

**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-FIFTH MEETING
June 1, 2012**

NACCAM Members Present

Dr. Brian Berman, Baltimore, MD
Dr. Adam Burke, San Francisco, CA
Dr. Daniel Cherkin, Seattle, WA
Dr. Gary Curhan, Boston, MA
Dr. Steven DeKosky, Charlottesville, VA
Dr. Stephen Ezeji-Okoye, Palo Alto, CA
Dr. Susan Folkman, San Francisco, CA
Dr. Jane Guiltinan, Seattle, WA
Dr. Frances Henderson, Jackson, MS
Dr. Janet Kahn, Burlington, VT
Dr. Mark Lebwohl, New York, NY²
Dr. John Licciardone, Fort Worth, TX
Dr. Philippa Marrack, Denver, CO
Dr. Lloyd Michener, Durham, NC
Dr. Richard Niemtzow, Clinton, MD
Dr. Linda Powell, Chicago, IL
Dr. Xiaoming Tian, Bethesda, MD
Dr. Larry Walker, University, MS¹

¹Ad-hoc & Telephone

²Speaker

NACCAM Members Not Present

Dr. Scott Haldeman, Santa Ana, CA
Dr. David Kingston, Blacksburg, VA
Dr. Katherine Shear, New York, NY

NIH Staff Present

Catherine Bennett, CSR, NIH
Barbara Sorkin, ODS, NIH
Dan Xi, OCCAM, NCI, NIH

Members of the Public

Steven Dentali
Pat Durning
Cathleen Kearns
Kerri Wachter

I. Closed Session

The first portion of the forty-fifth 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 269 applications were assigned to NCCAM. Of these, 156 were reviewed by NCCAM, 112 by Center for Scientific Review, and 1 by NIGMS. 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 118 applications, requesting \$ 41,894,408 in total costs.

II. Open Session—Call to Order

The open session convened at 10:20 a.m. Dr. Martin Goldrosen, NACCAM Executive Secretary, called the meeting to order.

The minutes of the February 3, 2012, NACCAM meeting were approved unanimously.

Dr. Goldrosen announced that a NACCAM teleconference would be held on August 27 at 1 p.m. and that the next in-person NACCAM meeting would be held on October 12.

III. Introduction to the Open Session

NCCAM Director Dr. Josephine Briggs introduced the open session and explained that NCCAM funds a sizeable body of work on natural products and their characterization. While some are skeptical of efforts to discover new therapeutic agents in natural product screening or cultural wisdom traditions, the next presentation illustrates reasons for supporting such research.

IV. Clinical Presentation and Treatment of Actinic Keratosis

Speaking by videoconference, Dr. Mark Lebwohl, professor and chair of the Department of Dermatology at The Mount Sinai School of Medicine, summarized recent advances in the treatment of actinic keratosis (AK), a precancerous skin condition common among light-skinned people with a history of extensive sun exposure. AK is treated by cryotherapy (freezing) or topical application of drugs. All current treatments for AK cause some degree of temporary local irritation, and their long-term success varies.

Recently, researchers have developed new drugs for AK that act through the immune system. These drugs are more effective than older treatments in producing sustained clearance of AK, and they can help to prevent the occurrence of new lesions in nearby areas of skin as well as in the specific locations that were treated. One of the new drugs, ingenol mebutate, which was approved by the U.S. Food and Drug Administration in January 2012, is derived from a plant, *Euphorbia peplus*, which is a common weed. People have traditionally used this plant as a home remedy for skin conditions, including skin cancer, especially in Australia. Ingenol mebutate is at least as effective as other AK treatments, and it has properties that encourage compliance with treatment: it requires only a few applications, and the local skin irritation produced by the drug resolves rapidly.

Discussion. In response to Council members' questions, Dr. Lebwohl acknowledged that the efficacy studies of ingenol mebutate could not be successfully blinded because of the local skin reactions caused by the active agent. This issue has arisen in clinical trials of other AK treatments as well. A Council member suggested that direct use of the plant could enable people to avoid paying the high price of the drug, but Dr. Lebwohl cautioned that use of the correct dose is important to maximize efficacy and minimize side effects, and close control of the dose of the active ingredient would be difficult to achieve if the plant was used directly.

V. Integrative Approaches to Managing Pain and Comorbid Conditions in U.S. Military Personnel, Veterans, and Their Families (Concept Clearance)

NCCAM Program Officer Dr. Kristen Huntley presented a concept for Council's consideration on initiatives to stimulate research on the use of complementary and integrative approaches to pain and symptom management in military and veteran populations.

The return of U.S. forces from Iraq and Afghanistan has created huge public health needs: 50 percent of veterans experience pain regularly; and high rates of post-traumatic stress disorder, traumatic brain injury, substance abuse disorder, and depression have also been reported. The U.S. Department of Defense (DOD) and U.S. Department of Veterans Affairs (VA) have launched a comprehensive pain management plan and expressed interest in complementary and integrative modalities.

