

Evaluation of Complementary and Alternative Medicine Therapies

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Principles and Practice of Clinical Research

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Presentation Overview

- **Nature, Use, and Claims of CAM**
- Conducting CAM Research
- Ethical Issues in CAM



What Is CAM?



... medical and health care practices outside the realm of conventional medicine, which are yet to be validated using scientific methods

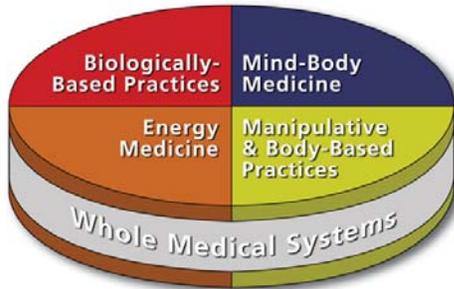
Complementary: together with conventional practices

Alternative: in place of conventional practices

Previous CAM Modalities Now in Mainstream Medicine

- Codeine for pain
 - Digitalis for heart failure
 - Ipecac for poisoning
 - Quinine for malaria
 - Aspirin for fever
-
- Behavioral therapy for headache
 - Hypnosis for smoking cessation
 - Low fat, low cholesterol diets
 - Exercise for diabetes
 - Support groups for breast cancer

The CAM Domains



NCAM

The Appeal of CAM

- Media reports of dramatic results
- Belief that CAM treatments are natural
- Patient empowerment
- Focus on spiritual and emotional well-being
- Therapist providing “touch, talk, time”



CAM Use in the USA

- National Health Interview Survey in 2002
- National random sample of 31,044 adults
- CAM use in last 12 months
 - 62%, including prayer for health reasons
 - 36%, excluding prayer



Barnes et al., *CDC ADR*, 2004

Most Common CAM Practices

	<u>%</u>
▪ Natural products	19
▪ Deep breathing	12
▪ Meditation	8
▪ Chiropractic	8
▪ Yoga	5
▪ Massage	5
▪ Diet-based therapies	4



Barnes et al., *CDC ADR*, 2004

Who uses CAM?

- More educated
- In poorer health
- More affluent
- Possess a holistic orientation to health
- Had a 'transformational experience'
- Identification with environmentalism, feminism, spirituality
- Report chronic anxiety, pain, UTI, back problems

(Astin et al. *JAMA*, 1998)

CAM Economics

- Americans spend more out-of-pocket for CAM than for all other health care needs
- CAM is big business



- 56% of Americans believe their health plans should cover CAM
- Many health insurers and HMOs now cover CAM: Blue Cross of Washington and Alaska, Oxford Health, Prudential, Kaiser Permanente

Biological Research - It's All "Natural"...!



"People can be induced to swallow anything, provided it is sufficiently seasoned with praise."
Jean Moliere

Jean Moliere



Dietary Supplements: DSHEA Definition

- Product intended to supplement the diet
- Contains one or more of the following:
 - Vitamin
 - Mineral
 - Herb or other botanical (not tobacco)
 - Amino acid
 - Any other dietary substance
- For oral intake as a concentrate, metabolite, extract, constituent, or combination



***Patterns of Supplement Use:
The Slone Survey***

- 2590 participants 18 years +
- Telephone survey, random sample
Feb 1998 - Dec 1999
- In the preceding week:
 - 14% of population used herbals
and/or supplements
 - 16% of prescription drug users
used herbals and/or
supplements

JAMA, 2002



***Patterns of Supplement Use:
The Slone Survey***

Ten Most Commonly Used Herbals / Supplements

- Ginseng
- Ginkgo biloba
- Allium sativum
- Glucosamine
- St. John's wort
- Echinacea
- Lecithin
- Chondroitin
- Creatine
- Serenoa repens



JAMA, 2002

***Patterns of Supplement Use:
The Slone Survey***

Ten Most Common Reasons for
taking herbs / supplements

- General health/good for you (16%)
- Arthritis (7%)
- Memory improvement (6%)
- Energy (5%)
- Immune booster (5%)
- Joints (4%)
- Supplement diet (4%)
- Sleep aid (3%)
- Prostate (3%)
- No reason (2%)
- All other reasons (45%)



JAMA, 2002

Environmental Challenges

- Important public health issues
- Inconsistent training, credentialing, licensure, access, regulation, reimbursement
- Highly variable products and product standards



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NCCAM's Mission

- Conduct rigorous research on CAM practices
- Train CAM researchers
- Inform consumers and health professionals



NCCAM's Unique Scientific Challenge: Conducting Rigorous Research

- Broad spectrum of CAM practices
- Inconsistent product and practice standards
- Few CAM practitioners experienced in research
- Market disincentives
- Dearth of credible scientific information



