



A brief discussion on evidence-based clinical research of traditional Chinese medicine

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Background: The evaluation of clinical efficacy of traditional Chinese medicine (TCM) is the focus of the development of Chinese medicine, but at present there is no internationally recognized clinical efficacy evaluation system, which prevents TCM going abroad. Evidence-based medicine (EBM) research methods have achieved good results in the evaluation of TCM, but there are still some problems. How to use EBM methods in accordance with China's national conditions and develop evidence-based TCM that meets its own characteristics is the key to the current discussion.

Methods: Search websites such as PubMed, China National Knowledge Infrastructure, Wanfang Data and VIP by computer, and search papers related to evidence-based clinical research of TCM.

Results: A total of 15 high quality representative research papers published in internationally renowned journals were selected for example, including 4 randomized controlled trials (RCTs) related to Chinese medicine, 9 RCTs related to acupuncture, and 2 observational studies on the safety of TCM.

Conclusions: EBM method is suitable for clinical research of TCM. There are differences between "disease" and "syndromes" in the use of TCM. Based on the further standardization of syndromes and classification of TCM, modern clinical research methods can be reasonably applied. However, the quality of clinical research related to TCM is not high, and there is a lack of research related to the safety of it, which should be paid attention to and improved in future research.

Keywords: Traditional Chinese medicine (TCM); evidence-based medicine (EBM); efficacy evaluation; clinical research

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Introduction

With the progress of natural science, the standardization and internationalization of traditional Chinese medicine

(TCM) has become a major issue at present. Establishing a rigorous and scientific evaluation system of TCM is the focus of TCM clinical research development. Evidence-

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based medicine (EBM) has been introduced into China and has produced evidence-based TCM in the collision and integration with TCM, which became one of the innovative achievements of the development of EBM in China (1). It provides a new idea and method for the evaluation of clinical effect of TCM. This is both an opportunity and a challenge for the development of TCM. Whether the evidence-based approach is suitable for TCM and how to solve the existing contradictions have become the focus of current discussions.

Characteristics of TCM

TCM is an excellent cultural tradition and knowledge treasure house of the Chinese nation. It has been developed on the basis of medical practice through thousands of years, and has exerted a positive and far-reaching influence on the life, health, survival and reproduction of people in the Oriental world, mainly in China. TCM is a typical experiential medicine, which emphasizes individual clinical practice and personal experience, but lacks prospective research. In terms of treatment methods, it stresses on syndrome differentiation, individualized treatment, with poor reproducibility of efficacy. In addition, its theoretical system is formed and developed under the specific historical and philosophical thoughts of China, theory, diagnosis, treatment, came into its own language, which makes it difficult to exchange and communication with western modern medicine. Therefore, if TCM wants to go abroad and be widely accepted and recognized in the world, it is necessary to use internationally recognized standards to measure the efficacy. The key technology is to make the research methods scientific and obtain objective clinical evidence.

Evidence-based road to TCM—inapplicable or a new opportunity

In recent years, research on the evaluation of clinical efficacy of TCM has been endless. However, there are still many problems in the evaluation of the characteristics of TCM, and no better clinical evaluation method that has been recognized domestically and internationally. The flexibility and usability of TCM cannot be widely recognized in the clinical trial data scale, nor has the research on the calculation and evaluation of syndrome points been recognized. The introduction of EBM has brought a new idea and method to the evaluation of

the efficacy of TCM, and has produced evidence-based Chinese medicine. Evidence-based Chinese medicine is an applied discipline, based on the theories and methods of EBM. It collects, evaluates, produces, and transforms the evidence of the effectiveness, safety, and economics of TCM, reveals the characteristics and laws of the clinical role of TCM, and guides clinical guidelines, pathways and health decision-making (2). Evidence is the cornerstone of EBM, and randomized controlled trials (RCTs) are the internationally recognized gold standard for clinical trials. But EBM is not a panacea. There are also many problems in the development of evidence-based Chinese medicine. The treatment based on syndrome differentiation of TCM advocates individualized treatment, so the applicability of RCT is worth discussing. And in practice, the phenomena of “treating the same disease with different methods” and “treating different diseases with same method”, and the large variability of intervention measures in TCM, all need to be studied in methodology.

Methods

Evidence-based approach: the need for the development of TCM

By consulting ancient books and related works on the development of Chinese medicine, searching PubMed, CNKI, Wanfang, VIP and other websites, searching for evidence-based Chinese medicine related papers and clinical research, comprehensively analyzing the relationship between TCM and evidence-based medicine and the feasibility of developing evidence-based Chinese medicine.