NCCAM's Third Strategic Plan highlights pain management as a top research priority; thus, NCCAM shares interests with DOD/VA, and there are opportunities for complementary partnerships. NCCAM researchers can contribute to these partnerships through their experience with complementary/integrative modalities, expertise in pain research, and NIH grant-writing skills. DOD and VA clinicians or researchers can contribute by implementing complementary approaches in their real world systems and by providing access to large datasets and patient populations.

NCCAM published a Funding Opportunity Announcement (FOA) in April 2012 that solicited applications for small administrative supplements to plan collaborative activities with DOD/VA researchers. The next steps in this initiative, if Council approves the concept, would be:

- An FOA to provide opportunities to expand funded research on the use of complementary approaches for pain and symptom management in military or veteran health care settings and populations
- Development, with other NIH Institutes and Centers, of a trans-NIH FOA to encourage research on management of pain and associated problems among U.S. military personnel, veterans, and their families.

Potential areas of emphasis for these FOAs include mining large datasets from electronic health records; efficacy, effectiveness, or implementation of complementary approaches in real world settings; and identification of mechanisms of action of complementary practices.

Discussion. In general, members' comments on this concept were highly supportive. Several members cautioned, however, that DOD/VA enthusiasm for some complementary approaches, such as battlefield acupuncture, may be moving ahead of the evidence. A member pointed out that self-care techniques, such as meditation and imagery, may be particularly appropriate for veterans. Another commented that in the military setting, pragmatic effectiveness trials may be more feasible than efficacy studies. One member recommended that complementary approaches to pain be compared with standard care (i.e., drug therapy). Another commented that much of the care of veterans occurs outside VA facilities, and this should be taken into account in research design. Members also noted that the concept of resilience, the role of the family, and the use of complementary methods in the management of acute as well as chronic pain should be considered.

A motion to approve the concept was made, seconded, and passed with 15 affirmative votes.

VI. Report From the Director

Dr. Briggs summarized recent NIH news, including the appointment of Dr. Gary Gibbons as Director of the National Heart, Lung, and Blood Institute and the selection of 11 Centers of Excellence in Pain Education. New staff members at NCCAM include Wendy Liffers, Executive Officer; Dr. Alberto Rivera-Rentas, Program Officer; Brenda Ryan, Management Analyst; and Theodore Woo, Information Systems Security Officer.

The President's fiscal year (FY) 2013 budget request for NIH, which includes \$128 million for NCCAM, is essentially unchanged from the FY 2012 appropriation. At recent hearings, broad bipartisan support for NIH funding was expressed in both the House and the Senate. At a February hearing on pain held by the Senate Health, Education, Labor, and Pensions Committee, Senator Tom Harkin, chair of the committee, expressed strong support for mind and body approaches to pain management.

In April, NCCAM Deputy Director Dr. Jack Killen attended a meeting entitled "Complementary Therapies in Rehabilitation Roundtable," organized by the White House Initiative on Asian Americans and Pacific Islanders. On June 19, Dr. Briggs is scheduled to meet with Representative Tim Ryan of Ohio to discuss NCCAM research on mindfulness meditation.

Between January and April 2012, NCCAM conducted 24 telephone interviews with thought leaders from medical professional organizations, patient and research advocacy organizations, and health plans, asking for their thoughts and opinions on various terms (such as complementary, integrative, and alternative), the use of and research on various therapies, and perceptions about NCCAM, its mission, and its direction.

Key findings included the following:

- “Integrative medicine” and “integrative health care” have very different meanings to different people. Some of the interpretations, such as “collaboration between a nurse and a doctor” or “environment, social, and hereditary factors,” do not relate directly to “complementary health practices” as NCCAM uses that term.
- “Alternative” generally has a negative connotation. While generally synonymous, “complementary” may be viewed a bit more favorably.
- Many interviewees were concerned about
 - Overstated claims of benefit for complementary health practices
 - The use of these practices instead of needed medical treatments
 - Possible harm from natural products because of poor quality control or interactions with drugs.
- Many interviewees expressed concern or uncertainty about the objectivity and rigor of research on complementary medicine.
- Few were familiar enough with NCCAM to give informed opinions about its work.
- Most agreed with NCCAM’s goals of improving pain and symptom management and providing evidence-based information to consumers and health care providers.
- Many were hesitant about NCCAM’s interest in developing strategies to help people have healthier lifestyles, both because other organizations are already working in this area and because the benefits are difficult to measure.

Dr. Briggs updated Council members on NCCAM outreach activities, including monthly Twitter chats, the new research blog, and the new Time to Talk Tips for consumers. A set of resources for researchers, including model documents for consent, protocols, a manual of procedures and expectations, and an extensive list of relevant databases and datasets, has been added to the Web site. Dr. Briggs also highlighted recent high-profile publications on NCCAM-sponsored research on probiotics, massage therapy for osteoarthritis, the relationship between stress and inflammation, and nutrient biomarkers and cognitive function.

