Traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and chronic fatigue syndrome (Review)

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[Intervention Review]

Traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and chronic fatigue syndrome

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ABSTRACT

Background

Chronic fatigue is increasingly common. Conventional medical care is limited in treating chronic fatigue, leading some patients to use traditional Chinese medicine therapies, including herbal medicine.

Objectives

To assess the effectiveness of traditional Chinese medicine herbal products in treating idiopathic chronic fatigue and chronic fatigue syndrome.

Search methods

The following databases were searched for terms related to traditional Chinese medicine, chronic fatigue, and clinical trials: CCDAN Controlled Trials Register (July 2009), MEDLINE (1966-2008), EMBASE (1980-2008), AMED (1985-2008), CINAHL (1982-2008), PSYCHINFO (1985-2008), CENTRAL (Issue 2 2008), the Chalmers Research Group PedCAM Database (2004), VIP Information (1989-2008), CNKI (1976-2008), OCLC Proceedings First (1992-2008), Conference Papers Index (1982-2008), and Dissertation Abstracts (1980-2008). Reference lists of included studies and review articles were examined and experts in the field were contacted for knowledge of additional studies.

Selection criteria

Selection criteria included published or unpublished randomized controlled trials (RCTs) of participants diagnosed with idiopathic chronic fatigue or chronic fatigue syndrome comparing traditional Chinese medicinal herbs with placebo, conventional standard of care (SOC), or no treatment/wait lists. The outcome of interest was fatigue.

Data collection and analysis

13 databases were searched for RCTs investigating TCM herbal products for the treatment of chronic fatigue. Over 2400 references were located. Studies were screened and assessed for inclusion criteria by two authors.

Main results

No studies that met all inclusion criteria were identified.

Authors' conclusions

Although studies examining the use of TCM herbal products for chronic fatigue were located, methodologic limitations resulted in the exclusion of all studies. Of note, many of the studies labelled as RCTs and conducted in China did not utilize rigorous randomization procedures. Improvements in methodology in future studies is required for meaningful synthesis of data.

PLAIN LANGUAGE SUMMARY

Traditional Chinese medicinal herbs for chronic fatigue

Treatment options for idiopathic chronic fatigue are limited. This review attempted to examine the use of traditional Chinese herbal remedies for this condition. Although some studies investigating traditional Chinese herbs for were found for chronic fatigue syndrome, no studies met the inclusion criteria. Choice of inclusion criteria was intended to narrow inclusion to methodologically rigourous and meaningful studies. Methodological limitations in the studies identified, such as type of control used and study design, limited the usefulness of the data

BACKGROUND

Description of the condition

Fatigue may be described as a pervasive sense of tiredness or lack of energy that is not related exclusively to exertion. Fatigue may result from behavioral problems such as excess physical or mental activity, sleep deprivation, and poor diet or a range of medical conditions including infection, and cardiovascular, metabolic, connective tissue and endocrine disorders (De Merlier 2003). Fatigue may be of known or unknown aetiology and ranges in duration from short-term to chronic. The more severe forms of fatigue include idiopathic chronic fatigue (ICF) and chronic fatigue syndrome (CFS) (Fukuda 1994). The aetiology of ICF/CFS is as yet unexplained, although numerous theories have been proposed and investigated. ICF/CFS has been identified by many names throughout its documented history; current terminology also varies depending on global region and diagnostic criteria. Some of the names that may be used to describe ICF/CFS or its subtypes include neurasthenia, post-viral fatigue syndrome (PVFS), myalgic encephalomyelitis (ME), and chronic fatigue immune deficiency syndrome (CFIDS) (Wessely 1998).

CFS is characterised by severe disabling fatigue and a combination of four additional symptoms that may include impairments in cognitive or neurological function, sleep dysfunction, musculoskeletal pain, and endocrine or immune dysfunction. Additionally, alternative medical and psychiatric causes must have been ruled out, and the condition must have been present for at least six months (Fukuda 1994). ICF meets all of the criteria for CFS except for the need for four additional symptoms (Fukuda 1994). The prognosis of ICF and CFS is often poor. Longitudinal studies have reported that less than 30% of ICF and 10% of CFS patients fully recover (Joyce 1997). The prevalence of ICF and CFS in primary care has been reported at 9% and 2.6% respectively (Wessely 1997).

