



Evidence-Based Medicine & Complementary & Alternative Therapies

**The Convergence
of Complementary,
Alternative &
Conventional
Health Care:**

**Educational Resources
for Health
Professionals**

This publication is one in a series of educational resource materials on complementary and alternative health care issues published by the Program on Integrative Medicine, University of North Carolina at Chapel Hill, entitled:

The Convergence of Complementary, Alternative & Conventional Health Care: Educational Resources for Health Professionals

Titles in the series include:

Understanding the Convergence of Complementary, Alternative & Conventional Care in the United States

Concepts of Healing & Models of Care

Evidence-Based Medicine & Complementary & Alternative Therapies

Assessing the Effectiveness of Complementary & Alternative Medicine

Safety Issues in Complementary & Alternative Medicine

Evaluating Information Sources for Complementary & Alternative Health Care

Information Sources for Complementary & Alternative Therapies

Integrating Complementary & Alternative Therapies With Conventional Care

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Evidence-Based Medicine & Complementary & Alternative Therapies

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THE CONVERGENCE OF COMPLEMENTARY, ALTERNATIVE & CONVENTIONAL HEALTH CARE

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Evidence-Based Medicine & Complementary & Alternative Therapies is one publication in a series entitled *The Convergence of Complementary, Alternative & Conventional Health Care*, developed as an educational resource for health professionals by the Program on Integrative Medicine, University of North Carolina at Chapel Hill, with support from the National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health.

This series responds to the many questions raised as conventional health care practitioners encounter widespread and increasing use of complementary and alternative therapies. Each publication in the series highlights one or more of the key issues facing health professionals today—including assessing information, safety, effectiveness, and the integration of conventional, complementary, and alternative health care.

Evidence-based Medicine and Complementary and Alternative Therapies explores how complementary and alternative therapies may be assessed using the methodology of evidence-based medicine, and the issues raised when conventional research techniques are applied to non-conventional health care.

Evidence-Based Medicine & Complementary & Alternative Therapies

foreword

The complexity of contemporary health care poses new challenges for clinicians in all fields. One such challenge has resulted from the dramatic increase over the last 10-15 years in the use of so-called “CAM” (Complementary and Alternative Medicine) therapies—a trend that appears to be continuing. In fact, there is no single or unified health care “system” in the United States, but a great many overlapping organizations and approaches to care. These include not only conventional but complementary and alternative health care options. Patients typically use not one, but multiple approaches to their illnesses, often without informing the health care providers involved.

It is in this context that the Association of American Medical Colleges (AAMC) advises physicians of their new responsibility to “be sufficiently knowledgeable about both traditional and non-traditional modes of care to provide intelligent guidance to their patients” (*Medical Schools Objectives Report*, 1998). This is a formidable challenge to clinicians

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who are often unaware of and untrained in other healing systems. Yet they are often called upon to advise their patients as to the safety and efficacy of these non-conventional practices. This publication is concerned with *how* practitioners can become “sufficiently knowledgeable” about complementary and alternative therapies so as to be able to provide “intelligent guidance to their patients.”

For most conventional clinicians, the inclination is to seek answers to questions about safety and efficacy from familiar research sources. But such “evidence-based medicine” may not always provide the best method of assessing the value of complementary and alternative therapies. The healing model practiced by many CAM practitioners is often complex and holistic, and is antithetical to the reductionist research methodology most commonly used to evaluate conventional therapies.

However, one cannot conclude that, because a healing system cannot be measured conventionally, it is ineffective or unsafe. Instead, one might come to appreciate the limitations as well as the strengths of the conventional research methodology. The need to answer the question “How do you know that complementary and alternative therapies are safe and effective?” may, in fact, require a rethinking of research strategies usually employed in evidence-based medicine.

In this publication, the reader is invited to examine the key issues raised in the process of assessing the safety and effectiveness of complementary and alternative medicine, including:

- the domains of evidence used to establish the value of complementary and alternative medicine;
- the strengths and weaknesses of the randomized controlled trial; and
- the role of the placebo in the effectiveness of complementary therapies.

Finally, a note about the terminology used in this publication. In recent years, the term “CAM” has come into common usage to describe, in the words of the National Center for Complementary and Alternative Medicine, “*a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine.*” Despite its convenient brevity, the acronym CAM has some unfortunate implications. It suggests, for example, homogeneity among the philosophies and practices included under the umbrella term. In reality, these practices are quite heterogeneous. It also implies a clear and complete distinction between conventional and CAM systems of care. That also is inaccurate.

The term CAM is therefore used sparingly here. And, when it is used, it is shorthand for that “group of diverse medical and health care approaches or therapies . . .” where the emphasis is on the word “diverse.”

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Evidence-Based Medicine & Complementary & Alternative Therapies

With the widespread and rising use of complementary and alternative therapies, clinicians are frequently asked by their patients for referrals to local CAM practitioners or for recommendations about treatment. A discussion about a particular alternative therapy between clinician and patient often begins with two basic questions: “Does it work?” and “Is it safe?” When confronted with such queries, many conventional health care practitioners feel inadequate to provide effective guidance or assistance (Ernst, Resch & White, 1995). Most have little knowledge or experience regarding many complementary and alternative therapies—and such knowledge is a necessary element in any discussion of their use.

Assessing the effectiveness and safety of complementary and alternative treatments is no simple matter. The conventional clinician is likely to turn to “evidence-based medicine” and familiar research methodology as the standard for judging clinical effectiveness. However, the treatments and healing techniques of many complementary and alternative therapies may not fit the methods and vocabulary used to evaluate conventional medical treatments (Richardson, 2002). Furthermore, sources of information about effectiveness of complementary therapies may not be readily available or research may be insufficient to demonstrate clinical effectiveness of a given therapy. Answering questions about safety and effectiveness may demand a rethinking of research strategies usually employed in evidence-based medicine.

Evidence-based medicine—or EBM—is the most recent expression of the idea that optimal medical care should be based on objective information about health conditions and treatment effects, as established through rigorously designed studies and valid testing.

THE GROWING USE OF COMPLEMENTARY & ALTERNATIVE HEALTH CARE

The number of annual visits to complementary and alternative health care practitioners grew by more than a third in the last decade. Furthermore, 1997 figures showed that the 629 million visits to CAM practitioners far exceeded the 386 million visits that year to conventional primary care doctors (Eisenberg, et al., 1998).

Such treatments are sought for a wide variety of common conditions and chronic diseases—back problems, allergies, arthritis, headaches, high blood pressure, anxiety, and digestive problems, to name a few. Moreover, patients are using complementary and alternative therapies in addition to, rather than instead of, conventional care (Eisenberg, 2001).

TABLE 1
PROPORTION OF EVIDENCE-BASED CARE GIVEN

	strong evidence (RCT)	moderate evidence (non-experimental)	unsupported
General Medicine (UK) 1995	53%	29%	18%
Surgery (UK) 1997	24%	71%	5%
General Practice (UK) 1996	30%	51%	19%
Tertiary Care Cancer Patients (US) 2000	14%	64%	22%

("What Proportion," n.d.)

The EBM concept was introduced about 15 years ago by researcher-clinicians at McMaster University in Canada (Sackett, Straus, Richardson, Rosenberg, & Haynes, 2000). They believed that, rather than making treatment decisions based on clinical experience, clinicians should, if possible, base their practice on reliable research, and described evidence-based medicine as "the conscientious, explicit and judicious

use of the best available evidence for the care of the individual patient."

The principles underlying EBM are as follows (Lockett, 1997; Sackett, et al., 2000):

- Although clinical experience and "intuition" are essential to the art of medicine, information gathered in clinical work must be recorded accurately and without bias to ensure that a body of knowledge is acquired.
- Symptoms do not necessarily represent a disease process, and pathophysiology does not necessarily produce symptoms or provide a basis for understanding illness. Therefore, the integration of evidence accumulated from all disciplines as well as the patient's life context is needed to understand illness.
- These rules of evidence should guide the use of clinical information to enable correct diagnosis and treatment.

In medicine, although some established results or data endure over time, scientific progress naturally leads to the discarding of what were previously considered "facts" or "truth" when new information contradicts old ideas. For example, a recent analysis of studies from the field of cirrhosis and hepatitis between 1945 and 1999 showed that 60 percent of conclusions were still thought to be true, 21 percent had been determined to be false, and 19 percent were now obsolete. The survival of these conclusions was no better when only data obtained from studies of high methodological quality were considered (Poynard, et al., 2002).

