used in health care settings and employer wellness programs despite very limited evidence of effectiveness. NCCAM hopes to build the portfolio of research in this area to help inform decisions on whether specific complementary approaches should be used in these ways.

Numerous studies have documented the link between healthy behaviors and decreased risk of many diseases. NCCAM's focus on promoting healthy lifestyles and behavior change will allow application of interventions that are found to be beneficial to a variety of populations. This approach may increase the integration of complementary interventions that demonstrate benefit for promoting healthy behaviors into many research studies and clinical settings.

Dr. Weber provided several examples of research in this area, including a pilot study in which yoga was incorporated into a smoking cessation program with promising results. NCCAM is not only beginning to pursue its own studies in this area but is also connecting to efforts in the broader NIH community—e.g., by participating in several Common Fund or trans-NIH projects related to behavior change. An important next step in this program area will be helping to connect complementary medicine researchers with opportunities for training in health behavior research, including summer training opportunities at NIH.

Discussion. Council members noted that statistics show that complementary health practices are very often used for self-care and health promotion, which reinforces the importance of research in this area. They also suggested that this is a research area in which industry, particularly insurance carriers, could play a role. Dr. Briggs noted that a large tobacco cessation project was funded by General Electric and that NIH has an interest in these types of cooperative efforts with industry. Council members said that behavioral treatments need to be better integrated into clinical practice and that initiatives focused on improved wellness, rather than secondary prevention, would be valuable. The methodology and experimental design of studies in this area need to be particularly rigorous. Current approaches to behavior change are inadequate, and new types of interventions are needed.

Mind and Body Approaches to Improving Health: A Focus on Meditation

For the mind and body priority area, NCCAM Program Officer Dr. John Glowa described research on meditation, a modality with widespread use and appeal in the United States. Challenges in meditation research include measurement of subjective outcomes, difficulty masking practitioners and participants, how to study individualized or complex interventions, and often, a lack of means to objectively measure meditation's impacts on biological processes.

Mindfulness-based meditation is well suited for scientific study, Dr. Glowa said, because it is reasonably well standardized and is typically used as an 8-week intervention. In an NCCAM-supported study, mindfulness was more effective than a support group in reducing irritable bowel syndrome severity. However, studies on mindfulness for stress and fibromyalgia had negative results.

Another approach to understanding the potential benefits of meditation involves studying brain mechanisms. Meditation affects areas of the brain thought to be involved in self-awareness, attention, and emotion. The results of neuroimaging studies are promising, but some unresolved issues remain. For example, the validity of brain activity as a biomarker has not been established.

Discussion. Council members commented that the term “mindfulness” has been widely misused; NCCAM may be able to play a role in clarifying terms. Meditation is a complex intervention and is often combined with other distinctive lifestyle features; the aspects of this lifestyle that are most important to health are not known. Some measures that are used to assess effects of meditation are based on jargon used in meditation training; more accessible and meaningful language should be used. Many types of meditation exist, and distinguishing among them is important.

In general discussion on the mind-body portfolio, Council members pointed out that most of the methods under study come from complex systems and have often been taken out of the context of the whole system for use in secular settings. It is important to recognize the complexity of the systems and not oversimplify them. Outcomes research and comparative effectiveness research are needed, and the use of highly rigorous experimental designs is essential. Although randomized, controlled trials are the predominant experimental method, they are not appropriate in every setting. The use of well-designed alternative study methodologies is crucial in the evaluation of mind-body methods. Dr. Briggs noted that at the health care systems level, study

designs that involve intervening at half of the available sites have promise, but good outcome measures must be used.

Natural Products

The final three presentations focused on the natural products priority area, with speakers addressing the topics of natural products mechanistic research, methodology in natural products research, and research on probiotics and prebiotics.

Natural Products Mechanistic Research

NCCAM Program Officer Dr. Craig Hopp explained that a current quandary in natural products research is whether efficacy studies or mechanistic research should be emphasized first. Arguments can be made in favor of both. In NCCAM's experience, clinical trials of natural products have usually failed to show hypothesized benefits, and their study designs have often been criticized. These trials might have benefited from stronger hypotheses based on prior mechanistic research. NCCAM is currently increasing its focus on mechanistic studies, with targets that include inflammatory, immunomodulatory, cell proliferation, and antioxidant pathways.