ICF/CFS is associated with considerable disability and public health burden. The impact of these conditions is not only physical in nature but extends to psychological, social, emotional, and economic dimensions as well. Approximately 26% of ICF and 37% CFS patients are unable to work (Bombardier 1996). Cost estimates in Britain have determined that each case of ICF/CFS in adults cost an average of £1906 over three months in informal health care and lost productivity (McCrone 2003).Similar estimates in the US reported annual individual and national losses of $20 000 and $9.1 billion (USD) respectively (Reynolds 2004).

There is no definitive cure for ICF/CFS. Due to the unclear etiology, diagnostic uncertainty, and the heterogeneity of these populations, there are also no firmly established treatment recommendations (Afari 2003), although treatment guidelines are available in some countries (Carruthers 2003, Turnbull 2007). Treatment options that are used in clinical practice are directed toward relieving symptoms and improving function, and include pharmacological, immunological and antiviral agents, cognitive/behavioral therapies and physical therapies. Few clinical studies have been published for any of these options (Afari 2003). Recent evaluation

of the levels of evidence for the various treatment options reported that with the exception of one pharmacologic agent for immune dysfunction, all of the treatments reviewed ranked at the lowest or second lowest levels of evidence (expert opinion of an individual or committee, respectively) (Carruthers 2003).

Given the limited treatment options offered by conventional Western medicine, the lack of evidence of effectiveness and safety for those options, and the occurrence of side effects common to conventional medications it is not surprising that sufferers of chronic fatigue use a range of complementary and alternative medicine (CAM) therapies (Afari 2003, Carruthers 2003). CAM treatments that have been documented in ICF/CFS populations include massage, megavitamins and nutritional supplements, herbals, acupuncture and homeopathy, although supporting evidence for these therapies is also limited. Few clinical trials have been conducted for CAM therapies, and those that have been published are contradictory (Afari 2003), inconclusive, or have not yet been replicated (Wessely 1998). Several of the CAM therapies that have been used for ICF/CFS fall under the domain of traditional Chinese medicine (TCM).

Description of the intervention

TCM is a health care system that evolved in China over a period of thousands of years. TCM is estimated to be used by over one quarter of the world's population, and as "a complete system of medicine, it has been selected by the World Health Organization for worldwide propagation to meet the health care needs of the twenty-first century" (Flaws 1993).

The approach to health and healing differs from conventional Western medicine in that disease is believed to be the result of imbalance and disharmony between organ systems in the body and between the body and the environment. In addition, blockage in or deficiency of the body's vital energy (known as qi) may result in illness. The goal then is to restore balance, harmony, and flow and to strengthen and support the body's innate healing capacities using therapies such as acupuncture, moxibustion, diet modification, Tui-na massage, therapeutic exercise, and medicinal products, including herbs. Treatment may include one or more of the available therapies and is customized and tailored to the needs of the individual patient. The aetiology of disease is not relevant to treatment, which is instead based on the presentation of patterns of symptoms. Patterns of symptoms may be as numerous as the patients who present them and are not tied to disease classifications. Patients with the same disease classification may present different patterns while patients with different diseases may present the same patterns.

Due to the large number of potentially useful herbs, as well as differences between TCM schools of thought and practice, and the natural variations in CFS patient symptoms, it is beyond the scope of this review to describe all the possible herbs or formulations that might be used in practice. Many TCM texts (old and new) provide treatment details for fatigue based on patient presentation; in one such text, herbs commonly used to 'invigorate qi' include ginseng, astragalus root, dioscorea rhizome, poria, common curculigo, and hairy deer-horn as well as glycyrrhiza root, atractylodes rhizome, Chinese jujube, Mornda root and Himalayan teasel root. Herbs that have been recently studied through clinical research for CFS and related symptoms include single herbs such as ginseng root, poria, glycyrrhiza root, angelica root, and peony root, as well as established formulations (Chen 2008).