The regularity of such occurrences suggests that all clinicians must be wary of the reliability and longevity of clinical "evidence" that is regularly presented and applied in health care. Indeed, the questions raised in evaluating complementary and alternative medicine can promote objectivity in our thinking about conventional medicine (Vandenbroucke & de Craen, 2001).

acquiring the evidence

Modern medical research seeks to demonstrate clear cause-and-effect relationships while trying to exclude the influences of possible confounding factors. The assumption is that only after control-

ling for factors such as regression to the mean, the natural history of the illness, and the placebo effect, can the efficacy of a drug or procedure be assessed. This stable and successful process—the scientific method—with its emphasis on reproducibility and generalizability, clarifies the content of medicine and provides evidence for decisions in clinical practice.

Despite many years of funded research, surprisingly few studies have examined clinical practice to determine how much is actually based on scientific evidence. One estimate is that about 10-20 percent of conventional practice is founded on evidence-based clinical trials (Starfield, 2001). (*Table 1 describes the proportion of conventional health care in different specialties that is evidence-based.*)

In 1983, the U.S. Congress Office of Technology reported that only 10-20 percent of all procedures in medical practice had been shown scientifically to be effective. Another study (Dubinsky & Ferguson, 1990) reported that only 20 percent of the 126 medical technologies covered by Medicare insurance were supported by evidence from clinical studies.

However, other studies (based on data from different countries) report that clinical practice based on “any reasonable evidence” is much more widespread (Imrie & Ramey, 2001). These studies indicate that, on average, some form of compelling evidence was found to support practice in 75 percent of the cases and evidence from randomized controlled trials supported clinical practice 38 percent of the time. (*See Table 2, below.*)

multiple strategies for obtaining evidence

Lewith, Jonas, and Walach (2002) remind us that any area of medical inquiry requires a balanced research strategy combining multiple approaches to gathering evidence. Correspondingly, each has different strengths, limits, costs, and usefulness for clinical practice (*see Figure 1 on page 4*). Although demanding no less rigor than conventional medical research, research on CAM therapies may require additional and more varied strategies to successfully answer questions about effectiveness and safety.

This balanced research strategy combines research methodologies so as to gain insight into both specificity of effect and clinical utility. Research designs and methods include outcome studies, clinical and other observational methods, laboratory techniques, randomized controlled trials, qualitative research methods, health services research and health technology assessment, and reviews (e.g., meta-analyses, systematic reviews). The authors also remind us that we must go beyond expecting only randomized controlled trials (RCTs) to provide the critical guidance for clinical practice.

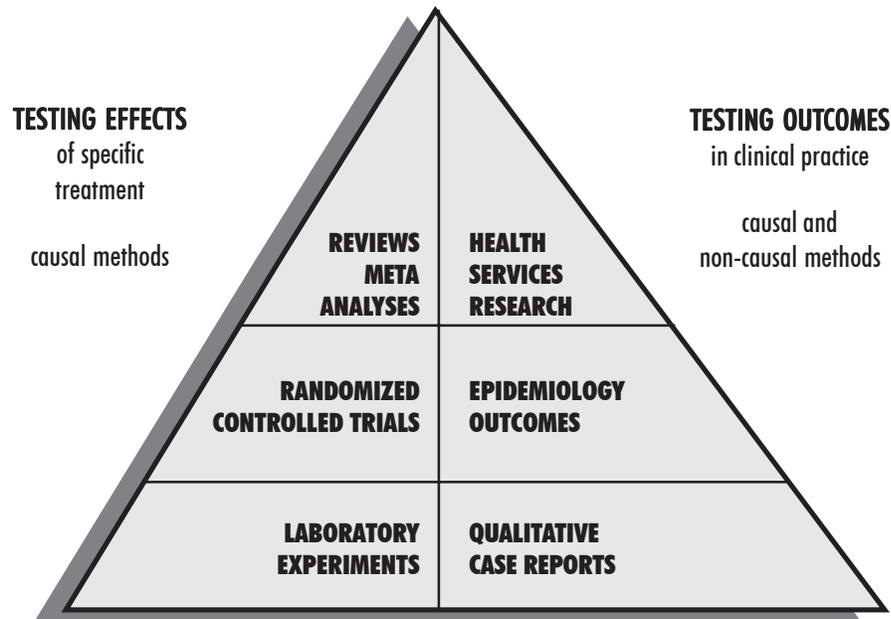
Given the availability of research data, how the clinician sifts the evidence to apply the therapy to clinical practice is summarized

TABLE 2
PERCENTAGE OF CLINICAL PRACTICE
SUPPORTED BY EVIDENCE

	ANY REASONABLE EVIDENCE	RANDOMIZED TRIALS
Anesthesia	97%	32%
Dermatology Therapy	77%	38%
Pediatric Surgery	77%	11%
Psychiatric Therapy	65%	65%
General Practice	81%	25%
Laparoscopic Procedures	78%	50%

(Imrie & Ramey, 2001)

**FIGURE 1
BALANCED EVIDENCE HIERARCHY**



SOURCE: Lewith, Jonas & Walach, 2002

below as a series of questions (Jonas & Levin, 1999):

- **Question:** How does the intervention or modality work?
Information Source: Laboratory
- **Question:** How specific is the treatment for the problem?
Information Source: Case reports and case series
- **Question:** How effective and reproducible is the treatment?
Information Source: Randomized controlled trials
- **Question:** What is the magnitude of the benefit or harm?
Information Source: Outcomes research
- **Question:** How generalizable is the effect/outcome to the population?
Information Source: Epidemiology

Further, different research questions and different audiences may be satisfied by different types of studies. For example, a new anti-diarrheal drug destined for a mass market must be approved by the FDA, and requires the specificity, blinding, randomization—and cost—of a randomized controlled trial, whereas a practitioner considering acupuncture for an individual patient with indigestion may require positive evidence from a meta-analysis or be satisfied with data from a qualitative case report.

evaluating the evidence for CAM efficacy & effectiveness

The evidence for the efficacy and effectiveness (or lack thereof) of complementary and alternative therapies accumulates continually. The weight of that evidence depends on the assessment of the **volume** of studies (the number performed and the number of subjects studied), the **quality** of studies (design and rigor), and the amount of **benefit and harm**. Increasingly, the weight of evidence is reported in a systematic review or a meta-analysis (Ernst & Pittler, 2000; Astin, Harkness, & Ernst, 2000). These approaches systematically assess the quality of the studies and, in the case of meta-analysis, are techniques to pool data from several studies for re-analysis. With the publication of more substantial and rigorous clinical studies, the strength and direction of evidence is continually changing.

The question then is what volume, quality, type, and number of studies are needed for the clinician to feel comfortable that a given treatment may benefit the patient? This question is usually addressed by evaluating levels of evidence. For example, Weiger and colleagues propose that positive results of three or more RCTs (with about 50 patients per trial) are adequate for a clinician to recommend therapy (Weiger, et al., 2001). In another less rigorous example in conventional medicine (*see Table 3*) the EULAR (European League Against Rheumatism) committee recommendations for the treatment of osteoarthritis evaluate levels of evidence in terms of strength.

The process of first examining the theory and practice of a particular complementary modality and then developing appropriate research methods for obtaining evidence of its clinical value is logical but has not been generally addressed. Rather, complementary and alternative medicine has been forced into the conventional scientific approach to demonstrate its benefit.

So, what might be suitable research designs for studying complementary and alternative therapies? As

TABLE 3
AN EXAMPLE OF LEVELS OF EVIDENCE
IN RECOMMENDING TREATMENTS FOR
OSTEOARTHRITIS

Treatments are first categorized in terms of strength of evidence, in rank order:

- 1A—meta-analysis of RCT
- 1B—at least one RCT
- 2A—at least one controlled trial without randomization
- 2B—at least one quasi-experimental study
- 3—descriptive studies (case-control, comparative)
- 4—expert opinions, clinical experience

Recommendation for treatment categories are then created:

- A—1A or 1B
- B—2A or 2B
- C—3
- D—3 or 4

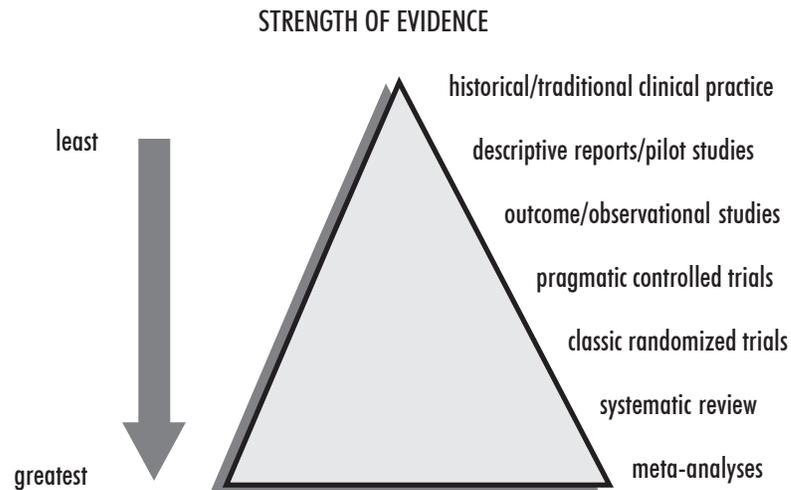
Thus, in non-pharmacologic trials of osteoarthritis, the strength of recommendations currently is:

- Weight loss - B
- Nutrients - C
- Education - A
- Knee taping - B
- Exercise - A
- Spa - C
- Knee replacement - C

NB: Many widely practiced surgical procedures, such as arthroscopy and joint replacement, are presumed to be evidence-based—but are not!

