

### Complementary Medicine and Evidence

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While clinical medicine is increasingly governed by demands for evidence-based practice and biomedical research increasingly moves towards molecular approaches in the search for new treatments, the public is moving in a different direction—one where science is not the starting point for decision making.

Concern over side-effects of pharmaceutical drugs and a search for more humanistic management of illness have led almost half of the public in most industrialised countries to use complementary forms of medicine on a regular basis.<sup>1-3</sup> In most countries, demand has outstripped the capacity of national health policy to keep abreast.

There is an economic face to this trend. Americans and Australians typically pay out of pocket for complementary medicine (CM) services. Americans spend more out of pocket on CM than on all US hospitalisations. Australians spend more on CM than on all prescription drugs. Major American medical insurers now routinely cover complementary medical services—a trend which is emerging in Britain as well.

At the same time, the World Health Organisation continues to estimate that the majority of people in most developing countries use traditional medicine for their everyday health needs. In some countries traditional medicine serves the needs of up to 90% of the public. The economic reality here is that even in the best situations, the medical systems that serve the majority of the population get no more than 1% of the national health budget. Thus, through marginalisation and policy neglect, traditional medicine research is not done, quality of care cannot be assured and training, if it exists at all, is generally below par.

Traditional medicine use in many non-industrialised countries is on the increase due to the fact that pharmaceutical drugs are available only intermittently, are expensive—often unaffordable, and are variable in their effect (e.g. rise in antibiotic resistant strains of bacteria and increasing resistance of the malaria parasite to conventional treatments).

The fact that traditional health care is familiar, available at the local level and is affordable ensures that it will continue to play an important role in national healthcare in most countries well into the 21<sup>st</sup> century.

Recognising the need for policy to reflect public healthcare demands and patterns of use, the 12<sup>th</sup> Commonwealth Health Ministers' Meeting in November 1998 established a Working Group on Traditional and Complementary Health Systems.<sup>4,5</sup> The Working Group was commissioned to develop an action plan to promote and integrate traditional systems of health and complementary medicine within national health systems giving consideration to:

- Policy Framework, including:
  - \* provision of services,
  - \* conservation of medicinal plants and related intellectual property rights
- Training of traditional and conventional practitioners
- Development of standards of practice
- Mechanisms for enhanced sharing of experiences in the Commonwealth
- Regulation and safety, involving practitioners of traditional medicine in the process
- Research—evidence-based research to promote mutual understanding and confidence, and establish efficacy
- Management of the integration of traditional and conventional medicine

Health Ministers representing most of the 54 countries of the Commonwealth noted that traditional medicine should be seen as “complementary” rather than “alternative”, indicating the need for collaboration and partnerships with conventional medicine.

#### The Call for Evidence

The call for evidence-based research by the Commonwealth Health Ministers reflects the wider climate of determining

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best treatment through a formal approach to gathering and synthesizing research data. Evidence-based medicine (EBM) has become a worldwide movement in clinical medicine. Such high standards are now being called for by established medicine in evaluating the claims of traditional complementary health practitioners.

But is there a catch ?

One often-cited counterpoint is that, due to the historical marginalisation of traditional and complementary medicine, no research funding has been allocated to evaluating their claims. The relatively limited availability of randomised controlled trial (RCT) data has thus led to charges of there being no evidence in support of the effectiveness of complementary and traditional therapies. However, as one Commonwealth Health Minister pointed out in debate on this issue, “absence of evidence is not evidence of absence”. Clearly, the call for evidence must be matched by resources to gather this evidence. Americans have been successful in their call for government to support the gathering of better information on the healthcare modalities that so many of them are now using. The US Congress recently increased the complementary medicine research budget of the National Institutes of Health to \$50 million per year and upgraded the office managing this research to full Center status.

Yet, there is still debate over what constitutes evidence in complementary and traditional medicine. How, for example does a scientist measure changes in *qi*—a concept of central importance in traditional Chinese medicine? Is it sufficient for conventional medicine to apply its standards of evidence to the entirely different theoretical assumptions of traditional health systems and therapies? Or is there a bridge that can be built between theories and therapies through an attuned and sensitive approach to evaluation?

