CAM EXPERTISE

Claudia Witt, Sienna Craig, Mingji Cuomu (Eds.)

TIBETAN MEDICINE RESEARCH

From Current Evidence to Future Strategies

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Karl und Veronica Carstens-Stiftung

Tibetan Medicine Research

From Current Evidence to Future Strategies: Advice from an Interdisciplinary Conference

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Research on Tibetan Medicine – Where Do We Stand, Where Should We Go?

Claudia M. Witt, Sienna Craig, Mingji Cuomu, Bertrand Graz, Michael Heinrich, Herbert Schwabl, Mona Schrempf on behalf of the discussion group (whole group see pp 73 et seq)

1. Introduction

Tibetan medicine, or science of healing (Tib. *gsopa rigpa*) is a holistic medical system which has been practiced for over 1200 years. Today, it is in use primarily in Tibet and spread also across other Asian countries such as Bhutan, India, Mongolia, Russia, Nepal (Khro-ru-tze-rnam 2003). Its classification of diseases, diagnostic methods, and treatment regimes are complex. Tibetan doctors principally rely on pulse diagnosis, but they also engage in case taking and tongue and urine diagnosis (Witt 2009). Compared with other traditional medical systems, principally Ayurveda and Chinese medicine, the practice of Tibetan medicine in Western countries remains minimal, if steadily increasing. Growing contemporary demand for Tibetan medicines and healing encounters with Tibetan medical practitioners in China are evident and may contribute to increased interest in the West (Witt 2009). Furthermore, training in Tibetan medicine is provided in both the US and Europe by Tibetan medical doctors.

To date, clinical research on Tibetan therapeutics (including external therapies and ingestible medicines) has been quite limited, both in scope and location of studies. In order to improve clinical research on Tibetan medicine and further develop methodological and epistemological approaches appropriate for the study of this whole system, we initiated a consensus process through an interdisciplinary workshop and convened in spring 2010 at the Charité University Medical Center in Berlin.

Our main objectives were to: 1) describe and appraise the current stage of previous clinical research on Tibetan medicine, and 2) develop recommendations for further research.

The following discussion and decision processes were based on input from experts with considerable experience in Tibetan medicine or research methodology and representing different cultures and disciplines.

2. Methods

Experienced Tibetan medicine doctors and Tibetan medicine manufacturers from both Asia and the West (China, Germany, Switzerland, UK and United States) as well as medical anthropologists and clinical research methodologists participated in the two-day workshop in Berlin. The workshop language was English with informal translations into Tibetan as needed. We employed an interactive approach for the duration of the workshop, with impulse lectures as intruductions to the field. Topics discussed included the framework of Tibetan medicine, evidence available from previous studies, the impact of regulation on the conduct of clinical research, and clinical research methodology. This was then complemented by breakout sessions in which three interdisciplinary groups running parallel discussed the same topics over the course of two days. These topics included: 1) describing the current stage of clinical research including advantages and limitations, and 2) developing recommendations for future research. Results from the three working groups were presented in a plenary session and merged through a consensus discussion.

The summarized results of the workshop were finalized in an additional written Delphi round of consensus building activities and collaborative writing.