(Pendleton, et al., 2000)

FIGURE 2
THE RELATIVE RIGOR OF STUDIES PROVIDING EVIDENCE
FOR TREATMENT EFFECTIVENESS



Thomas and Fitter (2002) elegantly show, there is value in a number of approaches. They classify these approaches as exploratory studies, effectiveness studies, and improving studies. Different types of studies (*see Figure 2*) represent different rigor or strengths of evidence, but they may all be useful in accumulating evidence. The purposes of these different types of studies and the application of the results are summarized below.

exploratory studies

These are *pilot* or *clinical outcome studies*, usually employing a before-and-after design in routine practice settings. Typically small-scale and low-cost, they do not provide definitive results, due to lack of statistical power. However, they can answer questions about safety, whether a larger clinical trial is justified, what outcome measures might be appropriate, or the study's feasibility. The results offer preliminary data that may suggest a cause-and-effect relationship or a likely outcome.

effectiveness studies

Effectiveness studies (which include efficacy studies) are those designed to demonstrate a specific effect of treatment—that is, “does it work?” Studies of *efficacy* are usually carefully and rigorously structured to involve two groups of study subjects who are randomized to receive the intervention or a control (placebo) treatment. Ideally, the investigators and subjects do not know what treatment they are receiving, thus excluding other possible causes of benefit. These randomized controlled studies normally work best to show the efficacy of a single intervention for large groups of subjects in the form of means or probabilities of benefit. They do not address the effectiveness of individualized patient treatment.

Pragmatic randomized trials are designed somewhat like RCTs, but the setting is kept close to real-world practice, and may include packages of services (e.g., a rehabilitation program) or combined modalities (e.g., Traditional Chinese Medicine, which includes meditation, acupuncture, and herbal remedies) rather than one carefully defined drug or treatment. These are compared to a control group of subjects. There will therefore be less certainty about what specific agent or part of the service package produced clinical benefit than about which approach or package of therapies worked best.

Comparative effectiveness studies ask the question: “How well does it work in practice compared to other treatments?” These are designed to compare two or more treatment modalities or packages of services for a medical problem. These are less rigorous than randomized trials with control groups because patients who are not assigned randomly to treatments may differ in many ways, as determined by their and their clinicians’ choices of care. Again, the mixture of modalities does not allow one to know which specific treatment or combination of treatments was effective.

Cost-effectiveness studies may simply describe the costs of providing complementary therapies or, more usefully, may be part of a pragmatic clinical trial comparing both clinical outcomes and costs between treatments.

Systematic reviews involve detailed searching of the literature to sift and assess the quality of the cumulative evidence for a particular therapy. These use rigorous criteria in searching the literature and evaluating studies, followed by synthesis of the information to provide a summary of the evidence. But quantity of data may not offer the best information. Data from high-quality studies involving small numbers of subjects (e.g., 200-300) are of much greater value and give stronger evidence of effect than those from large, poor-quality studies where there is considerable uncertainty about the validity of the data.

Meta-analyses take systematic review further by selecting high-quality studies and then, using statistical techniques, pooling all the data and reanalyzing them—thus providing greater analytic power to the assessment of benefit.

improving studies

Improving studies are important to the practicing clinician, because they ask about how a treatment or protocol might be improved. These can take the form of *case studies* (a classic form of medical research), which may discover new facts or unusual events (especially adverse effects). *Reflective reports* can provide insights to cultural or socio-economic aspects of practice. Other studies that improve practice include those that test the reliability or concordance of diagnostic skills and patient assessment, the usefulness of diagnostic tests, and evaluation of clinical services.

RCTs: the ‘holy grail’ of biomedicine

For ancient and traditional healing modalities, one could argue that history provides the evidence on which to base clinical practice. The reasoning is that a remedy that has been used successfully for a thousand years must have some inherent value beyond the placebo effect. For modern conventional medicine, however, the “gold standard” of efficacy is the randomized controlled trial (RCT).

TABLE 4
RCT DESIGN ASSUMPTIONS

The RCT is designed to eliminate bias and provide “true” information to the clinician. It arose as a consequence of the modern pharmaceutical era in which efficacy and safety of synthetic chemicals needed to be demonstrated beyond the natural course of the disease or the power of the therapeutic relationship. Techniques that define RCTs include randomization of subjects to create statistically similar or balanced baseline groups and the careful masking/blinding of subjects, clinicians, and study outcomes. These methods are used to remove biases of patient selection, treatment, and observation/outcome reporting, while controlling for other non-specific and often unknown effects. This “double-blinding” produces high internal validity. The RCT is based on the following assumptions:

- Treatment with the drug is better than no treatment
- Treatment should consist only of a specific intervention (e.g., new medication) rather than a non-specific intervention (e.g., clinic visit)
- The specific intervention must have efficacy (i.e., it must show clinically significant improvement)
- Improvement from an efficacious intervention must work better than the placebo
- Ideally, there should be equipoise (i.e., equal uncertainty for the investigator as to whether the treatment will work or won't work (Heron, 2001)).

As discussed above, between tradition and RCTs there are still a number of research models that are useful in assessing treatment effectiveness (Grollman, 2001). For example, a recent comparison of observational or descriptive studies of groups of subjects versus RCT studies of the same therapies, showed that estimates and calculations of the treatment effects (efficacy) were essentially similar for all research designs (Benson & Hartz, 2000), underscoring the fact that a great deal can be learned from research other than the randomized controlled trial.

Nonetheless, because the ultimate standard for evidence in biomedicine is the RCT, many complementary and alternative therapies are now being studied in this way in the United States, mainly through National Institutes of Health (NIH) funding. Indeed, many conventional practitioners argue that these therapies can be accepted in practice and education *only* through experimental methods (especially the RCT) that demonstrate their biological efficacy and value. They argue further that other forms of evidence are likely to be flawed (Fontanarosa & Lundberg, 1998). In contrast, other researchers and clinicians believe that RCTs have significant limitations and that less costly outcomes studies may be more appropriate (Walach, Jonas, & Lewith, 2002).

The belief in the strength and validity of the RCT is based on certain assumptions about this research methodology (see Table 4). While this may be the optimum model for studying an isolated drug

or treatment, the assumptions underlying the RCT often create problems in studies of certain complementary and alternative modalities. Holistic healing practices, which rely on many therapies or interventions working in concert and which most often involve a trained practitioner, are not adequately measured by the RCT model. The RCT—which requires blinding and elimination of variables—is at direct odds with such healing approaches.

reconsidering the “gold standard” in medical research

Although the RCT is considered the best method for proving the efficacy of a specific drug or treatment, the objectivity of the classic experimental method as well as the reductionist approach to assessment have recently come under scrutiny and criticism (Heron, 2001). (See Table 5) Criticisms of use of RCT methodology range from concerns about the selection of participants

and neglect of psychological factors, to challenges in measuring important variables. At the heart of the criticisms is the question of whether evidence of experimental validity translates into practical clinical validity for individual patients.

Another difficulty with RCTs is that the control devised as a comparison for an active intervention may be inadequate to delineate true effect. The outcome may in fact be the result of either the natural course of the illness, the study environment, or a change in the patient's perceptions of the illness and the study. Or, the control itself may have some unrecognized biological activity.

TABLE 5 **RE-EVALUATING THE RCT AS THE 'GOLD STANDARD' RESEARCH DESIGN**

Among the concerns raised about RCT-based research:

- RCT results obtained with great rigor in very controlled conditions (known as "high internal validity") may be of limited value in clinical practice where patients are more diverse and often have more complex clinical problems than the original research subjects.
- Specific effects (i.e., a single drug) may not be the most valuable therapeutic intervention for the patient.
- In selecting variables in the study, researchers may either ignore or be unaware of other factors that cannot be measured under these conditions. These excluded factors might influence the outcomes, and are not necessarily controlled for in a clinical trial.
- Medical studies do not usually clarify how, in each patient, the mind affects the body (placebo effect) or how this effect may vary among individuals or different cultural groups.
- Large-scale studies tend to obscure each individual's interactions with the drug/intervention, so these data do not reveal to the clinician how an individual patient will react to treatment. The question, "What is really best for this patient sitting in front of me?" is never addressed by large randomized studies.
- Treatment based on inferential statistics and RCT designs is bound to eventually harm some people, because of events that cannot be predicted, and many studies are not large enough to identify significant adverse events. Recent examples include the withdrawal in 2001 of Baycol (a statin drug for lowering cholesterol) because of serious adverse effects reported only after the drug was widely marketed and not noted or reported in development and assessment ("Bayer voluntarily withdraws Baycol," 2001), and the withdrawal of Vioxx (an anti-inflammatory) in 2004, because of adverse cardiac effects ("Vioxx (rofecoxib)," n.d.).
- The scientific study of therapies using RCTs systematically removes any analysis or understanding of how people feel about their illnesses. Each patient has a unique view of his or her own problem, a perspective that plays a role in clinical outcomes. This is not accounted for in RCTs.
- In randomized, controlled studies of conventional interventions, there is an emphasis on equipoise (i.e., "equal uncertainty for the investigator as to whether the treatment will work or won't work.") Equipoise implies an attitude of emotional distancing and ignorance of the subject and researcher regarding treatment outcomes. Equipoise is rarely achieved in those studies in which the experienced clinician strongly believes in the effectiveness of his/her treatment and subjects often have entered the study because of their specific preferences.