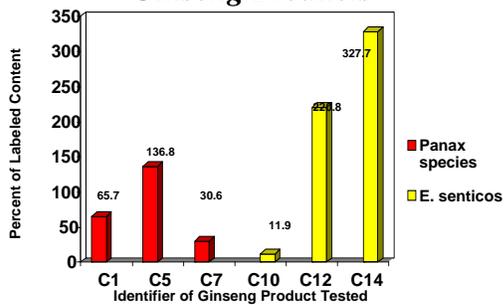
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Challenges of Natural Products Research

- Safety is assumed, not proven
- Products are not standardized
- Contamination and/or adulteration with drugs and heavy metals
- Allergic reactions
- Some are toxic
- Interactions with allopathic drugs
- Replacing proven therapies



Variability in Commercial Ginseng Products



Ginseng products vary greatly in ginsenoside and eleutheroside content relative to what is indicated on their labels. (Adapted from Harkey, AJCN, 2001.)

Ephedra: Safety Concerns

- Ma huang (*Ephedra sineca*) – Short-term TCM treatment for asthma, decongestion
- Contains L-ephedrine, pseudoephedrine
- Major recent use in U.S. in combination with caffeine for weight loss, athletic performance
- Dozens of reports of severe and life-threatening adverse events in young people



Prioritizing Studies

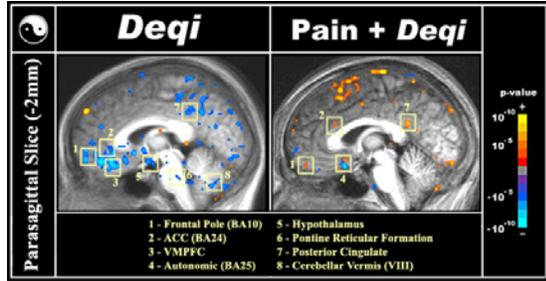


- Public health needs
- Preliminary data exist
- Good products available
- Feasible studies
- Ethical studies

NCCAM Phase III Trials January 2007

Therapy	Condition	Sponsor	Co-Sponsors
Acupuncture	Low Back Pain	NCCAM	
Acupuncture	Osteoarthritis/Knee	NCCAM	
EDTA Chelation Therapy	Coronary Artery Disease	NCCAM	NHLBI
Ginkgo Biloba	Dementia	NCCAM	NIA/NHLBI/NINDS
Glucosamine-Chondroitin	Osteoarthritis/Knee	NCCAM	NIAMS/ODS
Phytoestrogens	Atherosclerosis	NCCAM	ODS/ORWH
SAM-e	Major Depression	NCCAM	
SAM-e	Depression In Parkinson's Disease	NCCAM	
St. John's Wort	Minor Depression	NIMH	NCCAM/ODS
Vitamin E-Selenium	Prostate Cancer	NCI	NCCAM

fMRI Pinpoints Central Effects of Acupuncture



Hui, K. et al., MGH, NMR Center

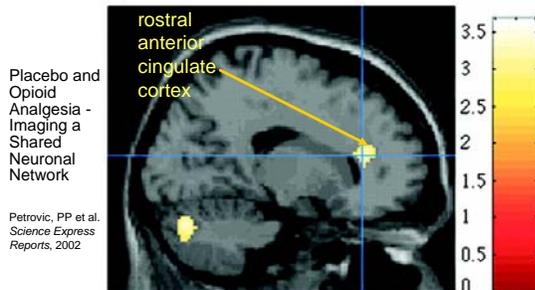


The Placebo



- An inactive substance given to encourage healing in the absence of an effective treatment
- Relied upon to 'control' for nonspecific effects that might confound calculation of the true benefits of an experimental treatment

This Is Your Brain on Placebo



‘The Powerful Placebo’

- Analysis of the aggregate percentage of patients satisfactorily relieved by a placebo across multiple clinical trials
- 1082 patients in 15 controlled trials
- 35.2 ± 2.2% “average significant effectiveness”

HK Beecher, *JAMA*, 1955

‘The Powerless Placebo’

- Systematic review of outcomes for 8525 subjects in 116 controlled trials
- No overall benefit attributable to placebo
- Significant differences only for continuous subjective outcomes
- 27% (95% CI of 15-40%) reduction in pain associated with placebo

Hrobjartsson & Gotzsche, *NEJM*, 2001

Acupuncture for Knee Osteoarthritis: Fulfilling the Vision for Rigorous CAM Studies



Location	University of Maryland
P.I.	Brian Berman, M.D., L.Ac.
Goal	Determine the short- and long-term safety and efficacy of acupuncture
Enrollment	570 patients with knee osteoarthritis (OA)
Design	Placebo controlled, 26 weeks
Intervention	True acupuncture vs. sham acupuncture, and education and attention control arms, in addition to standard care
Outcomes	<ul style="list-style-type: none"> ▪ significantly relieves pain ▪ significantly improves function ▪ an effective complement to standard care

Ginkgo Biloba: Prevention Trial for Dementia

Location: University of Pittsburgh

PI: Steven DeKosky, M.D.