How the intervention might work

Successful treatment of chronic conditions is reputed to be a strength of TCM (Huizing 1995, Cohen 2000, McCulloch 2002). Descriptions of chronically fatiguing illnesses can be found in a TCM text that is 2000 years old (Buchwald 1994). More recently, textbooks used for TCM training outline conditions that include ICF and CFS and the methods used to treat them (Maciocia 1994, Becker 2000, Flaws 2001, Maciocia 2004). Similarly, summary reports of treatment of chronic fatigue with TCM specifically describe common symptom patterns for CFIDS and CFS, and the corresponding approaches that are used to treat them (Vickers 1994, Chen 1999). Acupuncture, moxibustion, diet therapy, and medicinal products, including herbs, are among the therapies described.

There is a vast body of literature, dating back thousands of years, on the subject of Chinese medicinal products. Numerous texts have collected this information and a recent compilation, *The Encyclopedia of Chinese Medicinal Substances*, published in 1977, identified 5767 medicinal substances, of which 4773 came from plants. Through clinical experience, this list has been narrowed to 400-600 herbs in daily use (Zhu 1998). The use of Chinese medicinal herbs specifically for the treatment of fatigue was the topic of a recent publication that provides a comprehensive review of TCM e-books. This review compares modern definitions of CFS to ancient descriptions and symptoms of fatigue conditions and details herbs used for treatment (Chen 2008).

Diagnosis and treatment in TCM does not readily translate into terms understood in Western medicine. Goals for treatment of CFS may include removal of dampness or heat, tonifying of various systems, and modification of qi, yin, and yang. Mechanisms of action of TCM herbs is an active area of research but few definitive answers are yet available. Patients, especially in the West, often use TCM herbs without having a clear understanding of how they many be helped, relying instead upon the knowledge and experience of their TCM practitioner.

Why it is important to do this review

ICF/CFS are postulated to be the result of a complex and mulifactoral etiology (Afari 2003), which, combined with the changing

nature of symptoms over the course of disease, makes targeting of treatments very difficult. Since definitive aetiology, syndrome classification and static symptomology are not required for TCM treatment, exploration of the evidence regarding efficacy and safety is warranted.

Despite the popularity of TCM therapies, rigorous evaluations of the safely and effectiveness of TCM therapies for various conditions have, until recently, been lacking (Liu 2000, Liu 2002, McCulloch 2002, Wu 2005, Zeng 2007, Jing 2009). Based on the historical reports of use for chronic fatigue, existence of current treatment protocols and the need for effective treatment, the evidence associated with TCM herbal products for the treatment of ICF and CFS will be systematically evaluated.

OBJECTIVES

To assess the effectiveness of traditional Chinese medicine herbal products in treating idiopathic chronic fatigue and chronic fatigue syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials, including cluster and crossover trials. Quasi-randomized trials, assigning patients to groups based on date, order of entry, birth date, etc, will be excluded.

Types of participants

Participants were not restricted by gender, age or ethnicity.

Participants must have been diagnosed with chronic fatigue of unknown etiology, lasting at least 6 months, according to accepted diagnostic guidelines including Centre for Disease Control and Prevention (CDC) 1988 (Holmes 1988), Australia (Lloyd 1990), Oxford (Sharpe 1991), CDC 1994 (Fukuda 1994), and CDC 2005 (Reeves 2005).

Types of interventions

Intervention

Traditional Chinese medicine herbs or herbal products historically used in TCM. Herbs may have been ingested (as in a tea), inhaled or applied to the body (as in a lotion), and may have been used singly or in combination with other herbs. A (non-exhaustive) list includes: ginseng, astragalus root, dioscorea rhizome, poria, common curculigo, glycyrrhiza root, atractylodes rhizome, and Chinese jujube. Herbs that have been recently studied through clinical research for CFS and related symptoms include single herbs such as ginseng root, poria, glycyrrhiza root, angelica root, and peony root, as well as established formulations (Chen 2008).

Evaluation of participants and/or details of the intervention must have been applied according to TCM theory and practice. Other oriental medical therapies, not specified as TCM or Chinese medicine, were excluded. Kampo, defined as the practice of TCM-based herbology in Japan, was included as an acceptable intervention.

Control Interventions

Control groups consisted of placebo (either inactive substances or herbs known not to affect outcomes of interest), conventional standard of care (SOC) as defined by recommendations or guidelines followed in the country of treatment, or no treatment/wait lists.

Types of outcome measures

Primary outcomes

Fatigue (e.g. change in severity from baseline, comparison between treatment and control) as measured by the patient or clinician, using a standardised or validated measurement tool such as the Fatigue Severity Scale (Krupp 1989) or Chalder Fatigue Scale (Chalder 1993).