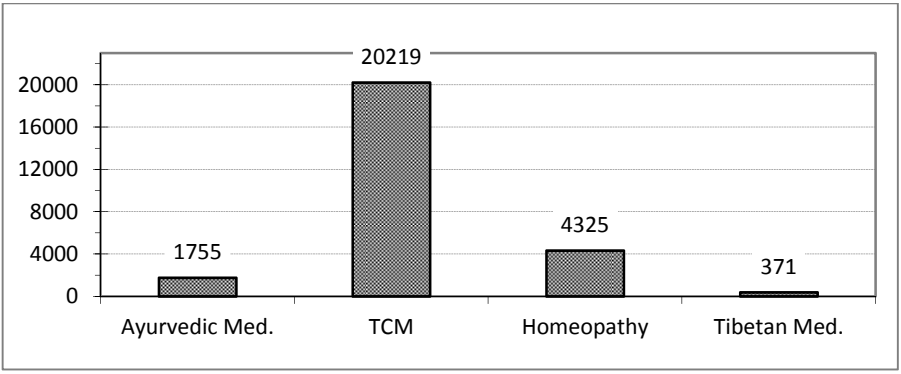
Evidence Available in the West

Philip Reuter, Claudia M. Witt

1. Introduction

Tibetan medicine has been practiced in the Western world for over 40 years, but compared with Ayurvedic or traditional Chinese medicine it is not well known. This lack of awareness is in marked contrast to the great popularity of Tibetan culture in the West (Geistlich and Schwabl 2003). Despite its centuries-old history and education at university level, this lack of knowledge is also true for research on Tibetan medicine (Figure 1). Scientific proof of safety, efficacy and efficiency according to the standards of evidence-based medicine is a prerequisite for the use of therapeutic measures (Coulter 2007).

Fig. 1: Medline hits per search strategy (dating 31.12.2010)



Research on Tibetan medicine has been conducted in Europe since the 1970s when medicinal formulas adopted from Tibetan medicine were introduced by the Swiss pharmaceutical company Padma Inc. A few systematic reviews describe their properties (Badmaev 2002, Melzer et al 2006, Röösli 2009). Research on individualized traditional Tibetan medicine as practiced originally in Asia has not yet been evaluated systematically.

This systematic review will summarize the clinical trials accessible in the West. The quality of the trials will be assessed and critically appraised in order to evaluate the evidence given in the trials. Additionally, the safety of the interventions will be evaluated.

2. Methods

According to the relevance of publications on complementary and alternative medicine (CAM) and on conventional medicine, the following databases were searched: AMED, ABIM, Biological Abstracts, CAMbase, CCMed, Cochrane Collaborative Library, Embase and Medline.

The following keywords were used for the search: (Tibet OR Himalaya OR Mongolia OR Buddhist) AND (herbal OR medicine) AND study. Further searches were carried out with partially modified search strategies in the database portals of the German Institute of Medical Documentation and Information (DIMDI) and the German National Library of Medicine (ZB MED) as well as the scientific search service of the internet search engine Google (DIMDI 2010, ZB MED 2010, Google 2010).

Furthermore, various collections of scientific literature on Tibetan medicine available online and offline were screened for relevant articles. Additionally, contact was established with experts including those from the clinical research faculties of the Tibetan Medical Universities in Lhasa and Dharamsala and the Swiss pharmaceutical company Padma Inc. (Padma AG 2009, Institut für Ost-West-Medizin 2008, Interessengemeinschaft Tibetische Medizin 2011, New Yuthog Institute 2011, Aschoff 1996, University of Virginia 2003). Reference lists from relevant articles were screened for further scientific publications.

In our review we included studies published prior to 1.1.2011 which were written in German, English, French or Spanish. Studies investigating specific therapeutic methods of Tibetan medicine were included as well as studies focusing on traditional Tibetan medicine. There were no restrictions on study type or population. While there were no restrictions on specific diseases researched, outcome measurement had to be patient-centered and clinically relevant for the assessment of the course of the disease.

The methodological quality of the studies was evaluated using the DIMDI checklist and the Jadad score. The DIMDI checklist for the assessment of primary studies in health technology assessments (HTA checklist) is applicable without restrictions for all types of primary studies. The Jadad score can only be applied to randomized controlled trials (Ekkernkamp et al 2003, Jadad and McQuay 1996, Kjaergard et al 1999).

The studies were sorted according to diseases, intervention and outcome measurement. Corresponding results were described in groups and individually.

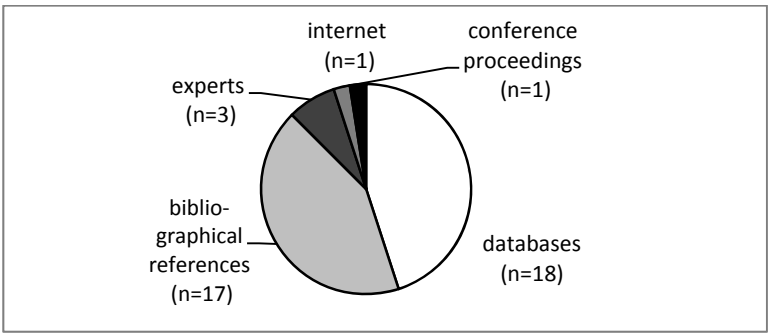
3. Results

3.1 Literature search

The literature search in the above databases yielded 900 articles, including 294 duplicates which were removed. Further 485 articles dealt with topics from sociology, ethnology, (ethno-)botany and medical history. 81 articles were narrative reviews, experimental studies on specific ingredients in Tibetan medicine or clinical trials with outcomes with no or low clinical relevance. Both groups were also removed. The remaining 40 studies were included.

