Research priorities in traditional Chinese medicine

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than arbitrary, policies. As early as the 2002-3 SARS outbreak, Guangdong's local government and department of public health summoned leading scientists and respiratory specialists to set up an anti-SARS steering committee. Implementation of measures endorsed by this committee achieved the lowest case fatality rate from SARS in the world (3.8%). During early 2004, when four new cases were identified in Guangdong, the government took strong action on strict control of wildlife markets, including a ban on rearing, sales, transport, slaughter, and food processing of small wild mammals, and implemented "four earlies" (early identification, early reporting, early isolation, and early management) to stop transmission from human to human. This control strategy seems to have been effective in preventing the second SARS outbreak from evolving into an epidemic. This policy also holds true in the management of human avian flu, especially in dealing with febrile patients who have a history of contact with live poultry or birds.

Thirdly, an international monitoring system with a far reaching network is crucial for the early alerting of infectious diseases. A nationwide monitoring system for emerging infectious diseases has been set up in China. Surveillance of 185 designated hospitals and a network of 39 laboratories found 16 cases of human avian flu. Most of these patients were identified by doctors working in local hospitals. As a result of targeted education and on-site training for management of avian flu, there was no delay in referrals and quarantines. If doctors providing primary care are alerted and part of a monitory programme, epidemics can be controlled at the outset.

Lessons taught by SARS have given us a new outlook on a devastating human health crisis. Surely, these lessons are not confined to China, and they have important implications worldwide. As Franklin P Jones said, experience is the marvellous thing that enables you to recognise a mistake when you make it again. What has happened with the spread of SARS-CoV must not be allowed to happen again with H5N1. Incessant efforts are needed to improve our preparedness.

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Two possible approaches to research

The mechanism centred approach is primarily concerned with the search for the molecular, cellular, and pharmacological bases of traditional medicines. It seeks to identify the active substances of herbal treatments and investigate the mechanism of action. This strategy is shaped by a belief that traditional Chinese medicine need not be evaluated, by the general prosperity of basic biomedical sciences, and by drug development models in conventional medicine. As many research activities in traditional Chinese medicine aim to develop new drugs, the model used by conventional medicine to design and develop new drugs, such as drugs for cancer, seems directly relevant. It has three important conventions (fig 1, left). Firstly, the potential drug must be a single chemical entity, or a combination of known substances. Secondly, for ethical reasons, evaluation of the drug’s safety and efficacy must begin in vitro and in animals. Thirdly, the drug’s pharmacology and mechanism of action must be well understood before it is evaluated fully in humans. This model has been successful in modern conventional medicine and is readily available for traditional Chinese medicine.

However, as traditional Chinese medicines are already in use, it would be better when studying them to start with showing efficacy in humans by randomised controlled trials (fig 1, right). Efficacy refers to the capacity of a drug to bring about more good than harm in human subjects and is what matters most for any medical intervention. In the efficacy driven approach, studies on mechanisms and active substances are still important but should be undertaken after efficacy has been confirmed.

Why an efficacy driven approach?

Studies of efficacy will have direct, immediate applications for patient care whether the results are positive or negative; if a treatment is proved to be efficacious, promoting its use will benefit patients; if a treatment lacks efficacy, stopping using it will save resources. Such studies would also avoid unnecessary basic research on inefficacious interventions. Even if a treatment is efficacious, it may not be possible to determine the mechanism of action and the active substances immediately, particularly in herbal treatments that contain many compounds. In scientific inquiries, success is often hard to predict. However, we need not wait for such successes. Lack of knowledge about mechanisms and active substances need not prevent the use of efficacious treatments. Many powerful interventions, such as penicillin and smallpox vaccination, were accepted well before their mechanisms were understood. Inefficacious interventions will eventually be discarded whether or not the mechanism has been explained. Bloodletting is a classic example, and vitamin E for preventing cancer provides a modern equivalent.

Mechanisms are really only theories and change over time as new knowledge becomes available. How does cowpox vaccine prevent smallpox? The answer to this question today differs from the explanation given 200 years ago. Some would even argue against needless searching for deep explanatory models: any good empiricist can attest that sound evidence is hard won and that the human mind can concoct a theory to support any set of notions and observations.