TCM has been practiced and developed for thousands of years. It can exist for a long time and endure, indicating that its effectiveness in preventing and treating diseases is worthy of recognition. But it also needs to be acknowledged that the process of development is also a process of continuous innovation. Not all TCM that have been passed down from generation to generation need to be inherited. The correct conclusions that have been clearly verified should continue to be implemented, and the uncertain parts need to be suspended and continue to be researched. The parts that have proven to be wrong should be deleted in time and no longer passed on. To promote the progress of TCM with the development of science (3). The purpose of carrying out evidence-based research on TCM is to promote and apply effective and beneficial TCM interventions better, and on the other hand, to avoid the abuse or misuse of

ineffective or harmful interventions. So as to save social health resources and make TCM research resources more reasonably and efficiently allocated and used.

Taking the compatibility of TCM as an example. During the Jin and Yuan dynasties, ancient Chinese medicine practitioners concluded the TCM compatibility taboos of “eighteen incompatibilities” and “nineteen counteraction”, on the basis of medical practice, which played a significant role in the safe compatibility of TCM. But from ancient times to the present, there are also a few examples using the compatibility of “eighteen incompatibilities” or “nineteen counteraction”, not only did not appear obvious toxic reaction, but presented some good results (4). Some ancient prescriptions have also recorded that the drug contraindications of “eighteen incompatibilities and nineteen counteraction” can be used safely. For instance, in “Gansui Banxia Decoction”, licorice is used with Gansui. In “Sanzhongkuijian Soup” and “Haizaoyuhu Soup”, licorice is combined with seaweed. And in “Dahuoluodan”, aconitum is used with Rhino Horn (3). In addition, the compatibility of “eighteen incompatibilities and nineteen counteraction” can also be seen in some modern Chinese patent medicines. Some pharmacological experimental studies showed that the compatibility toxicity of “eighteen incompatibilities and nineteen counteraction” was related to dose. However, whether the content of “eighteen incompatibilities and nineteen counteraction” is accurate, whether the advantages outweigh the disadvantages or the disadvantages outweigh the advantages for patients, whether it can be used in the clinic or should be banned, and what is the standard, still need to be verified through a large number of clinical trials. In response, evidence-based Chinese medicine is a feasible way.

TCM follows an evidence-based path and cannot be generalized

As mentioned above, the biggest conflict between TCM and EBM lies in the flexibility of TCM syndrome differentiation and treatment. The mode of TCM diagnosis and treatment is “principle, method, prescription and medicine”, emphasizing individual differences, and its treatment variability is large. However, in fact, although treatment based on syndrome differentiation is a major feature of TCM, not all TCMS need syndrome differentiation. In “Treatise on Febrile Diseases”, Zhang Zhongjing put forward the indication of “Xiaochaihu Soup”: “Exogenous febrile disease, have Chaihu syndromes, but see one

syndrome can be diagnosed, do not need all”. Furthermore, in clinical practice, some doctors have also suggested that the use of Classical prescription should be “with appropriate syndrome, with appropriate prescription”, not all need to base on syndrome differentiation. In this respect, the standardization research of classical prescription in Japanese Hanfang medicine has given us some reference and inspiration. Japanese research on classical prescription places great emphasis on practicality, emphasizing the correspondence between prescription and syndrome. While the syndrome is determined, the prescription has no addition or subtraction. So as to realize the standardization of Hanfang syndrome and treatment. As early as 1972, Japan’s Health Ministry had selected 210 classical prescriptions from the “Treatise on Febrile Diseases” and “Golden Chamber Synopsis” for approval as over-the-counter (OTC) drugs. So far, 233 classical preparations have been included in Japan’s National Health Insurance (NHI) (5). This way of “prescription and syndrome correspondence” is conducive to the development of modern evidence-based clinical research in TCM. Through standardized clinical trials, more objective evidence of the efficacy of TCM can be obtained.