Only a minority of the studies was identified by means of the database search (see Figure 2). Most of these publications were identified via Medline and Embase. Databases specializing on CAM yielded no further results.

Fig. 2: Number of studies according to place of finding (n = 40)



3.2 Quantitative study evaluation

The 40 included studies were published in 39 articles and 24 different journals or media. 21 articles were published in English and 19 in German. The articles were published between 1970 and 2009 by 34 different first authors. The past decade was the most proliferative with 16 published studies, two thirds of which were conducted on traditional Tibetan medicine.

Most studies were carried out in Poland (30 %) and Switzerland (30 %), whereas only eight studies (20 %) were conducted in Asian countries. All studies from Poland and Switzerland dealt with the effect of different formulas of Padma Inc. Traditional Tibetan medicine was investigated in all studies carried out in Asian countries. Half of the studies included were controlled, the majority of which were also randomized (= 15 RCTs). 14 studies were designed as observational trials and six were case reports or series. Of the trials included seven had multi-centered and four retrospective designs.

Patients

The trials reported a total of 4684 patients, the average population size per trial was 117 (range 1–967). The highest study population was seen in

RCTs (mean 135 patients), but close to 50 % of the patients treated in RCTs were included in a single trial (Miller et al 2009). 29 trials named the patients' sex. In these, 1956 women and 1080 men were examined, half of the first (n = 988) were included in two trials on gynecological diseases (Miller et al 2009, Leeman et al 1999). Distribution of females and males in other trials was uniform, except for trials on atherosclerosis-related diseases, which included a higher percentage of men (65 %). Information on patient age was given in 31 studies. The age range was between 10 months and 95 years. Five studies totalling 955 patients only treated children (Jankowski et al 1985, 1991, 1992, Mansfeld 1988, Prusek et al 1987).

Six studies were performed with in-patients (3.5 % of all study participants).

Dropouts

The number of dropouts was specified in 32 studies (3577 patients). The dropout rate was between 0 % (15 studies) and 44 % (Namdul et al 2001) with an average of 15 %. In RCTs, the rate was 8 %. The rate of dropouts in treatment (7 %) and control groups (8 %) was similar. Trials using pharmacological mono-therapy showed lower dropout rates than those using more complex interventions.

Diagnoses

Diagnoses from conventional medicine were the basic selection criteria in 39 trials (Figure 3). One further trial recruited patients on the basis of the Tibetan diagnosis *trung-bo* (corresponds to both arthritis and osteoarthritis in conventional medicine) (Ryan 1997). Although they did not constitute recruitment criteria, Tibetan diagnoses were the base of the treatment in eight further trials on interventions with traditional Tibetan medicine (Leeman et al 1999, Changbar 1998, Li 2001, Namdul et al 2001, Neshar 2000, 2007, Pauwvliet 1997, Sangmo et al 2007). Two further studies indicated Tibetan diagnoses; however, these were therapeutically not relevant (Miller et al 2009, Aschoff et al 1997). All other studies also used Tibetan healing methods based solely on conventional diagnosis.

Assessment of Traditional Medicines – Suggestions for Designs

Bertrand Graz

1. Assessment of traditional medicines in ancient and modern times

It has been said that the Tibetan medical tradition has its origins in the pre-Buddhist Bon period or in the revelations of the Buddha and the Four Medical Tantras. Historians ascribe the birth of the present sophisticated medical system, which completes previous systems of healthcare in Tibet, to the seventh century of our era, when King Songsten Gampo introduced a system of writing, invited physicians from foreign countries and ensured that their medical works be translated into Tibetan. This system of enriching local medicine went on for at least two centuries. Thus, Tibetan medicine was in large parts constituted of what appeared to be the best of Indian, Chinese, Persian, Greek, etc. medicines.

The selection of the best treatment modalities was done through criteria and methods which may have involved some kind of assessment, probably quite different from the ones we would chose today. However, the process seemed so effective at the time that Tibetan monk-physicians succeeded in converting the powerful court of the Mongols to Buddhism through what was perceived as a miraculous display of healing and predictive power (Baker 1997, Meyer 1992).