(Heron, 2001)

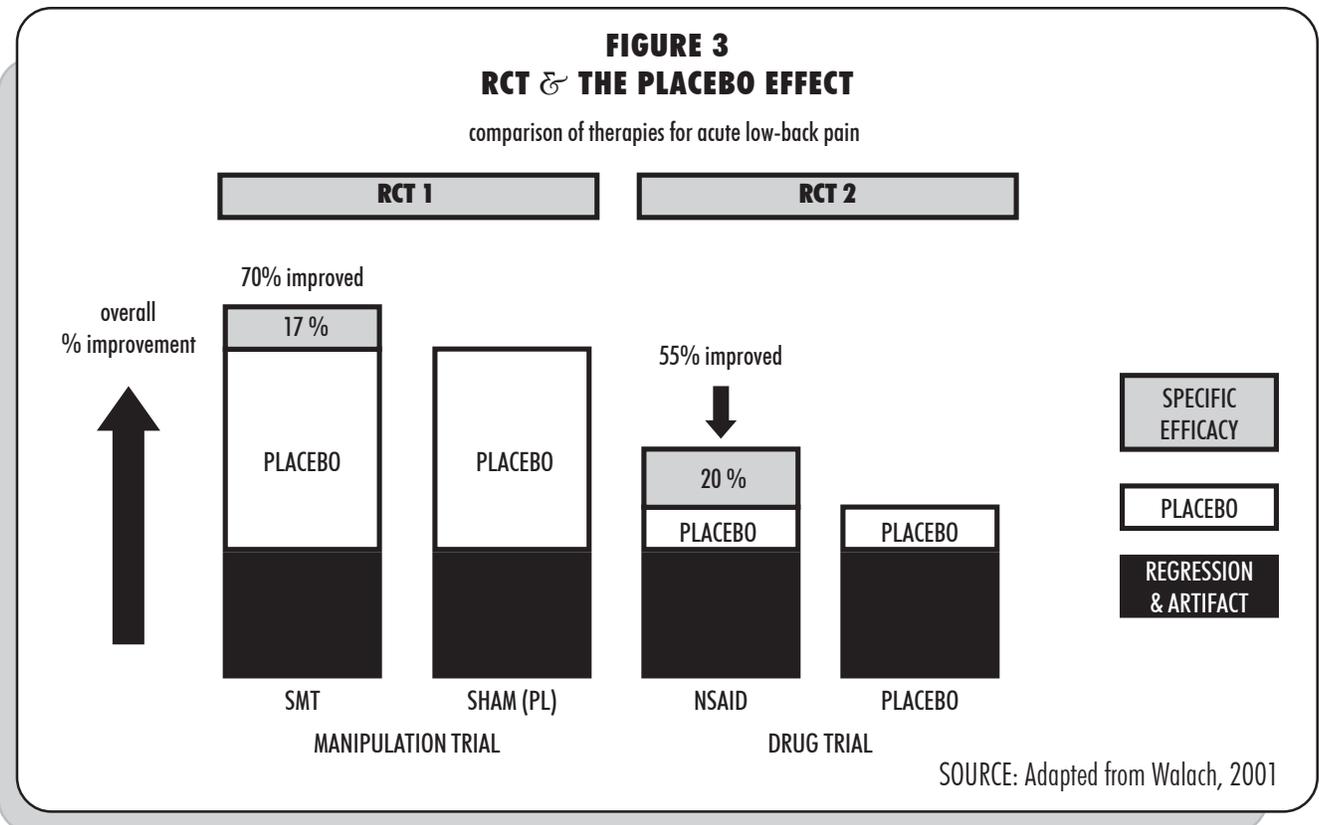
There also is evidence that aspects of medical research, clinical trials, and publications of evidence are often biased, poorly implemented, and tainted by commercial financial interests (Altman, 2002). It is interesting that only about 50 percent of RCTs reported at conventional medical conferences eventually materialize as published articles (Eisenberg, 2001).

RCTs can vary greatly in quality, as well, so one should not be persuaded about strength of evidence solely by the power of the initials ‘RCT’! In fact, rigorous reviews (using special scoring systems) of the quality of RCTs are needed to develop effective meta-analyses of clinical trials of specific therapies (Jadad, et al., 1996).

Finally, there appear to be substantial methodological discrepancies between the results of meta-analyses (studies that pool and re-analyze data from many clinical trials) and single large RCTs studying the same problem (Celermajer, 2001). This suggests that the “truth”—even with our most rigorous scientific methods—is still a moving target.

clinical research: what is being measured?

Clinicians making day-to-day decisions with patients often rely on evidence from RCTs to confirm the efficacy of specific therapies they recommend. That practice, however, has been described as the “prejudice of specificity”—the belief in the value of proving the effectiveness of a single agent (Walach, et al., 2002). While most pharmaceuticals are single agents designed to affect one or two



physiological/biochemical reactions or systems, complementary therapies often involve complex or simultaneous patterns of diagnosis and interventions that may be designed to affect the whole body through self-regulatory processes. A classic example is Traditional Chinese Medicine, which uses acupuncture, herbal formulas, meditation, and massage in combination (Kaptchuk, 2000). The question then becomes: Is the effectiveness of a complementary therapy either a specific effect of the complementary therapy itself or the result of a placebo or non-specific biological effect? Or is it the result of a combination of treatment modalities and approaches? Before answering this question, one must explore the power of the placebo in both CAM and conventional cases.

RCTS, CAM & the placebo effect

There is little research to clarify the degree to which complementary and alternative modalities produce specific or non-specific effects, but examples from pharmaceutical research are enlightening. For example, Moerman showed that placebo responses to the medication cimetidine for duodenal ulcers were substantial, delivering 66 percent of the clinical improvement while the drug itself added another 33 percent of the improvement (Moerman, 1983).

In considering the best outcome for the patient receiving treatment, one finds an interesting paradox (*see Figure 3*) in data based on low-back pain literature (Bronfort, 1997; van Tulder, Koes & Bouter, 1996; Walach, 2001). The diagram shows the efficacy of therapies for acute low-back pain in two randomized clinical trials. RCT #1 compared spinal manipulative therapy (SMT) against a sham (control) manipulation. This study had a strong non-specific placebo effect because of the special approach of the manual therapist and the use and symbolism of hands-on maneuvers for both the sham and correct treatments. The RCT showed that SMT produced only a 17-percent improvement in pain relief that was specifically due to the manipulative technique. This effect was not quite statistically significant, given the numbers of subjects and power of the study.

The second study, involving many more subjects, compared an NSAID (similar to Ibuprofen) to a placebo medication. Here the placebo effect was much less powerful, relying on an inert pill. The NSAID specifically produced a 20-percent improvement in pain relief—a statistically significant benefit.

Thus, the outcome in the SMT study (RCT #1) was an overall improvement of 70 percent relief (specific effect (17 percent) + placebo effect + non-specific artifacts). With an improvement that is not statistically significant compared to the sham procedure, this study would be reported in the literature as having only limited benefit at best. Although the overall improvement for the NSAID study (RCT #2) was 55 percent (15 percent less than RCT #1), the NSAID was statistically “proven” to be efficacious (20 percent specific improvement). The clinician scanning the literature based on these studies would get the message: “NSAIDs are useful and manipulation is ineffective for acute low-back pain.” And they would be likely to base their clinical decisions on this conclusion.