Secondary outcomes

1. Quality of life (such as SF-12, SF-36)
2. Global improvement
3. Symptom impact (e.g. employment status)
4. Symptoms specific to subtype (e.g. pain, sleep, exercise tolerance, mood)
5. Adverse events (i.e. adverse reactions to herbal products).
5. Resource use (such as physician visits, prescription medications), cost analysis

Search methods for identification of studies

Electronic searches

a) The Cochrane Depression, Anxiety and Neurosis Group Controlled Trials Register, CCDANCTR-Studies and CCDANCTR-References were searched up to August 2008 using the following search terms:

CCDANCTR-Studies

Diagnosis = Fatigue or Neurasthenia

and

Intervention = "Traditional Chinese Medicine" or Acup* or chi or "ch'i" or qi or cupping or Kampo or Meridian or Moxibus* or Moxabus* or qigong or tai or taichi or Tuina or Yin or Yang or Shenmai or "Tongue Diagnosis" or "Five Element"
CCDANCTR-References
Keyword = Fatigue or Neurasthenia
or
Free-text = CFS
and
Title or Abstract or Keyword = Chinese
or
Title or Abstract or Keyword = Traditional
b) Additional searches
The following databases were searched for the indicated time periods or from inception of the database. Searches were not limited by language or publication status. MEDLINE (1966-2008) (see Additional Table 1), EMBASE (1980-2008), AMED (1985-2008), CINAHL (1982-2008), PSYCHINFO (1985-2008), the Cochrane Central Register of Controlled Trials (CENTRAL), the Chalmers Research Group PedCAM Database, VIP Information (1989-2008) (see Table 2), and China National Knowledge Infrastructure (CNKI 1976-2008).
Additional material was searched through Ovid's Online Computer Library Center Inc (OCLC) Proceedings First (1992-2008), Conference Papers Index (1982-2008) and Dissertation Abstracts (1980-2008). Ongoing trials were identified through Current Controlled Trials, National Institute of Health, the National Research Register, and the Chinese Clinical Trial Registry (ChiCTR).

Searching other resources

Reference lists
Reference lists of included studies and review articles were examined.
Personal contact
Experts in the field were contacted for knowledge of additional studies.

Data collection and analysis

Selection of studies

Identified studies were independently screened by two review authors (DA/ST for the English databases, TW/XY for the Chinese databases), based on titles and available abstracts. The full texts for potentially relevant studies were obtained and reviewed for inclusion based on predetermined criteria. Disagreement was resolved by discussion.
In accordance with methodology employed by the Chinese Cochrane Centre in Chengdu, China, authors of studies identified through searches of the Chinese-language databases, that were described as randomized, were contacted by phone and interviewed about how patients were allocated to study groups, in order to verify that randomization was used. Studies that did not meet the specified criteria or that were unverified were excluded (Wu 2006).

Methods for future updates

This review did not locate any studies which met the inclusion criteria. Updates will be undertaken according to methods from the original protocol which are reproduced in Appendix 1.

RESULTS

Description of studies

See: Characteristics of excluded studies.

Results of the search

Searches returned a total of 2484 references, 1004 from the English databases and 1480 from the Chinese databases. After screening of titles and abstracts, full papers of 16 unique references were obtained and assessed for eligibility, 4 from the English searches and 12 from the Chinese searches. All were excluded.
Searches of trial registries did not identify any ongoing trials in this area.

Included studies

No studies met all the inclusion criteria.

Excluded studies

Studies were excluded based on the following reasons: (i) not an intervention study (de Ruyter 1995, de Sylva 1992); (ii) intervention was not TCM herbs alone (Jiao 2006, Meng 2006); (iii) the control group used another experimental intervention (such as acupuncture or another herb) (Lijue 2005, Ni 2002, Wang 2004, Wang 2006, Xiong 2000, Yuan 2006); and (iv) the design was not that of an RCT,based on information gathered from author interviews (Ning 2002, Peng 2000, Pu 2002, Shu 1997, Zhang 2004, Zhang R 2004). All 16 studies were conducted in China.

Risk of bias in included studies

No studies that met all inclusion criteria were identified.