The President of Dongzhimen Hospital, Wang Xian, pointed out that the integration of traditional Chinese and western medicine is a combination of research methods and clinical practice. The development of TCM has gone through three stages: prescription, component and monomer (6). Prescription Chinese medicine is the main body of TCM, which needs to emphasize the differentiation of symptoms. The component Chinese medicine is the main body of modern TCM, which is composed of the active ingredients in the extracted Chinese medicine, partial emphasis on syndrome differentiation, while most can be administered by disease or symptom. For example, “Danshen Dropping Pill” and “Shexiangbaixin Pill” can be used at the treatment of coronary heart disease. Monomer Chinese medicine refers to the extraction of the active ingredients of a drug. The typical example is that professor Tu Youyou extracted artemisinin to treat malaria. This part of TCM has clear target and clear mechanism of action, and no need for syndrome differentiation. Through the classification, it can be found that different research methods can be adopted for different kinds of TCM. The component Chinese medicine and monomer Chinese medicine are the products of the integration of traditional and western medicine, which can achieve standardized research by modern EBM methods. Academician Chen Keji

put forward at the kick-off meeting of the cardiovascular disease project team of the China Center for Evidence Based Traditional Chinese Medicine (CCEBTTCM) in 2019 that clinical scientific research and affirmative effects of TCM should be practical and realistic, and the scientific and rational application of EBM methodology should be emphasized (7).

Results

Examples of high-quality evidence-based clinical studies of TCM published in international journals

As early as 1998, the *Journal of the American Medical Association (JAMA)* published a study on the effectiveness of TCM in the treatment of irritable bowel syndrome (8). The study was carried out in Australia and involved 116 patients. Those who met the inclusion criteria were divided into individualized TCM group, standard TCM group, and placebo group. After treatment, it was concluded that the symptom improvement in the standard TCM group was significantly better than the placebo group and non-standard TCM group. This is an earlier international study that proven the effectiveness of TCM. In addition, in August 2011, the international authoritative medical journal *Ann Intern Med* published a clinical study of oseltamivir and Chinese traditional therapy (maxingshigan-yinqiaosan) in the treatment of H1N1 influenza (9). This study showed that maxingshigan-yinqiaosan can significantly reduce the fever time in H1N1, and its effect is similar to that of oseltamivir or has a trend of better efficacy. It provides new options and methods for the treatment of influenza. Besides, in March 2019, the clinical research of “Carotid artery plaque intervention with Tongxinluo capsule” was published in *Scientific Reports*, a subsidiary journal of the internationally authoritative science and technology journal *Nature*. This was a multicenter randomized double-blind parallel-group placebo-controlled study, led by Zhang Yun, academician of Qilu Hospital of Shandong University. The study was carried out in 35 grade-a hospitals in 18 provinces in China, and a total of 1,212 patients with carotid atherosclerotic plaque were included as subjects. On the basis of conventional clinical treatment, Tongxinluo capsules were added to observe the changes of bilateral carotid intima-media thickness, plaque area and vascular remodeling index after 2 years. The results showed that the combination with Tongxinluo therapy could delay the progress of the average internal media thickness

(IMT), plaque area and vascular remodeling of the carotid artery, and reduce the cardiovascular events with a good safety profile (10). Furthermore, In September 2019, the international top journal of *Critical Care Medicine (CCM)* published the research paper “XueBiJing Injection Versus Placebo for Critically Ill Patients With Severe Community-Acquired Pneumonia: A Randomized Controlled Trial” online (11). The study was led by Zhongshan Hospital affiliated to Fudan University, was conducted over 10 years in 33 hospitals in China, involving a total of 710 critically ill patients with severe community-acquired pneumonia. The results showed that in critically ill patients with severe community-acquired pneumonia, the combination of XueBiJing injection on the basis of anti-infection could significantly improve the improvement rate of the risk rating of pneumonia severity index (PSI), significantly reduce the mortality rate of the patients, and shorten the duration of mechanical ventilation and ICU stay. This research breaks the bottleneck of western medicine treatment and provides an effective treatment for severe pneumonia patients. On the other hand, injection preparations of TCM, especially injection preparations of complex ingredients, have been widely controversial. This study builds confidence for the development of injection preparations of TCM in the future (the summary is shown in the *Table 1*).

The above-mentioned studies can be included in internationally renowned journals, shows that these studies have a rigorous and reasonable design, and the results have a strong credibility, which is recognized by the international community, and also proves the feasibility of evidence-based research on TCM. On the other hand, although the efficacy of TCM is worthy of recognition, not all TCM is effective. We must objectively recognize the shortcomings of some TCM and develop the good parts. Just as academician Chen Keji said, “seek truth from facts”, rational use of EBM methods, take the essence and discard the dregs, to provide more clinical evidence for the use of TCM.