In fact, SMT, in conjunction with a large placebo effect, produced better overall pain relief than NSAIDs. Is it not likely that either a patient or a clinician would be more interested in treatment that produced a 70 percent improvement rather than a 55 percent improvement? This is the paradox inherent in efforts to measure non-conventional therapies. They may work well for the patient, but may be unproven (or unprovable) scientifically. What is the clinician to do? The enhanced placebo effect presented here raises clinical, scientific, and ethical questions of what is

THE POWER OF THE PLACEBO

The power of the placebo is illustrated by two clinical examples. A meta-analysis of 39 randomized controlled studies (1974-1995) of drug therapy for depression found that 27 percent of the response to therapy was directly due to medication, 50 percent was due to placebo effect, and 23 percent was due to other non-specific factors (Sapirstein, 1995; Kirsch, 1997). No doubt the placebo effect was maximized by the clinicians' and patients' strong belief in the efficacy of the drug. A recent RCT of arthroscopy for pain relief of osteoarthritis (reported to relieve pain in 50 percent of patients) showed that pain and functional improvement using sham arthroscopy was just as good. Though patient and clinician expectations may have been moderate, the power of the procedure was clearly substantial in producing a placebo response (Moseley, et al., 2002).

“legitimate” healing (Kaptchuk, 2002). Why should the patient be denied manipulation because the therapy is perceived as “placebo” and therefore scientifically ineffective?

the role of placebo in the healing process

The word “placebo” is Latin, meaning “I shall please.” Clinically, *placebo* is defined as “an intervention designed to simulate medical therapy that, at the time of use, is believed not to be a specific therapy for the condition for which it is offered” (Brody, 2000). A *placebo response* is defined as “a measurable, observed, or felt change in a person’s bodily state attributable to the symbolic import of a treatment or treatment setting, rather than a specific pharmacological or physiological property” (Hart & Dieppe, 1996). The administrator of the placebo usually believes that the substance itself is inert or innocuous, yet the placebo can produce benefit either through the patient’s belief in the effectiveness of the “inert” substance—or

through the caring interaction in which treatment occurred.

A *nocebo response* is the adverse effect of a placebo, produced through the expectation of a negative effect. For example, patients given excessive details of rare side effects of medication are more likely to report side effects; a physician expressing diagnostic uncertainty to the patient can delay symptom resolution; and the bustle, sounds, and long wait in uncomfortable circumstances in an emergency room can make patients’ symptoms worse (Helman, 2001).

the history of the placebo: from bread pills to research controls

Placebo medicines were widely used by physicians up to the early 1960s (although few physicians today will admit to knowingly using them). They took the form of liquid medicines or tonics (usually containing coloring agents and flavoring agents such as Angostura Bitters) or sugar pills and were used to relieve minor symptoms and manage self-limited illnesses. Studies dating from the 1850s have shown the positive effects on disease of hope, faith, and imagination when giving “inert” substances. Placebos were seen as a useful and paternalistic screen behind which clinicians could observe nature taking its course (now called self-healing), either because nothing else could be done or because the problem was chronic or self-limited.

Placebos began to be used as a control intervention in clinical trials (for angina pectoris) in the 1930s. Their use was to control for the effects of non-specific factors affecting the course of the disease and improvement from caring for the patient. In the 1970s, the Food and Drug Admin-

istration (FDA) began requiring double-blind, placebo-controlled studies to prove efficacy and safety of new therapies (Shapiro & Shapiro, 1997).

In 1955, Beecher reviewed 15 placebo-controlled clinical trials and reported that, on average, the magnitude of placebo effect was 35 percent (Beecher, 1955). This study did not, however, take into account the natural history of the disease, which is usually improvement over time. We now know that the magnitude of the placebo response rate is quite variable—from 5-70 percent. And, in a review of 89 randomized controlled studies, Linde and colleagues (1997) reported an average placebo response rate of 35 percent. The placebo effect diminishes over time or when the patient's belief in it has been undermined (Peters, 2001).

Despite what is known about placebos, little understanding of their value and effectiveness has been transferred to clinical practice. Over the years, placebos have been linked to “quackery,” and research findings have been ignored. Today, most clinicians regard the placebo as an inert substance with no value in clinical practice; although they may inadvertently use potent drugs in a placebo fashion—prescribing valium for stress, for example.

how does the placebo effect work?

How the placebo effect works is not really understood, although theories abound. In Engel's biopsychosocial model of healing, the placebo response connects psychosocial and cultural variables with physiological and cellular processes (Engel, 1979).

The range of factors that stimulate the placebo response is extensive—from pills and prescriptions to bedside manner and conversation. Most studies of the placebo effect have focused on patient responses to medications or surgical procedures, not on the healing effect of the clinician-patient encounter/relationship, or the ritual of the office visit/prescription. But these less tangible factors can have powerful effects. One study that did explore the visit/prescription ritual revealed a significant placebo response. In the 1970s, psychologist Michael Balint and colleagues showed the healing effect of the ritualized repeat prescription even when the physician never actually saw the patient (Balint, Joyce, Marinker, & Woodcock, 1970).

Although there is no clearly articulated mode of action, the placebo response (in which the patient feels better or actually promotes his/her own healing ability) has been explained in several different ways. These include: behavioral conditioning; personality; the “meaning response;” and psychoneuroimmunology.

Behavioral conditioning/previous experience. Behavioral conditioning is a learned response based on prior experience or association with stimuli that brought about change (Ader, 1997). For example, people who have responded well to chiropractic manual therapy will do better than those who never have experienced manual therapy. Similarly, previous negative experiences with medical care may cause concern about the next similar experience. For example, a difficult birthing experience may make the mother fear the next pregnancy and may modify the progress of subsequent labor. These experiences also can change how patients trust and respond to clinicians.

Personal response expectancy/personality. Personal response expectancies are automatic responses to treatment or health encounters that develop over time as a result of individual personality characteristics. This phenomenon is also based on the patient's personal experience,

family beliefs, culture, and social attitudes (Kalauokalani, Cherkin, Sherman, Koepsell, & Deyo, 2001).

The meaning response. To try to separate the role of the inert pill from other placebo effects, Moerman and Jonas (2002) have recently coined the term “the meaning response.” This refers to the physiological or psychological effects provoked by the symbolism or meaning that patients give to the origins of their illness or to the treatments they received in health care settings.

Psychoneuroimmunology. Endorphin response, catecholamines, and cortisol levels all change with emotional states and affect the patient’s physiological functioning (Kirsch, 1997; Peters, 2001). It has been shown that interaction between healer and patient, expectancy, and other aspects of the meaning response all produce changes in the above physiological parameters.

perspectives on the placebo response

Another explanation for how the placebo effect works is that it is the result of the interaction of patient and clinician beliefs: the patient’s belief or expectancy of treatment and outcome; the clinician’s belief or expectancy of outcome; and the belief or expectancy engendered by the relationship and interaction between the two.

The importance of being heard and of being able to talk openly about one’s symptoms and fears is an example of the power of these interconnected beliefs. In one study, the rate of functional recovery of elderly hip fractures was related to the amount of discussion about the injury and hopes for a return to daily life (Borkan, Quirk, & Sullivan, 1991). In another study, Thomas showed that patients with viral illness would improve more rapidly if given strong positive reassurance of recovery by the physician, rather than being told they would get better only as the illness took its natural course (Thomas, 1987).

Other recent research sheds a different light on the subject. A major survey of 114 clinical trials involving placebos suggests that the clinical effects of placebos may be minimal except for patients suffering pain (Hrobartsson & Gotsche, 2001). On first impression, this finding seriously questions 30 years of placebo research. However, the trials reported in the survey involved mostly severe medical conditions in very rigorous research settings—factors that tend to inhibit the placebo effect. In fact, the study only confirmed the “inert” attributes of the placebo intervention and did not address the “meaning response” (Feinstein, 2001).

This finding has numerous implications. If, as in the above meta-analysis, the placebo effect is indeed shown to be minimal, it may alter perspectives on research measuring complementary and alternative therapies. One might conclude that the effectiveness of these therapies, demonstrated in a range of clinical trials, would be more likely due to a specific biological effect than to the placebo effect, as previously thought.

Until recently, established medical practice and education have not really accepted the value of the healing effect of the placebo, partly because there are few studies in the field and partly because the research is not biomedical—that is, it cannot easily be explained in mechanistic terms. Furthermore, the placebo currently has no obvious dollar value. Therefore, funding for research will most likely come from foundations and the federal government, not the health care industry. To wit: the National Center for Complementary and Alternative Medicine has recently supported a national conference and research proposals in this field.

Another reason for this lack of interest may be the current economic and medico-cultural climate, where falling reimbursement rates translate into less and less time given patients by health care professionals. This theoretically inhibits convenient clinical applications of the placebo, such as the clinician-patient relationship. However, some clinicians intuitively come to learn the value of the placebo effect as they learn that conventional medicine has substantial limitations in treating many chronic and self-limiting conditions.