First of all, it is important to note that EBM is not an unchallenged orthodoxy within conventional medicine. Critics have charged that EBM seems likely to become the new dogma in medicine. They consider that the proponents of EBM are ignoring criticisms, seeming to take it as self-evident that EBM is valid. And there is concern that EBM relies principally on meta-analysis, a statistical methodology that is fraught with disagreement even among its proponents.<sup>6</sup> RCTs, the unit from which the meta-analyses of EBM are built, have also been challenged as being limited in both principle and procedure.<sup>7</sup> RCTs are seen as an inadequate tool for measuring infrequent adverse outcomes such as infrequent adverse effects of drugs. They are also, due to limitations in study size, unable to evaluate interventions designed to prevent rare events, such as accident prevention schemes. And they are unable to adequately evaluate the long-term consequences of therapies—e.g. oral contraceptives, HRT to prevent femoral fractures, and the loosening of artificial hip joints for which a 10- to 15-year follow-up is needed.

In order to address areas not readily studied using RCT methodology, and also to correctly design and interpret RCTs, observational studies are receiving new attention. Observational studies are based on quantitative epidemiological methods and quantitative sociological methods in which data are collected through observation. In traditional medicine, it may be assumed that a natural experiment is already taking place—practitioners are prescribing, patients are using. Observational research of existing practice allows for a first line of data to be collected without the ethical difficulties of assigning subjects to novel treatments. No one is assigned, data are gathered on what is actually happening and what the outcomes are from these interventions.

It has been suggested by Arthur Margolin of Yale University that the validity and ultimate value of RCTs of complementary therapies would be diminished if they were conducted without preliminary foundational studies. Foundational studies should investigate such issues as the reputed efficacy of the active treatment or the reputed non-efficacy of the control treatments.<sup>8</sup>

We took this approach in recommending a research strategy to one of our Oxford medical students in evaluating herbal anti-malarials in Uganda during a student elective. The results, while not pure, provided a sound basis for hypothesis generation and further clinical evaluation.<sup>9</sup> It is this approach that has led our group to establish a partnership with WHO’s Tropical Disease Research Division to develop a research agenda for evaluating promising traditional anti-malarials for use locally as herbal preparations in the fight against malaria (<http://users.ox.ac.uk/~gree0179>).

## Safety

A primary concern regarding traditional and complementary therapies is “Are they safe?”. Recent studies in the UK have found that there has been adulteration with steroids of some traditional Chinese dermatological preparations. In an analysis of Chinese herbal creams prescribed for dermatological conditions, Keane et al<sup>10</sup> found that eight of eleven creams analysed contained steroids. Clearly, policy gaps need to be plugged and effective regulation of herbal medicines is needed, while ensuring that regulation is not simply a means of limiting public access to these preparations. Limiting access through professional controls and regulatory means can be seen as constituting monopolistic trade practice. Such activity has been

challenged in US courts where it has been found to be not in the public interest and constituting restrictive trade practice.

Safety must be the starting point for national drug development strategies for herbal medicines. While most of the published research on herbal medicine is pharmacological, WHO's 1993 Guidelines on the Evaluation of Herbal Medicines consider that clinical evaluation is ethical where drugs have long been in traditional use. Roy Chaudhury has offered a model for the clinical evaluation of herbal medicines:

1. Toxicity testing of the plant in two species of animal for acute and sub-acute toxicity
2. A modified, shorter toxicity testing if the plant has already been used in man or is in such use now
3. Administration of the total extract or combination of plants, if used, in exactly the same way as it is prepared and used by the population.

The differences between this approach and that of conventional drug evaluation methodology are that:

- efficacy testing is carried out on humans rather than on animals, human studies are undertaken subsequent to modified, shortened toxicology studies have shown that the substance is not toxic in animals,
- the duration of the toxicity studies is reduced to six weeks for plants that are already in common use,
- the plant or mixture of plants is administered to subjects in the same manner in which it is used in traditional medicine.<sup>11</sup>

Research should consider best evidence for safety, including evidence for adverse effects from treatments (including magnitude, percent of people so affected, etc), as well as from inappropriate applications of traditional therapies. Postmarket surveillance studies can provide information on adverse effects of botanical herbal preparations. Pharmacognostic and pharmacologic research can provide information on the quality, efficacy, safety or toxicity of botanical/herbal medicinal preparations.

More broadly, a basic question in addressing safety in herbal medicines is "Safe with respect to what?". Research has found that in the US, 51% of FDA-approved drugs have serious adverse effects not detected prior to their approval. 1.5 million people are sufficiently injured by prescription drugs annually that they require hospitalisation.<sup>12</sup> Once in hospital, the problem may be compounded. The incidence of serious and fatal adverse drug reactions (ADRs) in US hospitals is now ranked as between the fourth and the sixth leading cause of death in the United States, following next after heart disease, cancer, pulmonary disease and accidents.<sup>13</sup>

Clearly, the safety of and risks associated with medical interventions is an issue across all categories of health care.