Acupuncture, as an important intervention in the treatment of diseases in TCM, is widely recognized internationally, which is also based on a large number of basic and clinical studies on acupuncture. Liu *et al.*'s study found that among women with stress urinary incontinence, treatment with electroacupuncture involving the lumbosacral region, compared with sham electroacupuncture, resulted in less urine leakage after 6 weeks (12). Zhao *et al.* found through two RCTs that acupuncture-assisted treatment of chronic stable angina can reduce the frequency of angina attacks (13), and in the

Table 1 examples of evidence-based clinical studies of traditional Chinese medicine in the treatment of related diseases

Disease	Interventions	Published year	Author	Nation	Journal	IF
Irritable bowel syndrome	Individualized TCM/standard TCM/placebo	1998	Bensoussan A	Australia	<i>JAMA</i>	31.71
H1N1 influenza	Oseltamivir/traditional therapy (maxingshigan-yinqiaosan)	2011	Wang C	China	<i>Ann Intern Med</i>	19.315
Carotid artery plaque	Tongxinluo capsule + conventional treatment/ conventional treatment	2019	Zhang M	China	<i>Scientific Reports</i>	4.011
Critically ill patients with severe community-acquired pneumonia	XueBiJing injection/placebo	2019	Song Y	China	<i>Critical Care Medicine, CCM</i>	6.971

treatment of migraine, acupuncture may be able to reduce migraine recurrence for a long time (14). Brinkhaus *et al.* studied on 422 patients with seasonal allergic rhinitis and found that acupuncture led to significant improvements in disease-specific quality of life and antihistamine use measures after 8 weeks of treatment compared with sham acupuncture and with rescue medication (RM, cetirizine) alone (15). Moreover, acupuncture also plays an important role in the treatment of cancer. Hershman *et al.* found that among postmenopausal women with early-stage breast cancer and aromatase inhibitor-related arthralgias, true acupuncture compared with sham acupuncture or with waitlist control resulted in a significant reduction in joint pain at 6 weeks (16). Molassiotis *et al.*'s study found that acupuncture can also improve the cancer-related fatigue symptoms of breast cancer patients and improve their quality of life (17). And Enblom *et al.* studied 215 patients with cancer radiotherapy, found that both acupuncture and sham acupuncture had a relieving effect on nausea and vomiting caused by radiotherapy, and had positive effects on relaxation, mood, sleep and pain relief (18). On the other hand, in some diseases, the therapeutic effect of acupuncture is still unclear. Hinman *et al.* researched 282 patients with moderate or severe chronic knee pain aged ≥ 50 years in Victoria, Australia, and found that neither laser nor needle acupuncture conferred benefit over sham for pain or function (19). Its findings do not support acupuncture for these patients. Besides, Wu *et al.*'s study found that among 926 Chinese women with polycystic ovary syndrome, the use of acupuncture with or without clomiphene, compared with control acupuncture and

placebo, did not increase live births. This finding does not support acupuncture as an infertility treatment in such women (20). All in all, more scientific and rigorous clinical trials are needed to provide guidance and evidence for the use of acupuncture (the summary is shown in the *Table 2*).

Study on the safety of TCM

With the development of the modernization of TCM, the safety of TCM has attracted more and more attention. Safety is the basis of efficacy, and the introduction of TCM to the world should be based on safety, effectiveness, stability and quality. Although there is a general traditional understanding that TCM has "good effects with few side effects", the toxicity of TCM objectively exists. As early as in "Sheng Nong's Herbal Classic", the toxicity of TCM has been recorded, which has played a significant role of reference for the later generations in terms of safe medication. In addition, there are numerous reports of serious adverse events about the TCM both at home and abroad, such as the bupleurum event in Japan, berberine event in Singapore, polygonum multiflorum event and rhizoma corydalis event in China, which have caused negative effects on the clinical application of TCM. Therefore, strengthen the safety evaluation of TCM is one of the important research directions of TCM modernization strategy (21). At present, China has given strong support to the modernization and safety research of TCM, such as the strong promotion to the safety reevaluation of TCM injection preparations, and in the past years, the State Food and Drug Administration (SFDA) has intensively revised the

Table 2 examples of evidence-based clinical studies on acupuncture in the treatment of related diseases