As examples of the work NCCAM is funding on the antioxidant pathway, Dr. Hopp discussed the Missouri Botanical Center's work on signaling pathways targeted by botanical compounds. He also showed results from NCCAM-funded studies that investigated the mechanisms of action of alpha-lipoic acid and American ginseng. Future challenges for the natural products portfolio include determining whether manipulation of pathways will lead to disease prevention, translating findings to the clinical setting, and determining how the results of mechanistic research can lead to stronger hypotheses regarding the activity of natural products.

Discussion. Dr. Briggs commented that antioxidants are a consistent puzzle. Clear mechanistic evidence of their health benefits is lacking, but better ways to measure oxidant stress in people may emerge from current research. In response to a Council member's question, Dr. Hopp stated that the composition of the product tested in the American ginseng study is known, but the components responsible for the observed effects have not been identified.

Methods in NCCAM-Funded Natural Products Research

NCCAM Program Officer Dr. Carol Pontzer cited fluorescent binding assays, single nucleotide polymorphism (SNP) analysis, single cell analysis, and synergy-directed fractionation as examples of cutting-edge methodology used in NCCAM-supported natural products research. A fluorescent binding assay was used by NCCAM-funded researchers to gain understanding of the interaction of vitamin E isoforms (alpha- and gamma-tocopherol) with protein kinase C. SNP analysis was used to identify differences in frequencies of occurrence of variants in the fatty acid desaturase (FADS) genes, thus helping to explain differences in the metabolism of polyunsaturated fatty acids between Americans of African and European descent. Single cell analysis was used to assess whether cranberry juice compounds have molecular-scale anti-adhesive activity after passing through the digestive system and reaching the urinary tract. Synergy-directed fractionation was used to examine the activity of components in goldenseal,

resulting in identification of three flavonoids that synergistically enhance the antimicrobial activity of berberine even though they have no inherent antimicrobial activity themselves.

NCCAM's goals in this area include continuing to raise awareness of technological opportunities available to NCCAM grantees and maintaining a leadership role in the development of methods for natural products research.

Discussion. A Council member commented that the synergy-directed approach is useful because activity can be missed if synergistic effects are not taken into account. Also, just as work with isoforms illustrates that they can have opposite effects, work with mixtures shows that they can have effects that differ from those of their components. Dr. Briggs noted that a core hypothesis in natural products research is that complex mixtures may work better, and some studies at mechanistic levels support this hypothesis but it has been difficult to confirm.

NCCAM's Support of Probiotics/Prebiotics Research

NCCAM Program Officer Dr. Linda Duffy explained that *probiotics* have been defined by the United Nations' Food and Agriculture Organization and by the World Health Organization as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. *Prebiotics* are indigestible carbohydrates that stimulate the growth or activity of specific bacteria in the colon.

Research on probiotics and prebiotics represents 10 percent of NCCAM's total research portfolio; of that, 40 percent of studies focus on basic mechanisms and 60 percent on translational/clinical research. NCCAM is one of 21 agencies involved in NIH's Probiotic and Prebiotic Working Group and accounts for about 20 percent of that group's research.

Probiotics could exert their hypothesized beneficial effects through a number of mechanisms, including production of pathogen inhibitory substances, blocking of pathogenic bacterial cells' adhesion sites, nutrient competition and production, degradation of toxins and toxin receptors, and modulation of immune responses. Better understanding of these specific mechanisms will facilitate optimum selection of microbial strains. NCCAM-supported investigators are using new technologies to study the mechanisms of action of probiotics and are targeting a variety of disorders, as well as conducting safety trials to better understand adjuvant effects and immunomodulatory responses.

Dr. Duffy explained that the June NACCAM meeting will feature presentations by NCCAM investigators on various aspects of probiotic and prebiotic research.

Discussion. Dr. Briggs noted that systematic reviews support the use of probiotics in necrotizing enterocolitis and antibiotic-associated diarrhea. Probiotics are regulated by the U.S. Food and Drug Administration (FDA) in a way that is similar to the regulation of vaccines. Discussions with the FDA about regulatory hurdles related to probiotics are ongoing.

VII. Public Comment Session and Closing

No public comments were offered. Dr. Briggs thanked Council members and adjourned the meeting at 3:45 p.m.

We hereby certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.

Martin Goldrosen, Ph.D.
Executive Secretary
National Advisory Council for
Complementary and Alternative
Medicine

Josephine Briggs, M.D.
Chairperson
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