Focus: Determine the effect of *G. biloba* in decreasing incidence of dementia, especially Alzheimer's disease

- Changes in cognitive function
- Incidence of cardiovascular disease
- Total mortality

Design: RCT in 3,073 adults age ≥ 75



Grantee Research: Studying Cellular Mechanisms of Ginkgo Biloba

Three studies determined that Ginkgo extract:



- **Increases stress resistance and extends the lifespan of *C.elegans***
J Smith, et al., *Cellular and Mol Biol*, 2002
- **Protects cultured neural cells from undergoing apoptosis**
Z Wu, J Smith, et al., *Cellular and Mol Biol*, 2002
- **Inhibits beta-amyloid aggregation**
Y Luo, J Smith, et al., *Proc Natl Acad Sci USA*, 2002

Women's Health: Better Management of Menopausal Transition



- Supporting research on CAM modalities for hot flashes, other menopausal symptoms
- Convened workshop to assess existing tools for measurement of hot flashes (January 2004)
- With NIH, NIBIB, & ORWH, issued RFA for SBIR applications to improve objective measures of hot flashes (September 2004)
- Cosponsored, with NIA, state-of-the-science conference on Management of the Menopausal Transition (March 2005)
- Clinical trials to follow

Low Intensity Permanent Magnets in the Treatment of Chronic Lumbar Radicular Pain (Sciatica)

Objective: Assess efficacy of 200 G static magnetic belts vs 50 G magnets

Design: double-blind, randomized, 2 phase cross-over study in patients with chronic sciatica

- Phase I - 3 random periods of 2 wks each: 2 with 200 G, and 1 with 50 G.
- Phase II - two 5 wk periods with the more effective magnet from Phase I and its corresponding 50/200 G device

Primary outcome: Daily leg pain (0-10 scale) in each phase II period.

Results: 38/40 patients completed Phase I; 28/31, Phase II

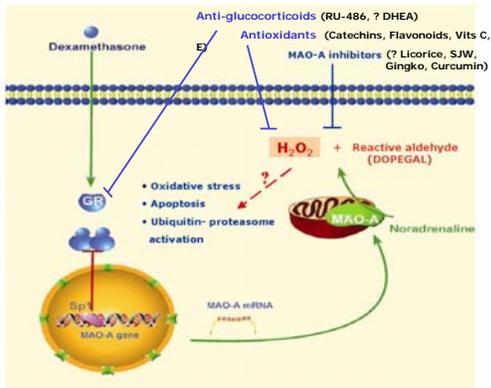
- Phase I, pain scores 200 G vs 50 G magnets (NS)
- In the last week of Phase II, pain scores were slightly lower with 200 G ($p < 0.06$); scores tended to improve in weeks 3 & 4
- Global pain was reduced more with 200 G ($p < 0.002$)

S. Khoromi et al, J Pain Symptom Management, 34:434, 2007

Mitochondria and Stress- Hypotheses

- Mitochondrial dysfunction and increased oxidative stress are thought to contribute to a wide range of chronic stress-related disorders
- CAM modalities that aim at improving mitochondrial biogenesis and function could prevent or alleviate such adverse effects

Manoli, I. et al, Trends Endocrinol Metab, 18: 190, 2007



Manoli I et al, FASEB J 19:1359, 2005

DHEA and Aging

- Weak adrenal androgen; exerts its effects after conversion to androgen and/or estrogen
- Most abundant steroid in humans; receptor not identified
- Levels decrease 80% with aging; may contribute to many age-related declines
- In animal models, reverses features of aging
- Widely used as dietary supplement for anti-aging and athletic enhancement purposes
- **Safety and efficacy in humans not established**

Original Article

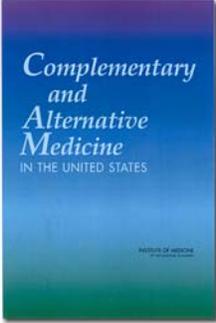
DHEA in Elderly Women and DHEA or Testosterone in Elderly Men

K. Sreekumaran Nair, M.D., Ph.D., Robert A. Rizza, M.D., Peter O'Brien, Ph.D., Ketan Dhatariya, M.D., M.R.C.P., Kevin R. Short, Ph.D., Ajay Nehra, M.D., Janet L. Vittone, M.D., George G. Klee, M.D., Ananda Basu, M.D., Rita Basu, M.D., Claudio Cobelli, Ph.D., Gianna Toffolo, Ph.D., Chiara Dalla Man, Ph.D., Donald J. Tindall, Ph.D., L. Joseph Melton, III, M.D., Ph.D., Glenn E. Smith, Ph.D., Sundeep Khosla,