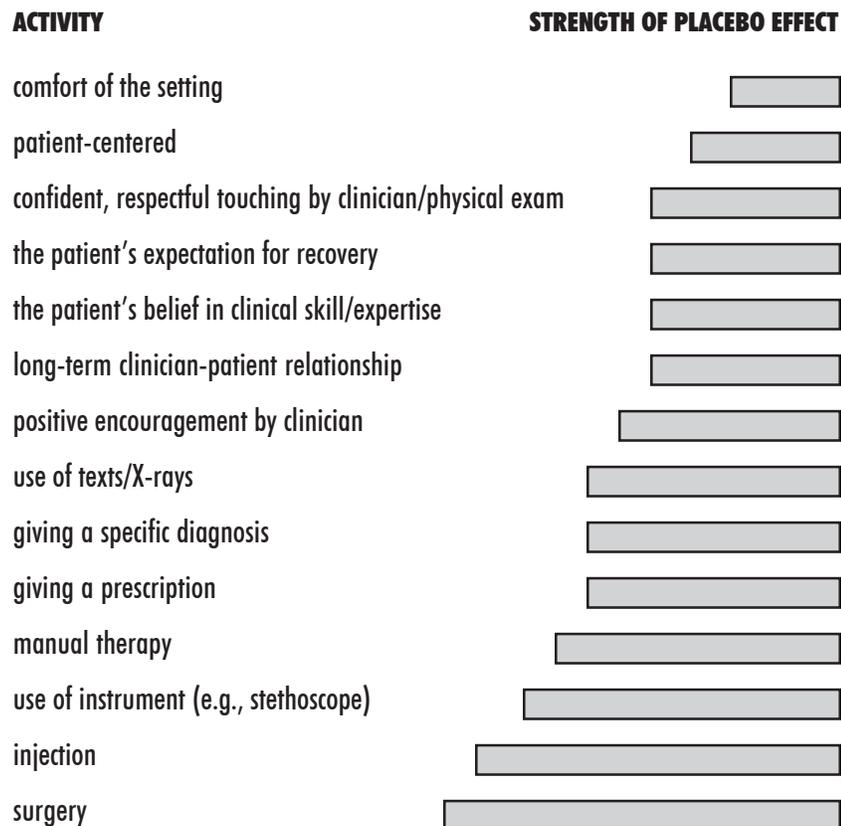
placebo “personalities” and dose response

There is little evidence to support the notion that there is a “placebo personality type,” although highly anxious personalities often have a more pronounced placebo response. The effect is independent of intelligence (Peters, 2001).

One of the more interesting questions is whether there is a “dose response” to placebos. For example, in clinical trials of surgical procedures, the placebo response may be quite strong, while in the case of a medication there is only a small effect. It has been suggested that there may be a graded effect based on the characteristics of the placebo, but there has not been much research. Based on the little research available, Figure 4 represents a possible dose/intensity grading (Kaptchuk, Goldman, Stone, & Stason, 2000).

The clinical approach of many complementary and alternative health care providers may be one important explanation of the attraction they hold for patients. This clinical style—typical of many so-called CAM practitioners—inherently incorporates patient-centered aspects of the “placebo effect” and gives substantial time for patients to articulate the meaning of their illness and maximize the placebo response.

FIGURE 4
RELATIVE POWER OF THE PLACEBO



SOURCE: Kaptchuk, et al., 2000; Peters, 2001

maximizing the placebo response: reviving the caring approach

The evidence strongly suggests that the healing effect of the placebo may be of value in medicine, although in some instances its use may pose the ethical dilemma of “deception.” Some believe that it is always wrong to use deception in clinical practice; others believe it is justified if used with care (Spiro, 1998).

the symbolic meaning model

Clinicians desire to maximize the outcome of any treatment; the placebo response can be a valuable tool in achieving that goal. Specifically, the placebo can be used to assist clinical outcomes using the symbolic meaning model (Moerman & Jonas, 2002). The illness experience is shifted to a positive direction when:

- The patient feels listened to, and receives coherent explanations aligned with his or her world view.
- The patient perceives that care, concern, and support are being offered.
- The patient feels in control of the situation.

Based on that understanding, the following guidelines offer practitioners a way to boost the placebo response in dealing with patients.

- ***Use the patient-centered approach:*** Demonstrate an interest in the whole person; know the patient over time; show sensitivity and empathy; be viewed as trustworthy; adapt medical management to the patient’s values; use a collaborative model of decision making (Stewart, et al., 1995).
- ***Ask what the patient perceives*** to be the problem or reason(s) for the problem. And ask what the patient thinks should be done to resolve the problem.
- Adjust explanation and reassurance to ***align with the patient’s belief systems*** and independence.
- ***Be positive about the potential effects*** of clinical management without exaggerating the benefits. Enhance the promise of mastery over the problem and the expectation of improvement.
- Consider the ***placebo as a useful intervention*** whose action is not clearly articulated.
- Tell the patient that ***the intervention may also work by stimulating the body’s innate healing ability.***
- ***Don’t use the word “placebo”*** in discussion with the patient. The positive effect may vanish into thin air!

Several examples illustrate this approach to using placebo effectively. In a 1964 study at a well regarded teaching hospital, anesthesiologists visited patients before surgery and, with half the patients, engaged in a five-minute, friendly, hand-holding explanation of the procedure and expectations of postoperative pain management. The other patients received just the routine, cursory introduction. Those treated in the patient-centered fashion required 50 percent less post-op analgesia, and were discharged nearly three days sooner than the other group (Shapiro & Shapiro, 1997).

In a second study, asthmatic patients were given an inhaler with nebulized saline. When they were told they were inhaling an irritant, bronchial obstruction increased. But after being told they were inhaling a bronchodilator, pulmonary function improved substantially (Hahn, 1999).

A third example is a recent systematic review of 19 randomized-controlled trials of the therapeutic effect of the doctor-patient relationship. The study generally confirmed its clinical value in improving outcomes of patient satisfaction, but was equivocal in terms of biological improvement (Di Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001).

the nocebo effect

The nocebo is the placebo's negative manifestation—the expectation of a negative effect (Hahn, 1999). The ultimate placebo/nocebo effect is exemplified when someone lives or dies by sheer will, fear, or belief. The dying Thomas Jefferson expressly clung to life so that he could die on July 4, 1826—50 years after the signing of the Declaration of Independence. Another example of a major nocebo effect is voodoo death caused by abject fear and terror from the death spell (Cannon, 1942; Golden, 1977).

Nocebo effects in medicine can arise from fears aroused in patients either by the lack of an adequate explanation of medical procedures or by raising possibilities of adverse effects even when these might be very rare or unlikely (Sox, Margulies & Sox, 1981). The following scenario illustrates the nocebo effect at work: A patient complaining of a headache asks the doctor what might be causing it. The doctor proceeds to list meningitis, stroke, aneurysm, and cancer—even though most headaches are not life threatening. Upon hearing these serious options, the patient arranges an urgent office visit or goes to the emergency room where he waits for four hours to be seen, and then gets a CT scan, which is found to be slightly questionable. Although the headache has now gone away, he makes a follow-up ap-

THE PLACEBO EFFECT: A CASE SCENARIO

Mr. Jones has had the "flu" for three days. He wants to get back to work, but is worried about continued high fever and fatigue. He comes to see the nurse practitioner. What factors might affect his recovery? Some possibilities:

Natural process: The natural history of an illness that ends in recovery: Mr. Jones will be better in another few days.

Placebo Effect A—iatrotherapy: From the nurse, Mr. Jones gains understanding and information about the natural history and prognosis of the illness, reassurance and comfort, a form of healing symbolism. This either affects Mr. Jones positively in a physical sense or helps him cope more effectively with the symptoms.

Placebo Effect B—the psychic effect: Mr. Jones may have a certain attitude towards being sick—perhaps either a tendency to suffer and become dependent, or maybe to fight it and get on with daily tasks. Consequently, his beliefs and actions while sick may well alter the course of the illness.

Placebo Effect C—specific symbolic intervention: The nurse practitioner advises a specific cold remedy, although she knows it is not known to alter the course of flu. This is a form of symbolic healing.

Valid biological intervention: The nurse practitioner prescribes a new antiviral that is shown in clinical trials to possibly shorten the duration of the symptoms by one day.

Thus, the patient may experience a placebo response to reassurance that he will get better—especially if the nurse practitioner is very positive about the situation; or from being given a "symbolic" prescription for a cold remedy or the "anti-viral" by a clinician who "believes it to be scientifically shown as effective" and that may or may not shorten the course of the illness; or from the whole empathic interaction. Probably several of the above factors might speed Mr. Jones's recovery.

pointment with a neurosurgeon. The ultimate impact of the nocebo response—in the form of costs, tests, stress, and anxiety—may be considerable.

the placebo response and complementary therapies

Is there a relationship between the placebo response and complementary and alternative therapies? Yes, and as far as we know it is no different than the response experienced in conventional medicine. However, the more leisurely and patient-centered approach of complementary practitioners, with aligned expectations, usually in a relaxing environment, fits the principles laid out by Benson (1997) for maximizing the non-specific placebo effect. In addition, the modality itself may have a specific or additional biological regulatory effect to enhance improvement over and above the placebo response. The assertion that CAM therapies induce a more powerful placebo effect than conventional medicine has not been studied.