### **Research Methodologies for Complementary and Traditional Medicine**

Consumer satisfaction is of importance in evaluating health services. Satisfaction with care is one component of well-being, which has in turn been identified by WHO as a marker of good health. Our own research at Oxford University suggests that a search for satisfaction in the treatment of chronic disease is the primary reason why people in Britain—particularly women—seek the services of complementary health care providers. Consumer satisfaction studies merit a high place in national research programmes into complementary and traditional healthcare.

As noted, the RCT does not provide data on the effects of a treatment over time. Clinical observational studies are called for here. Population studies are needed to look at patterns of utilisation, expenditure, benefits and adverse effects.

While evidence of mechanism of action is clearly not needed to promote utilisation or to achieve consumer satisfaction—this is happening of its own accord—basic research into the physiologic links and molecular bases of therapeutic outcomes and mechanisms of action is needed in the longer term. Where employed, basic research methodologies need to be generated to sensitively capture aspects of CM practice and theory that may appear intangible—e.g. energy (*prana*, *qi*) etc.

The needs of interest groups in special situations—e.g. women, children, the poor, the elderly and those with special medical conditions—must be recognised and given priority in the development of national research agendas into CM and traditional health care (THC). Our own research indicates that older women with chronic conditions are the most frequent users of CM providers. Ethnic minority groups in the UK, for example, prefer their own traditional forms of medicine, such as acupuncture and traditional herbal medicine, to such western CM systems as chiropractic and osteopathy. The specific needs, health status and utilisation patterns of special interest groups should be addressed. Also of interest are diseases for which current treatment regimens are unsatisfactory, e.g. many cancers and chronic debilitating conditions.

Prevention of disease is an area of fundamental importance in complementary health systems. Dietary and nutritional approaches to prevention provide opportunities for the study of prevention, as does the use of herbs and traditional forms of exercise (e.g. yoga) in promoting a balanced state of health. Accordingly, systematic research should be conducted into

effective prevention practices.

In all therapeutic settings, western and traditional, belief and attitude have an influence on treatment outcomes. A “placebo”, or “meaning response,” effect is an important component of many therapies. The extent to which therapeutic outcomes are based on expectancy is an important area of study.

WHO’s Quality of Life Assessment includes spiritual dimensions in assessing an individual’s quality of life. Here, “spiritual” relates to the sense of meaning regarding the self or extending beyond the self. The spiritual dimension of life and well-being is central to many traditional and complementary health systems. Our own research indicates that 12% of those who use CM providers in Britain use the services of “spiritual healers”. This trend, its origins and outcomes are important areas of research.

There is a need for comparative evaluation of both CM and conventional medical methods for treating the same condition to identify safe and efficacious treatments that are locally available. This may also include the study of cross-cultural/cross-geographic healing practices to identify common treatments and/or to combine evidence for a specific herb or treatment regimen. Comparative studies could assess feasibility, cost-effectiveness, and environmental impact as well as specific biomedical outcomes.

Combination therapy should also be studied. For example, traditional medicine and Western-based medicine are often used simultaneously in the treatment of certain chronic diseases in Asian medical systems, such as the Ayurvedic medical system of India and Traditional Chinese Medicine. Caution should be exercised to address cultural bias in the assumptions, methodologies and concepts employed in comparative research.

A range of evaluative methodologies, then, can and should be employed in evaluating traditional and complementary therapies. These should be applied in a manner that is sensitive to the theoretical and clinical assumptions of the modality being evaluated in order to ensure that the research design adequately measures what is being studied.

A national research agenda into complementary and traditional medicine should promote research on the individual, the family and community, the wider population, and the ecosystem/environment.

Both political and scientific will are needed to support such an agenda. Legislators in industrialised countries are coming to recognise that the use of complementary medicine is linked to votes—votes of the wealthier and more educated sectors of society. In poorer countries, the search for effective and affordable treatments for such epidemics as malaria and opportunistic infections associated with AIDS is driving renewed policy interest in traditional medicine.

In each case, substantial increases in research funding are needed. New directions in clinical evaluation must also be forged by researchers who are able to transcend limitations in research orthodoxy in the interests of providing sound information to the public on what constitutes good healthcare.

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