Evaluation of Complementary and Alternative Medicine Therapies

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Intro to Principles and Practice of Clinical Research
March 5, 2012
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

Biologically based practices
Mind-body medicine
Manipulative & body-based practices
Whole medical systems
The Appeal of CAM

Media reports of dramatic results

Belief that CAM treatments are natural

Patient empowerment

Focus on spiritual and emotional well-being

Therapists 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
<table>
<thead>
<tr>
<th>CAM Practice</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural products</td>
<td>17.7</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>12.7</td>
</tr>
<tr>
<td>Meditation</td>
<td>9.4</td>
</tr>
<tr>
<td>Chiropractic</td>
<td>8.6</td>
</tr>
<tr>
<td>Yoga</td>
<td>6.1</td>
</tr>
<tr>
<td>Massage</td>
<td>8.3</td>
</tr>
<tr>
<td>Diet-based therapies</td>
<td>3.6</td>
</tr>
<tr>
<td>Progressive Relaxation</td>
<td>2.9</td>
</tr>
<tr>
<td>Guided Imagery</td>
<td>2.2</td>
</tr>
<tr>
<td>Homeopathic treatment</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Who uses CAM?
More educated
In poorer health
More affluent
Posses a holistic orientation to health
Had a “transformational experience”
Identification with environmentalism, feminism, spirituality
Report choric 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
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
Ten Most Commonly Used Natural Products Among Adults - 2007

Fish Oil-Omega 3
Glucosamine
Echinacea
Flaxseed Oil/Pills
Ginseng
Combination Herb Pills
Ginkgo biloba
Chondroitin
Garlic Supplements
Coenzyme Q10
Presentation Overview
Nature, Use and Claims of CAM

Conducting CAM Research

Ethical Issues in CAM
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
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

Graph: percent of labeled content, panax species and E. senticos.

Ginseng products vary greatly in ginsenoside and eleuteroside 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 -- removed from U.S. Market
Prioritizing Studies

Public health needs

Preliminary data exist

Good products available

Feasible studies

Ethical studies
fMRI Pinpoints Central Effects of Acupuncture
Graphic: Parasagittal Slice (-2mm) showing Deqi and Pain + Deqi

Hui, K. et al., MGH, NMR Center
Mindfulness Based Stress Reduction (MBSR) Increases Regional Brain Gray Matter Density

Graphic showing three brain photos with changes in GMC

BK Holzel et al, Psychiatry Research 191: 36, 2011
MBSR Increases Brain Gray Matter Density in Regions involved in learning and memory, emotional regulation, self-referential processing, and perspective taking

4 graphs showing changes in GMC

BK Holzel et al, Psychiatry Research 191: 36, 2011
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

Placebo and Opioid Analgesia – Imagine a shared Neuronal Network

Petrovic, PP et al. Science Express Reports, 2002

Graphic: brain with arrow pointing to rostral anterior cingulated cortex and graph measuring 0 as the lowest and 3.5 as the highest. The brain is on 3.
‘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

$35.2 \pm 2.2\%$ “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

PI: Brian Berman, M.D., L.Ac.

Goal: Determine the short- and long-term safety and efficacy of acupuncture

Enrollment: 570 patients with knee osteoarthrosis (OA)

Design: Placebo controlled, 26 weeks

Intervention: True acupuncture vs. sham acupuncture, and education and attention control arms, in addition to standard care

Outcomes: Significantly relieves pain, significantly improves function, an effective complement to standard care
Grantee Research: Studying Cellular Mechanisms of Ginkgo Biloba

- Increases stress resistance and extends the lifespan of C.elegans
- Protects cultured neural cells from undergoing apoptosis
- Inhibits beta-amyloid aggregation
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 3.069 adults aged 72-96 yrs

Results: No effects on cognitive decline or incidence of Alzheimer’s or other dementia
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 200G static magnetic belts vs 50 G magnets

Design: double-blind, randomization, 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 50G 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)

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)
Graphic: Flow chart
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., Rober A. Rizza, M.D., Peter O’Brien, Ph.D., Katan Dharariya, M.D., M.R.C.P., Kevin R. Short, Ph.D., Ajay Nehra, M.D., Janel L. Vittone, M.D., George G. Klee, M.D., Ananda Basu, M.D., Claudio Caobelli, 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,
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

Graphic: Cover of Complementary and Alternative Medicine in the United States Institute of Medicine of the National Academies
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
CAM on PubMed

Launched: February 2001

Contains nearly 500,000

Access via NCCAM website: Click on icon

Access via NLM’s PubMed: Complementary Medicine Subset
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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, 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
Graphic: 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.

Photo: George Santayana (1923)