Disease	Interventions	Published year	Author	Nation	Journal	IF
Stress urinary incontinence	Electroacupuncture/ sham electroacupuncture	2017	Liu Z	China	<i>JAMA</i>	51.273
Chronic stable angina	Acupuncture	2019	Zhao L	China	<i>JAMA Internal Medicine</i>	20.768
Migraine	Acupuncture/sham acupuncture	2017	Zhao L	China	<i>JAMA Internal Medicine</i>	20.768
Seasonal allergic rhinitis	Acupuncture/sham acupuncture /medication	2013	Brinkhaus B	Germany	<i>Annals of Internal Medicine</i>	19.315
Early-stage breast cancer	Acupuncture/sham acupuncture	2018	Hershman DL	America	<i>JAMA</i>	51.273
Cancer-related fatigue (breast cancer)	Acupuncture/blank	2012	Molassiotis A	Britain	<i>Journal of Clinical Oncology</i>	28.245
radiotherapy-induced nausea	Acupuncture/sham acupuncture	2012	Enblom A	Sweden	<i>Annals of Oncology: official journal of the European Society for Medical Oncology</i>	14.196
Chronic knee pain	Acupuncture/laser/sham acupuncture/sham laser	2014	Hinman RS	Australia	<i>JAMA</i>	51.273
Polycystic ovary syndrome	Acupuncture/sham acupuncture	2017	Wu XK	China	<i>JAMA</i>	51.273

specifications of Bupleurum injection, Salvia miltiorrhiza injection, Xuesaitong injection, Shenmai injection and other TCM injection preparations to ensure the safe use of TCM injection preparations. In terms of clinical research, Zheng and other experts conducted intensive monitoring of 31,913 patients using Xuebijing injection in 93 hospitals. It found that the incidence of adverse drug reactions was 0.3%, and the symptoms were relatively mild or not serious (22). There was no significant relationship between the adverse reaction and solvent, route of administration, bad habits, allergy, first use of Xuebijing injection or the dose of it, but there was a significant relationship between the adverse reaction and washing syringe and rapid dripping of liquid. The large-scale investigation shows that the adverse reactions can be prevented by rational medication and standard operation. Another study based on 31,556 patients who used Yunnan Baiyao capsule in 163 hospitals found that the overall incidence of adverse reactions to Yunnan Baiyao capsule was 1.17%, with abnormalities mainly in the digestive system, skin and respiratory system (23). It was found that functional diarrhea and gastric discomfort were the definite adverse reactions of Yunnan Baiyao capsule,

and the symptoms were mostly moderate without life-threatening conditions. Research on the safety of TCM is helpful to guide the standard and rational use of TCM, reduce or prevent the occurrence of adverse reactions in a certain range, which is of great significance to the development of TCM. However, in general, there is still a relative shortage of clinical studies on the safety of TCM at home and abroad, and more large-scale, multi-center and high-quality clinical studies on the safety of TCM should be carried out in the future to provide evidence for the safe use of TCM.

Discussion

Prospect of evidence-based clinical research of TCM

At present, evidence-based research on TCM in China has just started, and there are still many quality problems in the clinical trials of TCM. Through the sampling analysis of the literature quality of TCM RCT in China in the past 10 years, Zhang Junhua and other experts found that the quality of most research reports still needs to be improved,

and there are many problems in the methodology and implementation of the research (1), which will affect the reliability of research results, and makes that the evidence of efficacy is difficult to obtain international recognition (24). Therefore, for the future evidence-based clinical research of TCM, the following Suggestions are put forward: (I) design a reasonable and rigorous clinical research trial program, and calculate enough samples according to the test; (II) make the use of blinding more rigorous; (III) add the end point indicators to outcome indicators, such as the observation and report about case fatality rate, disability rate, etc.; (IV) standardize the operation, strictly control the quality of each part of the trial, and conduct quality supervision; (V) increase research reports on the safety of TCM; (VI) conduct a meta-analysis on previously published clinical trials with the method of systematic evaluation, especially randomized controlled clinical trials; (VII) collect and sort out the existing high-quality clinical trials, establish the corresponding efficacy database according to different therapies and diseases to promote international communication and dissemination (25).

All in all, a large number of studies and practices have shown that evidence-based method is suitable for TCM. There is no conflict that some Chinese medicine cure syndromes and others cure diseases. For those parts are suitable for evidence-based research methods, modern standardized research should be conducted to provide solid scientific evidence for the efficacy of TCM. Although the path of evidence-based TCM is difficult and arduous, it will be achieved through efforts, and there is a long way to go.

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