Given the biomedical model of care, one can understand why the effect of a complementary therapy such as ginseng—which is used to boost the immune system as an aid to self-healing—might be regarded by conventional medicine as a placebo, rather than an agent directly addressing the cause and treatment of a specific illness.

problems facing research on complementary & alternative medicine

There are a number of problems inherent in the development of useful studies of effectiveness in medicine, including both methodological and organizational issues (Nahin & Straus, 2001). These problems exist for conventional medicine, but may be particularly relevant for complementary and alternative therapies.

research methods

One problem is **the use of premature explanatory models** or mechanisms of the intervention that may not account for all the effects of the modality/treatment. For example, in 1970, it was theorized that acupuncture acted by enhancing endorphin activity in the body as the result of needle insertion. Subsequently, this explanation did not account for other discovered effects of acupuncture such as vasodilation, gastric changes, effects on the uterine blood flow, and contractility (Peters, 2001; Shapiro & Shapiro, 1997).

Many healing systems (e.g., Native American medicine, Traditional Chinese Medicine, naturopathy) deliver **complex, individualized interventions** based on diagnostic skills that may not be familiar to the conventionally trained health professional. The study of such complex interventions is more challenging than that of a “pure” intervention that can be isolated in a conventional randomized controlled study.

Inappropriate or insufficient methods often are chosen to evaluate or measure an intervention. One example is the use of a global health functioning measure to assess improvement of only one symptom, such as “nausea.” Similarly, merely measuring pain levels of patients with low-back syndromes offers no data on the patient’s physical function. Measuring the speed of disap-

pearance of symptoms without measuring long-term benefit or untoward side effects may offer unfair advantage to one therapy over another.

Optimal dosage schedules and administration routes of herbals and supplements are not always known or established, and standard dose-related interventions may be difficult to set up.

There is often great **difficulty in developing control/placebo interventions** for studies of complementary and alternative therapies. In a pharmaceutical study, it is a simple matter to prepare an inert “pill” to serve as a control. An “inert” massage is hard to imagine. And is it possible to develop a “control” magnet that the patient cannot recognize? Unlikely—a control magnet would not stick to a refrigerator door, so the patient would soon discover it was a dud!

organization of research

Publication bias. Publication bias may halt or slow useful research. For example, healing touch, currently used by thousands of nurses, was first proposed as a healing energy field, focused and manipulated by the therapist. A single negative study of this mechanism published in a prestigious medical journal “proved” to the scientific community that the human energy field does not exist and the therapy was dismissed as useless (Dossey, 2003). There is also evidence for a strong publishing bias in favor of conventional studies (odds ratio 3.01) compared to studies on complementary therapies (Resch & Ernst, 2000). Until recently, the medical press has often misrepresented or generalized from negative findings in complementary medicine.

Limited studies. There are many published studies (mostly small) of just one part of a healing system (e.g., moxibustion as part of Traditional Chinese Medicine, or meditation as part of Ayurveda). But because the research design isolates components of the system, the results from the studies do not reflect true clinical practice and thereby may not relate directly to outcomes in the normal clinical environment.

Limited funding. In the United States, substantial funding has not been available to support research on complementary and alternative medicine, so the criticism that these therapies have not been validated must be tempered.

Commercial influences. Research and funding may be biased toward treatment of specific conditions because of medical/herbal/supplement industry market forces that promote certain products. St. John’s wort for depression and glucosamine sulfate for arthritis—popular remedies for two very common conditions—are examples of alternative therapy products that have been researched and marketed extensively.

Few pilot studies. Developing large studies in any health care field usually requires considerable piloting to work out the kinks. Well trained researchers and funding for such projects in complementary and alternative medicine are in short supply (Nahin & Straus, 2001).

evaluating the delivery of complementary & alternative care

The overwhelming majority of research data on complementary and alternative medicine relates to biological processes and clinical outcomes. At the same time, a growing trend toward integrated health care delivery systems demands the attention of researchers. The fact that “integrative medi-

TABLE 6 EVALUATING QUANTITATIVE RESEARCH REPORTS ON THERAPY & PROGNOSIS

a checklist for evaluating reports on therapy

Therapy: any intervention used to prevent, ameliorate or cure illness.

- ✓ In the report:
 - Is the dosage/therapy what you usually use in clinical practice?
 - Is this treatment relevant to your practice?
 - Were validated measures used?
 - Were all relevant outcomes assessed?
 - Were all subjects accounted for at the end of the study?
 - Were these subjects similar to those you see in practice?
 - Can the intervention be feasibly integrated into practice?
 - Are you likely to change your practice as a result of this article?
- ✓ **Is the intervention described in sufficient detail?** Does it describe a **controlled study** (i.e., two groups compared, one with intervention, one with control; or even adding another group with no treatment)?
- ✓ **Are the two (or three) groups similar in characteristics? Randomization:** the best way to make intervention and control groups similar—protects against the influence of unknown factors.
- ✓ **Were other possible factors accounted for?**
- ✓ **Were the data from subjects analyzed according to their groupings?**
- ✓ **Were interventions/outcomes masked? Blinding:** removing patient, observer, therapist and measurement biases from the study by hiding what group they are in or what the intervention is.
- ✓ **Were the people involved unaware of what group of subjects got what intervention?**
- ✓ **What statistical tests were used?** odds ratio? p value? **Statistical significance:** the demonstration that the effect produced was more than a chance happening (better than 50/50). Can be shown in small or large studies.

clinical significance

- ✓ **Are the results clinically significant?** (i.e., the difference shown between groups has actual clinical relevance to caring for patients).
- ✓ **Is the research appropriately powered? Power**—the likelihood of showing a difference between intervention and control groups—usually requires a substantial number of subjects, and is dependent on the strength of the intervention and the variability of subjects' response.

a checklist for evaluating an article on prognosis

Prognosis: an understanding of the natural history of an illness that can be modified by treatment allows the clinician to decide whether and how to treat patients—and, even more, allows the risks and benefits to be discussed.

- ✓ Apart from the criteria already identified as being essential for a good scientific study, every study on prognosis should address five issues:
 - Was there an “inception” cohort—a group of subjects with well defined symptoms or diagnosis?
 - Where did the subjects come from? specialist referral or general population?
 - How well defined were the standards of entry into the study?
 - How complete was the follow up? Should be >85 percent.
 - Were the subjects similar to your patients?

“ciné” clinics are springing up all over the country and health insurance companies are beginning to offer coverage for alternative therapies serves to highlight the lack of data on “systems of care” that include complementary and alternative modalities. Although some leaders in conventional medicine propose a more “integrated” approach to health care services (Snyderman & Weil, 2002), there are, as yet, few data to support this concept.

For the time being, much of the ongoing research on the delivery of complementary care is descriptive—documenting the kinds of patients, problems, and treatments being used by CAM providers or in integrative medicine clinics. Efficiency, effectiveness, organization, quality of care, costs, and outcomes have not been studied in depth in the United States (Walach, et al., 2002). Suggestions for such studies include a stepped, graded process moving from documentation of CAM practice, to non-randomized quasi-experimental comparisons on cost-effectiveness, to open RCTs comparing complementary/alternative and conventional care, and to efficacy studies using blinded RCTs (Ernst, 2001). Questions that health services research should address include:

- Is complementary medicine more economical than conventional primary care?
- Is complementary medicine a cost-effective approach to improving health outcomes?
- Will complementary therapies reimbursed by health insurance reduce subsequent health costs for certain health problems?
- Does integration of care between conventional clinicians and complementary practitioners accelerate or delay diagnosis and treatment?
- Can CAM therapies reduce costs and improve outcomes in chronic diseases?
- Will the use of complementary and alternative medicine reduce the adverse effects of conventional pharmaceutical agents?
- How will ethical, legal, and policy issues affect the development of integrated medicine?
- Do outcomes of care take place at different rates between complementary and conventional medicine?

evaluating CAM therapy: the experimental approach

The case scenario evaluating the effectiveness of mud therapy (*see Case Scenario, on pages 24-25*) highlights some of the issues related to designing appropriate research methods for complementary and alternative therapies. The development of study design, methodology, outcome measures, and analysis of results of the case illustrates the process of adapting conventional research methods to study the effectiveness of non-conventional therapies and treatments. Table 6 offers a checklist that can be used for evaluating clinical articles on effectiveness of therapy and prognosis.

evaluating CAM therapy: the clinical reality

Advising the patient about complementary and alternative medicine relies on knowledge of the modality and its effectiveness and safety. Little is known about how advising is best done, although there are suggestions from experts. In 1997, Eisenberg suggested that patients should have tried and exhausted conventional medicine before moving to complementary therapies. While this approach is taken by many patients, others may be using CAM treatments prior to, or simultaneously

with, conventional care. Eisenberg also suggested that the conventional clinician find out what alternative therapy was selected, identify the practitioner, and review treatment issues with the patient. Subsequently, the clinician should follow up and review the alternative practitioner's treatment plan, assess its safety and its costs. While perhaps sound advice in theory, it may be quite unrealistic given the pace and financial pressures under which medicine is currently practiced.