I shall try to show some of the present time assessment designs for traditional medicines. As a physician trained in Swiss and American universities, I have been using research designs derived from Western-type, conventional medicine studies. Despite the limitations, my goal has been to conduct research projects that can answer meaningful questions and produce useful results for those directly concerned, mainly users, traditional practitioners, and physicians trying to work with traditional practitioners and policy makers. This chapter does not pretend to cover the

whole area of research designs for traditional medicine; it only contains a few lessons learned from my own field experience.

2. Research for whom?

The assessment of a traditional medicine (TM) can be conducted for different groups:

– Health policy makers
– Physicians
– Traditional healers/ practitioners
– Population
– Pharmaceutical companies
– Academics (e. g. anthropologists, ethnopharmacologists, historians)

The questions and the type of research will be different in each case. Two principles can guide the choice of appropriate research designs:

– The scientific criteria of meaningful research,
– The needs of those supposed to use the results of the assessment.

Before embarking on the assessment of a TM, it is useful to have a thorough discussion with those supposed to immediately use the results of the assessment: physicians willing to collaborate more closely with TM practitioners, health authorities, etc. In most cases, those performing the assessment will also need to comply with their institutional setting, e. g. a university, which implies conducting research along international scientific standards and publishing results in a peer-reviewed journal.

TM can and should be studied with methods that are, as much as possible, the same as those methods used for conventional medicines. To do this will produce results that are understandable and acceptable by the scientific community. Since the same scientific standards tend to be accepted by health authorities, research conducted along such principles will have the broadest potential use.

3. What is the question?

Before the assessment itself, when one starts a study on TM, the first questions can be:

> "What are the various traditional treatments used, and for which health conditions are they used?"

During this phase it is already possible to collect indices of effectiveness and safety through questions on observed results. Two questions can be studied through a formal method which will be explained below (see 6.2 Selecting the most promising treatment – retrospective treatment-outcome study):

> "Which is the most promising among numerous treatments for the same disease?"

Answering such a question can be the starting point for a whole research program leading to the discovery of a new drug and/or the official recommendation for a traditional remedy on a larger scale. Another question of interest can be:

> "How reliable is a traditional healer (and his or her practice as a whole)?"

Such a question will be of use for health policy makers, as well as neighboring physicians and will require a completely different design (see below "prognostic-outcomes"). When speaking of assessment, however, the most common question is:

> "Is this particular treatment – for this particular disease – effective and safe?"

… fostering a lively debate on whether such a question can or cannot receive an answer with today's conventional research designs.

4. Can the effectiveness of traditional medicine be evaluated?

It is of course tempting to simply evaluate TM on observed improvements, "if someone has been cured after using this treatment, this treatment is effective" – most users do so and many practitioners as well. Such a statement, however, does not bear up to a thorough scrutiny because of two aspects of the reality: Most ailments tend to get better over time even without any care; most care tends to help healing through an indirect effect called "placebo" or "placebo-like", the stimulation of the patient's healing potential, e. g. through the "endogenous pharmacy" of endorphins etc. (Kaptchuk et al 2010).

I have nothing against the placebo effect and believe that it should be stimulated as much as possible. Nevertheless, if one is interested in specific effects of a treatment, the method needs to be more sophisticated in order to overcome the two aspects of reality mentioned here.

Another tempting manner of assessing TM is to justify statements by "reputation", i. e. by the number of independent authors recommending the treatment or by the antiquity of citations. The problem with such methods is that discrepancies have been often observed between strong reputation and laboratory results, as well as between laboratory results and clinical outcome (Bourdy et al 2008).

In academic settings, hospitals and health administrations, the current gold-standard for evaluating a medical treatment or procedure is the prospective, double-blind, randomized controlled clinical trial (RCT) or, even better, a meta-analysis of several of them. One of the reasons given for that is historical: many treatments, sometimes widely used, have eventually proved (once tested through RCTs) to be of no better value than placebo, and sometime worse.