Dr. Briggs expressed concern about a recent commentary in *JAMA* by Dr. Paul Offit, both because it focused on NCCAM’s past history rather than its current research portfolio and because it minimized the value of NCCAM clinical trials that had negative results. Dr. Briggs has been in contact with Dr. Offit, and NCCAM leaders plan to meet with him to give him the

opportunity to learn more about the Center's current activities. NCCAM has written a letter to the editor of *JAMA*, and Dr. Briggs expects that it will be published.

Dr. Briggs briefly reviewed the new Federal Government policy on oversight of Dual Use Research of Concern (DURC). The term DURC refers to research that can be reasonably anticipated to provide knowledge that could be misapplied to pose a significant threat to public health, the environment, or national security (e.g., research on the smallpox virus). This policy is particularly relevant to several other ICs; NCCAM is not currently funding any research which meet the criteria outlined in the policy.

Discussion. Council members expressed agreement with Dr. Briggs' views on the public health importance of clinical trials with negative results.

In response to a member's question, Dr. Briggs explained that the Board of Governors of the Patient-Centered Outcomes Research Institute (PCORI) is interested in complementary and integrative approaches. NCCAM is pleased to be part of the dialogue on this subject. PCORI is charged with quickly developing and implementing a national approach to comparative effectiveness research. NIH is broadly partnering with PCORI in a variety of settings, including the Health Care Systems Research Collaboratory project.

Council members and Dr. Briggs discussed issues regarding terminology, including the definition of "integrative" and the ongoing dialogue about the Center's name. Dr. Briggs observed that one way to describe NCCAM's research priorities does not depend on definitions; instead, the focus is on asking which practices from outside the medical mainstream should be incorporated into comprehensive health care based on scientific evidence. She also voiced concern that making definitions too rigid could limit NCCAM's ability to have an impact on health care. The boundaries between complementary and mainstream practices are fluid, and NCCAM does not want to be in a position where it would be required to discontinue research on a practice if that practice becomes accepted as mainstream. Members pointed out, and Dr. Briggs agreed, that mainstream medicine can be changed by its interaction with complementary medicine; a number of practices that were once considered outside the mainstream are now well accepted and have changed health care.

VII. Interdisciplinary Complementary and Integrative Medicine Clinical Research Training Award (Concept Clearance)

Dr. Rivera-Rentas presented a concept on training awards to enhance the development of researchers at the postdoctoral or early faculty levels. This program would pair complementary medicine educational institutions with institutions that have research-intensive environments, with the goal of developing a cadre of research clinicians with integrative health knowledge and research expertise. The program would build on NCCAM's previous efforts to support a variety of high-quality research training and career development opportunities for complementary medicine researchers and would formalize previous partnerships between complementary medicine institutions and research-intensive institutions. It would include both focused trainee development in clinical research and a clinical research training practicum with mentored research training.

Discussion. One Council member expressed support for the concept but cautioned that people who complete the program might not be able to obtain research funding and develop successful research careers. Council members pointed out that only a few complementary medicine institutions have the institutional support for this type of effort. Dr. Briggs explained that with current low funding rates, optimizing the number of people to be trained for research careers is a concern throughout NIH. She also explained that this concept is targeted at the small number of complementary medicine institutions with the capacity to participate. In response to a member's question, Dr. Briggs clarified that this program would focus on clinical rather than basic research. Members inquired about how the awards could work in situations where a complementary medicine program is located within a larger institution with research capabilities and about how the program could be adapted to the very different time schedules and constraints of postdoctoral researchers versus faculty members. Dr. Briggs suggested that further discussion is needed on the training environment in complementary medicine institutions and on the capacity of faculty to build teams for research purposes.

A motion to approve the concept was made, seconded, and passed with 12 affirmative votes.

VIII. Updates: Dietary Supplement/Drug Interactions Workshop to Concept (Concept Clearance 3)

NCCAM Program Officer Dr. Craig Hopp reviewed a recent workshop on dietary supplement/drug interactions and presented a concept for a future initiative on this topic.

The Dietary Supplement-Drug Interactions Workshop, which was cosponsored by NCCAM, the Office of Dietary Supplements, and the National Cancer Institute, was held on March 27, 2012. It included 59 attendees from Federal agencies, academia, and other stakeholders. The workshop goals were to discuss outcomes that may result from the concomitant use of multiple botanicals or other dietary supplements and pharmaceuticals, and to explore ways to improve research on this topic. Key points that emerged from the meeting included the following:

- Drug-supplement interactions have the potential to be either beneficial or harmful.
- Currently available information on supplement-drug and supplement-supplement interactions is often based on theoretical considerations, case reports, or animal studies. There is a need to develop better, more reliable, and clinically relevant information.
- In general, animal models are poor predictors of clinically significant drug-drug, herb-drug, or herb-herb interactions in humans. Clinical trials are the only way to establish the significance, and more importantly, the clinical relevance of any combination.
- Because of pharmaceutical research over the past 50 years, much is now known about how chemicals are metabolized and transported in the human body, and many *in vitro* technologies from that field can now be applied to screening for interactions.