The primary value of medical theories lies in successfully guiding medical practice and generating efficacious interventions. Thus, demonstrating efficacy would be the best empirical test of the theories behind traditional Chinese medicine. Based on therapies of confirmed efficacy, newly developed and improved theories of traditional Chinese medicine will be on a more solid ground.

A long history of use, traditions, faith, popularity, and anecdotes are widely taken as evidence for the efficacy of traditional Chinese medicines. Some traditional therapies are undoubtedly effective (Qinghao, for example; see fig 2) but this does not mean that all are. Randomised controlled trials are the most rigorous method for evaluating the efficacy of any interventions. Is it ethically acceptable to study traditional Chinese medicines in humans first? These medicines have been used for thousands of years. Whether tested...
or not, they will continue to be used in places where traditional Chinese medicine is officially recognised. New treatments will continue to be invented and given to patients by individual doctors without any systematic evaluation. A randomised controlled trial is simply a systematic use of the medicine, with an explicit research objective. In determining what and how much basic research should be required before randomised controlled trials of traditional medicines are allowed to start, it is important to note that the delay in starting a trial is proportionally related to the amount of basic research required, and also that it is unethical not to conduct or to delay trials of treatments that are widely used but have uncertain efficacy.

Difficulties in conducting clinical trials of traditional Chinese medicine

A small number of randomised controlled trials in traditional Chinese medicine have been done; most are of poor methodological quality.15 The situation may partly be due to methodological difficulties, such as design and implementation of placebo blinded trials of individualised treatments. Other crucial matters also need to be addressed.

Incommensurability

Both traditional and conventional medicine originated from different world views: the former from ancient Chinese philosophy and the latter from ancient Greek and Roman medicine.16 17 Consider the old Buddhist tale, where a few blind men try to find out what an elephant is like. The man who touched the leg thought that the elephant was like a post, while the one who grabbed the tail believed that it was like a rope. Conventional medicine may see only the “leg” and traditional Chinese medicine only the “tail.” The same disease presents different problems in the two paradigms of medicine. For example, in traditional Chinese medicine, hypertension would be several different syndromes (for example, Gan Yang Shang Kang—predominance of the yang of the “liver”), and blood pressure need not be referred to in either making the diagnosis or in judging whether the syndromes have improved or deteriorated.

Would this incommensurability mean that traditional Chinese medicine can be evaluated only within its own paradigm but not by the standards of conventional medicine (particularly those for diagnosis and outcomes), and that conventional medicine could not understand and accept it? To continue with the tale: if the elephant is gone, all the men would agree that there was no longer an elephant. The very existence of the elephant is essential to any deduction from the evidence. If the two medicine systems see and deal with the same underlying disease in different ways and the disease is “cured” by either form of medicine, the disease will be “gone” regardless of methods. This suggests that traditional Chinese medicine could be evaluated by using outcomes defined in both medical systems, especially when a disease can be cured.

To resolve the problem of incommensurability in diagnosis, patients for trials of traditional Chinese medicines can be recruited in two ways. Firstly, patients with the same traditional Chinese medicine syndrome can be recruited from those with a particular disease in conventional medicine. In such a trial, the same traditional treatment can be evaluated, and generalisation about the therapy would be valid, but the eligible patients available for study could be small in number and difficult to recruit. Secondly, patients with the same disease in conventional medicine could all be recruited, regardless of their diagnosis in traditional Chinese medicine. The eligible patients would be many, but they must be given different traditional treatments. Many current traditional Chinese medicine trials fall into the latter category. They may show that it is efficacious, but generalisation about each treatment is difficult unless the trial is sufficiently large to allow subgroup analyses.

Individualised treatments

It has been argued that because in traditional Chinese medicine treatment is individualised, randomised controlled trials cannot be used as such trials require similar patients who need similar treatments. This misunderstanding is not new. Sir Austin Bradford Hill noted 40 years ago: “The most frequent and the most foolish criticism of the statistical approach in medicine is that human beings are too variable to allow of the contrasts inherent in a controlled trial of a remedy.” He challenged his critics: “If each patient is unique, how can a basis for treatment be found in the past observations of other patients?”