Those interested in evaluating TM will often be able to use a standard research method. For example, it is possible to conduct an RCT of an herbal treatment, provided one can make a placebo. Even for acupuncture, a "placebo acupuncture" (e. g. "sham acupuncture") has been developed. And for very individualized treatments (e. g homeopathy) an evaluation through an RCT can be designed. Sometime blinding between "real"

and placebo treatment is not feasible, for example in the case of surgery research, but non-blinded studies can still be of high value.

The mechanism of action of TM may often remain unknown. However, this is not an obstacle anymore because the treatment validation rule in medicine has moved from understanding the underlying mechanism to a more "black-box" attitude, the "evidence-based medicine" with a focus on clinical outcome. Within the concept of "evidence-based medicine" a treatment can be used if it is safe and effective, whether we know how it works or not.

Contrary to a commonly held myth, clinical studies can be conducted at relatively low costs if the researcher works with local/ regional research institutes and with doctoral students, focusing on meaningful clinical measures rather than sophisticated laboratory analyses.

And contrary to another commonly held myth, a lot of research has already been conducted on TMs and can be easily retrieved.

5. Databases on complementary, alternative and traditional medicine

The following databases on complementary, alternative and traditional medicine shall be briefly introduced:

Cochrane Complementary Medicine Group:

- Cochrane Reviews on Complementary Medicine; listed at http://cochrane.org/reviews/en/topics/22_reviews.html
- University of Maryland School of Medicine Cochrane CAM Field (plain language summaries of CAM Cochrane Reviews at www.compmed.umm.edu/integrative/cochran-plainlang.asp)

HerbMed is an interactive, electronic herbal database. It provides hyperlinked access to the scientific data underlying the use of herbs for health. The US Library of Congress, United States Patents and Trademarks Office (USPTO), and FDA currently license HerbMed (see www.herbmed.org).

MedicinesComplete provides information on interactions; clinical evidence and/or experimental evidence; mechanism, with a rating system based on strength of evidence, severity and management of interaction (see www.medicinescomplete.com).

Natural Medicines Comprehensive Database allows the physician to enter all of the patient's conventional drugs and natural products and generate an interaction report. The website also provides data from effectiveness studies (see www.naturaldatabase.com).

In the USA, the **National Insitutes of Health** offer a selection of relevant publications on non-conventional medicines (www://nccam.nih.gov/research/camonpubmed).

PasseportSanté.net gives a synthetic overview of many non-conventional medicines with comments by scientific experts from Laval University and others in French (www.passeportsante.net).

For Tibetan medicine the literature provides information on medical complaints and treatments in health care settings of Sikkim and Nepal (Witt et al 2009), on medicinal plants used in Tibetan traditional medicine (Zhao et al 2010), on feasibility and cross-cultural problems in the organization of a clinical trial etc (Adams 2001, Adams et al 2005, 2007). We can see from these examples that not only can TM be evaluated in terms of effectiveness and safety, but many other questions of interest can receive an answer through different types of assessments.

When assessing TM the most common question is about safety and effectiveness. This can be measured with very different types of variables such as:

- Laboratory tests (e. g. glucose concentration in the blood)
- Clinical measurement (e. g. "patient can walk 10 meters")
- Clinicial decision, including TM practitioner decision (e. g. to treat or to refer the patient)
- Patient opinion (e. g "less pain")

In the following sections we shall have a closer look at how the measurement of such variables can be incorporated in TM assessments.

Western conventional medicine has defined itself in large part through the scientific paradigm, of which clinical research is an important cornerstone. Asia's traditional medical systems have relied on comprehensive theoretical frameworks and thousands of years of experience as a basis for validating knowledge. This is true for Tibetan medicine, a holistic medical system with centuries of history in Asia and, more recently, increasing practice, production, and consumption in Western countries.

In order to enhance understanding and expand the study of this traditional and holistic medical system, Professor Claudia Witt, Professor Sienna Craig and Dr. Mingji Cuomu initiated an interdisciplinary consensus process in spring 2010 at the Charité University Medical Center in Berlin. Experienced Tibetan medicine doctors, Tibetan medicine manufacturers from Asia and the West, medical anthropologists and clinical research methodologists participated in this two-day workshop.

Tibetan Medicine Research presents the consensus document produced through this event in three languages (English, Tibetan, Chinese) as well as relevant articles on the production and evaluation of clinical evidence, manufacturing and training regulations and methodological aspects of conducting clinical research on Tibetan therapeutics.

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