N Engl J Med
Volume 355(16):1647-1659
October 19, 2006

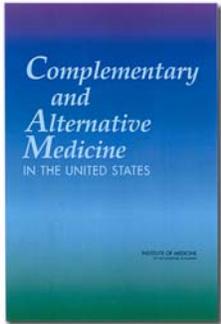


IOM Study on CAM



- NCCAM and 16 NIH ICs and AHRQ commissioned the study in 2002
- Panel asked to address a wide range of CAM science, policy, and practice issues
- Study released on January 12, 2005

IOM Study on CAM



Key Conclusions

- Same principles and standards of evidence of treatment effectiveness should apply to all conventional and CAM interventions
- Emphasize health services research and consider ethical, legal, and social implications of CAM research and integrated medicine
- Ensure rigor in CAM studies

Key Principles of CAM Research

- Use the same designs and outcome instruments as for definitive studies of conventional practices
- Randomized, double-blind controlled trials are the 'gold standard'
- Some modalities can not be blinded
- Studies of whole CAM 'systems' require creativity and flexibility
- CAM experts and patient advocates should be included in study design and oversight

Designing CAM Studies

- Individual botanical or nutritional supplements can be tested in randomized, double-blind controlled trials.
- Combinations of agents, especially if custom-tailored for each subject are harder to blind.
- Complex CAM systems and physical modalities, among others, can not be blinded
- It is hard to study the approach of an individual practitioner

NCCAM Training Opportunities

Mechanism

F30, F31, F32 NRSA Pre- and Post-Doctoral Fellowships

K01 Mentored Research Scientist Development Award

K23 Mentored Clinical Scientist Development Award

K24 Mentored Patient-Oriented Research Career
Development Award

K30 Clinical Research Curriculum Award

T32 NRSA Institutional Research Training Grant

R25 CAM Education Project Grant

The Challenge: Finding Good Mentors

Integrating CAM Education into Conventional Medical Curricula

- **Goal:** Integrate information on CAM practices into academic curricula
- **Settings:** 15 medical, nursing, pharmacy, osteopathy, dental schools
- **Funding:** Up to \$300K per year each for 5 years through R25 grants



CAM on PubMed

- Launched: February 2001
- Contains nearly 350,000 citations
- Access via NCCAM Web site: Click on icon
- Access via NLM's PubMed: Complementary Medicine Subset



Communications Information and Outreach

- **NCCAM Web Site**
More than 2 million visitors a year
- **Information Clearinghouse**
15,000 Inquiries per year
- **CAM at NIH** - quarterly newsletter
- **NCCAM update** - monthly e-bulletin



- **CME seminars**- online
- **Live Help**
online assistance
- **Public Education**
More than 100 fact sheets, reports, alerts, and other information products
- **Outreach via mass media**, web chats, teleconferences, town hall meetings



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- Nature, Use, and Claims of CAM
- Conducting CAM Research
- **Ethical Issues in CAM**



Requirements for Ethical Research

- Social value
- Scientific validity
- Fair subject selection
- Favorable risk:benefit ratio
- Independent review
- Informed consent
- Respect study subjects

Emmanuel, Wendler & Grady, *JAMA*, 2000

Ethical Issues Posed by CAM

Social value

- Extensive public use without proof
- Emerging evidence questions traditional assumptions of safety and efficacy

Scientific validity

- The literature is dominated by under-powered, poorly designed studies, conducted by people with limited scientific credentials

PWRSRCH1

*The plural of anecdote is **not** evidence*



Critique of Ongoing CAM Research

- Sets a **higher standard** than for conventional practices – few allopathic practices are proven with double-blind RCTs
- Is too **reductionistic** – CAM is multi-modal
- Does not test the **approach** as traditionally delivered – wrong herb; wrong dose; wrong needling point ...
- The investigators have no **expertise** in CAM

Ethical Issues Posed by CAM

Fair subject selection

- Advocates and skeptics refuse enrollment, comply poorly and withdraw prematurely
- These biases risk the generalizability of the study findings

Risk:benefit ratio

- Lack of formal preclinical and clinical data challenges assumptions of safety, optimal dose and schedule

Ethical Issues Posed by CAM

Independent review

- IRBs may oppose or lack expertise in CAM

Informed consent

- Undermines expectations of healing
- Difficult to inform where objective data on potential risks and benefits are lacking

Respect for subjects

- Cannot ethically study everything to which a person is willing to be subjected

Unethical Studies

- Practices or placebo arm would displace life-saving therapies
- Irreproducible products
- Unsafe practices or products





***Skepticism is the
chastity of the
intellect, and it is
shameful to
surrender it too soon
or to the first comer.***

George Santayana (1923)