Can similar patients who need similar treatments be found in traditional Chinese medicine and studied in clinical trials? It is true that no patients are exactly the same. What matters, however, is whether the dissimilarity is relevant to the efficacy of the treatment. Like conventional medicine, traditional Chinese medicine has a limited number of “syndromes” available (the state of a disease in a person at a particular time, which determines the choice of treatment) and probably only a few hundred are common. In traditional Chinese medicine, it is legitimate to give patients with the same syndrome similar treatments.

For example, classic herbal formulas and proprietary drugs, such as Liu Wei Di Huang Wan for deficiency in the yin of the “kidney,” were developed for specific syndromes. Good evidence for further tailoring beyond the standard formulas is often lacking. In addition, the same traditional medicine is often prescribed to patients with the same disease, regardless of the syndrome.1 It would be unreasonable to deny the value of randomised controlled trials in traditional Chinese medicine as that would be to refuse the scientific tenets of induction and causation.

Despite these arguments, it is possible to design randomised, blinded trials of individualised treatments in traditional Chinese medicine. In such a trial, every patient can consult the doctor and be prescribed the herbs best tailored to their needs. Then the patient will go to see the trial administrator, who will randomise him or her to receive either the herbs as prescribed by the doctor or placebo herbs. Placebo herbs should be chosen by experienced traditional Chinese medicine doctors to make sure they are highly unlikely to have relevant effects. Then the prescribed and placebo herbs can be prepared in an identical ready to use form (such as solutions) or made into small pieces and packed in gauze bags which can be simmered in water by patients at home without being opened.
Analysis and comment

Summary points

Research in traditional Chinese medicine has been dominated by the search for its biological basis, identifying active substances, and investigating mechanisms of action.

Searching for active substances and mechanisms of action is meaningless if a treatment has no clinical efficacy.

As traditional medicines are already in use, research should adopt an efficacy driven approach, and start by showing efficacy in humans through randomised controlled trials.

Cultivating a culture around uncertainty and evaluation is needed more than resolving the methodological difficulties in conducting randomised controlled trials of traditional medicines.

However, as the efficacy of individualised treatments is determined by two factors: the treatment itself and the competence of the treating doctor, trials of individualised treatments could have problems for the explanation and application of their results: the efficacy shown in a trial may not be reproducible in other doctors and the absence of efficacy could be explained as resulting from poor skills of the doctor rather than from the treatment. Cluster trials that randomise patients to practitioners of traditional Chinese medicine and conventional medicine and allow practitioners to treat in an individualised manner have the same problems.

Attitude towards evaluation

In social research, “One of the greatest methodological fallacies of the last century . . . is the belief that science is a particular set of techniques; it is, rather, a state of mind, or attitude, and the organisational conditions which allow that attitude to be expressed.” Is this also true of research in traditional Chinese medicine? The attitude towards the need for evaluation, rather than methodological difficulties, has been the greatest hindrance in evaluating traditional Chinese medicine. For advocates, every treatment works, so evaluation is unnecessary. For sceptics, traditional Chinese medicine is quackery, so evaluation is pointless. The truth probably lies somewhere in between: in some treatments the art may be efficacious, and some are probably not. This stark division between proponents and opponents shows the collective professional uncertainty about traditional Chinese medicine and represents a typical clinical equipoise that calls for a randomised controlled trial.

Methodological difficulties can be resolved only when the need for evaluation is widely endorsed.

Many interventions in the current practice of conventional medicine are of doubtful value and have not been proved by scientific research, and are thus also candidates for the efficacy driven approach to research. Research on basic mechanisms that is crucial for future advancement should not be downplayed in the new approach—but clinical research should precede basic research for interventions already in use.

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Endpiece

Questions to members of the College of Physicians

Whether they take as much medicine and remedies as the like number of men of other societies?
Whether of 1000 patients to the best physicians, aged of any decad, there do not dye as many as out [of] the inhabitants of places where there dwell no physicians?
Whether of 100 sick of acute diseases who use Physicians, as many dye and [in] misery, as where no art is used, or only chance?


Submitted by Jeremy Hugh Baron, honorary professorial lecturer, Mount Sinai School of Medicine, New York, USA