Jonas offers the "4 P's guidelines:" Protect, Permit, Promote proven practice and Partnership (Jonas, 2001). The therapy should be economical and safe, treatment should be permitted (whatever the effectiveness) if safe and low-cost, effective treatment should be encouraged, and conventional clinicians should collaborate with alternative health care practitioners to optimize care and help meld conventional and complementary/alternative medicine.

Given the vast array of information on complementary therapies, systems of care, and herbal and nutritional products, clinicians face a formidable challenge. How does one keep abreast of the necessary information? How does one evaluate what is effective, useful, and safe for the patient without extensive reading and/or laborious computer time? This point-of-care information must be relevant, valid, and require minimal additional work (Ebell, 2003). It must necessarily be pre-digested. Unless the clinician wishes to delve into the specific quality of studies of a particular therapy, he or she must rely on a few efficient strategies, such as the following:

- Obtain a reference textbook on complementary and alternative medicine that provides an accurate and concise description of the range of modalities and systems, including descriptions of how practitioners provide their services and are trained. This can be used as a background resource when working with patients. Options include: *Essentials of Complementary and Alternative Medicine*, W.B. Jonas and J. S. Levin, editors (Lippincott, Williams & Wilkins, 1999); *Clinician's Complete Reference to Complementary and Alternative Medicine*, D. W. Novey (St. Louis: Mosby, 2000); *ABC Clinical Guide to Herbs*, M. Blumenthal, A. Goldberg, and J. Brinckmann, editors (Thieme, 2003); *Integrative Medicine*, D. Raket, editor (W. B. Saunders, 2002); and *The Desktop Guide to Complementary and Alternative Medicine*, E. Ernst (Mosby, 2001).
- Become familiar with three or four databases or websites that provide regular updates on studies of effectiveness and safety, such as: The Cochrane Collaboration, PubMed (a subset of the National Library of Medicine), Web MD, MD Consult, and Natural Products Comprehensive Database. These sites do the hard work of evaluating the quality of various CAM studies and making recommendations based on the weight of evidence.
- Subscribe to a newsletter or journal addressing issues related to complementary and alternative medicine and research. *Focus on Alternative and Complementary Therapies*, edited by E. Ernst, provides a well organized, evidence-based summary publication four times a year covering a wide range of CAM therapies (but it is expensive).
- Purchase a hand-held computer (PDA) and obtain access to conventional databases, such as Infotriever, Clinical Evidence, and Cochrane Collaboration. Complementary databases for hand-held hardware are only just being developed and have not been widely tested for validity and reliability. (A companion volume in this series, *Information Sources for Complementary & Alternative Therapies*, describes some of this software.)

summary

Today's health care "system"—in reality a convergence of multiple healing modalities—creates increased demands for understanding by conventional health care providers. Not only must they be knowledgeable about the safety and effectiveness of their own practices, but they must also be generally familiar with a wide range of complementary and alternative practices. They are challenged, in short, to practice evidence-based medicine in a world where conventional and complementary/alternative medicine converge.

The challenge is compounded because conventional sources of information about safety and efficacy do not necessarily provide reliable, practical information about complementary and alternative medicine. Good research is not plentiful; and conventional research standards—such as the randomized controlled trial—do not always apply when examining complementary and alternative therapies. Further, there is growing awareness that conventional research methodology—particularly the RCT—does not suffice to provide answers to many kinds of questions about clinical effectiveness.

To successfully practice evidence-based medicine in the current health care system, clinicians must understand the kinds of research that yield valid, useful information about safety and effectiveness of different healing modalities; must be aware of both strengths and limitations of RCTs and other conventional research methods; and must understand and appreciate the role and power of the placebo effect in healing.

CASE SCENARIO

EVALUATING CAM THERAPY: THE EXPERIMENTAL APPROACH

The following scenario illustrates some of the issues discussed previously on evaluating the efficacy of a CAM modality. In medicine, therapy is used to prevent, ameliorate, delay deterioration, and even cure illness—a diverse range of possibilities. CAM therapy can be used not only to promote healthy lifestyles but also to help treat illnesses such as arthritis or asthma. So—from the conventional medical perspective—how would one test the efficacy of a particular CAM therapy?

scenario

In the town of Spa, in the gently undulating Ardennes mountains of Belgium (the original spa where Frederick the Great of Russia took the waters in the 18th century), the spa physicians have claimed for years that the yellow mud used by white-coated assistants to plaster the bodies of their patients five times a week is effective in the treatment of psoriasis, hypertension, kidney problems, and obesity. They say this treatment works by ion-transfer across cell membranes. And, sure enough, special testing by physicists demonstrates clearly that this mud has a lot more electromagnetic energy (measured by dosimeter) than mud from Brussels 150 kilometers away. But, how the ion-transfer then produces symptom improvement is not known. At least, for the clinicians, these data on electromagnetic effects give some rationale to hold on to and explain to future patients!

What is the problem to be studied? If we want to prove their claim of efficacy is correct, we should first select one of the diseases (e.g., hypertension, kidney stones, or psoriasis) for which this mud is used, that is easy to study. Probably we would choose psoriasis—because it is easy to observe, define, measure with a ruler, and identify color change, and it has precise localized symptomatology, i.e., itching.

study design

Next we must devise a “controlled” study. That is, we must find a “control” mud for one group of patients (same color, consistency, smell, and volume, but without the high electrical energy that produces the “effect”). The therapeutic Spa mud will be used for the “active treatment” group. The white-coated assistant mud slappers would, of course, have to be blinded as to which mud contained the “ions,” and so would the patients (double-blinding). The two groups of patients—say, at least 30 in each group—would need to be as similar as possible in terms of their illness and personal characteristics at the beginning of the study.

methods

Masked randomization would protect against the influence on the results of unknown factors that could affect the results. Someone would have to set up boxes of mud in the mud-slapping rooms, carrying a code that randomized the bionic mud and the control mud applications so that no one, not even the investigators, would know which was which or what the sequencing was. Clear, precise outcomes would need to be decided upon and measured by unbiased observers. Outcomes might include improvement in skin texture, reduction in the area of psoriatic inflammation, an itching score, or color change (using photos and an independent judging committee).

selecting measures to study outcomes

Before completing the design of the study, we would then need to decide what the clinical relevance of the outcome measures were. Would “shrinking the size of the patch of psoriasis” or “reduction in itching” be most important? An expert dermatologist and a patient panel would provide useful advice. Often researchers may choose to study several outcomes.

Finally, we would need to decide whether the improvement would be statistically significant. For example, if the patch of psoriasis was reduced by 25 percent, although the improvement would not be clinically very important, it would most likely be statistically significant. Clinical significance is obviously at least as important as statistical significance because it almost always means that patients are better. Ideally the statistical and clinical significance would be aligned with each other and would show a reduction in size of the patch as well as decreased symptoms.

results

In analyzing the results after six months, we would have to be sure that drop-out rates were similar (people who drop out tend to do worse) so that comparisons could still be made fairly. If the drop-out rate were >20 percent, the study would probably be of limited clinical value due to inadequate data to draw conclusions about efficacy.

If significant differences were found, the confidence intervals (range of minimum and maximum benefit experienced in 95 percent of similar situations) should be narrow to be of clinical relevance. However, if no difference was shown it could mean either that the therapeutic mud did not work, or that there were not enough patients in the two comparison groups to show a small or moderate beneficial effect. This need to have enough patients to study is known as the power of the study.* (*If some data are available about the magnitude of efficacy of the therapy before developing such a study, a power calculation will greatly enhance the precision of the research design.)

In this study, to show a statistically significant difference in outcome of 10 percent improvement in symptoms, 50 patients might be needed in each study group. Since we only had 30 in each group, an improvement of 5 percent in the bionic mud group might not be statistically significant or have any clinical meaning.

This situation occurred in a recently reported double-blind RCT of an oral 30C homeopathic prescription for perennial allergic rhinitis. Valid airflow outcome measures were used as an end-point. Results showed a positive beneficial effect—but not enough patients were recruited to give the desired 80 percent power at 5 percent significance level (Taylor, Reilly, Llewellyn-Jones, McSharry, & Aitchison, 2000).

The final question about the mud study is whether the results could be generalized to and be “effective” in your practice. In other words:

- Are the Belgian patients similar to those in the United States?
- Is the therapy available locally or would patients have to travel to Belgium?
- What is the risk/benefit ratio for patients?

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