- Although *in vitro* models have some limitations, they can be useful in screens for interactions. For example, high-throughput screening can permit a large number of substances to be screened for biochemical interactions. When interactions are identified in screens, additional preclinical and clinical research can be pursued. While some false positives are expected, false negatives in such systems are rare.

NCCAM is proposing a three-stage approach to developing a fuller understanding of supplement-drug interactions. The first stage—which is the concept Council was asked to consider at this meeting—involves conducting an extensive literature search, assembling an expert panel to critically evaluate the literature, establishing criteria for priority setting, and generating an interaction testing matrix (i.e., making decisions about what combinations of supplements and drugs should undergo further evaluation). The second stage would involve methods development where needed, *in vitro* screening, and when indicated by *in vitro* screening results additional preclinical or clinical studies. The third stage would involve dissemination of findings, including the creation of a data repository.

Discussion. Dr. Briggs commented that current knowledge of drug interactions has developed in a hit-or-miss fashion and that there is a need to explore this area systematically. In response to several members' questions and concerns, Dr. Briggs clarified that the focus of the discussion at this meeting is the first stage of the concept. Members also expressed concern regarding the number of substances to be screened. Dr. Hopp replied that one of the primary roles of the expert panel would be to help develop a framework for setting priorities.

A motion to approve the concept was made, seconded, and passed with 12 affirmative votes.

IX. Research Agenda on Acupuncture for Pain

Drs. Killen and Huntley presented background information about acupuncture research and initiated a discussion on the future of NCCAM's acupuncture research portfolio.

A 1997 NIH Consensus Development Conference concluded that there was sufficient evidence of acupuncture's value to encourage further studies. Use of acupuncture in the United States has been growing since the 1990s. Acupuncture is most often used for painful conditions. NCCAM has consistently spent about 10 percent of its overall budget on acupuncture research. Clinical trials and mechanistic studies accounted for most of the FY 2011 acupuncture portfolio, and the majority of studies focused on pain.

Research since the 1997 conference now points to the following key findings regarding acupuncture for pain:

- In general, both real and sham acupuncture are helpful for pain management compared to usual care.
- In general there is little or no clinically significant difference between real and sham acupuncture.

- Animal and human mechanistic studies of acupuncture show quantifiable physiological responses relevant to endogenous mechanisms of pain processing and control.

The similarity in the results obtained with real and sham acupuncture has been interpreted to mean that sham conditions may not be inert or, alternatively, that expectancy, context, patient-provider interaction, and placebo effects account for most of the reported improvement.

Given this background, and acknowledging that many methodological (and even conceptual) challenges and controversies still confront the field, Drs. Killen and Huntley asked Council to consider these questions:

- Why should we continue to invest in research exploring acupuncture for pain, given that current evidence suggests
 - Nonspecific effects are responsible for most of the observed therapeutic benefit
 - Specific effects are, at most, modest?
- Does acupuncture provide a special window into the study of expectancy, context, and placebo effects in treating pain?

Discussion. One member pointed out that a fundamental difference between research on acupuncture and research on drugs is that acupuncture is already in widespread use. An argument in favor of continued research can be made on that basis. He also noted that nonspecific effects are not limited to complementary treatments; they also occur with conventional treatments, including drugs, and need to be better understood. Several Council members expressed support for further research on acupuncture because it provides an opportunity to better understand nonspecific factors and to develop ways to use them deliberately to enhance the effectiveness of treatment. Council members expressed doubt that existing research has proven that sham acupuncture is inert and supported the idea of pragmatic trials that could provide information useful in clinical practice. One member recommended that further research be conducted to better understand the mechanisms of acupuncture's effects on the brain. A member also suggested that more needs to be learned about the types of patients for whom acupuncture is helpful and whether factors such as gender and severity of symptoms make a difference. Dr. Briggs emphasized that NCCAM wants to sponsor research that makes a difference and builds an evidence base that is maximally informative to the public, practitioners, scientists, and policymakers.

X. Public Comments and Adjournment

During the public comment period, licensed massage therapist Pat Durning complimented NCCAM on the materials currently posted on its Web site and recommended that the site should also provide information on the results of studies performed in other countries, even if those studies do not meet current scientific standards.

Dr. Briggs adjourned the meeting at 3:20 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
National Advisory Council for
Complementary and Alternative
Medicine