Effects of interventions

No studies that met all inclusion criteria were identified.

DISCUSSION

Summary of main results

Numerous studies of TCM interventions for chronic fatigue, many of which were described as randomized, were found, however, no studies that met all inclusion criteria were identified. Upon assessment, two common reasons for exclusion were identified. The first reason was the comparison of two active treatments, neither having been previously tested for chronic fatigue. The second reason was the inappropriate use of the term 'randomized' to describe allocation of patients to groups. Patient choice or order of enrolment was often used for treatment allocation in these so-called "randomized trials", while other studies were found to be retrospective in nature.

What we conclude from this review is that although studies in this topic area are being conducted, methodological flaws prevent inclusion and synthesis of the results, limiting their usefulness in guiding treatment. Serious flaws in the conduct and reporting of clinical studies conducted in China have been identified, both for conventional medicine and TCM (Wu 2006). The extent of this problem is alarming and needs to be immediately addressed. The Chinese Cochrane Center has initiated steps intended to address these flaws, but in the meantime systematic review authors should be cautious in including Chinese studies based solely on published information.

Despite the utilization of TCM herbs for chronic fatigue, a solid evidence base for or against this treatment approach is lacking.

Overall completeness and applicability of evidence

Not applicable.

Quality of the evidence

Not applicable.

Potential biases in the review process

Strengths of this review include the use of extensive search terms and multiple databases, including two Chinese-language databases, to ensure that the search was comprehensive. In addition, use of author interviews to verify methodology ensured that invalid studies were not mistakenly included. Limitations include the widespread lack of complete reporting by study authors.

Agreements and disagreements with other studies or reviews

As, to our knowledge, this is the first systematic review of this topic, comparisons with other reviews cannot be made.

AUTHORS' CONCLUSIONS

Implications for practice

Due to the lack of studies which meet inclusion criteria, forming conclusions about practice is not possible. RCT evidence, as defined in this review, does not currently support the use of TCM herbs for ICF/CFS.

Implications for research

Methodological improvements, such as use of placebo/sham or a therapy that is known to be effective, rather than another unproven therapy, and use of unbiased methods for treatment allocation in future studies is required for meaningful results from controlled studies, and would facilitate subsequent data synthesis.

Improvements in reporting are also strongly urged. Guidance on these may be found in the CONSORT statements (Altman 2001, Gagnier 2006). Well-designed randomized controlled trials are needed to assess promising treatments and guide practice in the area of chronic fatigue.

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REFERENCES

References to studies excluded from this review

de Ruyter 1995 *{published data only}*

* de Ruyter P. Herbalism: a potent tool in management of chronic fatigue syndrome. 1995 NHAA (National Herbalists Association of Austrlia) International Conference. 1995:77–80.

de Sylva 1992 *{published data only}*

* de Sylva R. Herbal therapeutics and treatment of chronic fatigue syndrome, Epstein-Barr virus and Candida albicans. 1992 NHAA (National Herbalists Association of Australia) International Conference. 1992:14–18.

Jiao 2006 *{published data only}*

* Jiao YX, Li YT, Zhao Q. Liaoshen Daoqi method in the treatment of 36 patients with chronic fatigue syndrome. *Journal of Acupuncture Clinical Practice* 2006;**22**(12):51–52.

Lijue 2005 *{published data only}*

* Lijue Z. Acupuncture and Chinese patent drugs for treatment of chronic fatigue syndrome. *Journal of Traditional Chinese Medicine* 2005;**25**(2):99–101.

Meng 2006 *{published data only}*

* Meng H, Zhao WH. Clinical observation of traditional Chinese medicine with manipulation in the treatment of chronic fatigue syndrome. *Academic Periodical of Changchun College of Traditional Chinese Medicine* 2006;**22**(1):20–21.

Ni 2002 *{published data only}*

* Ni KQ. Acupuncture and TCM in the treatment of 35 patients with chronic fatigue syndrome. *Journal of Fujian College of TCM* 2002;**12**(4):22.

Ning 2002 *{published data only}*

* Ning TC, Li YP. Variated Sijunzi decoction in the treatment of 23 patients with chronic fatigue syndrome. *Research of Traditional Chinese Medicine* 2002;**18**(4):16–17.

Peng 2000 *{published data only}*

* Peng ZY. Shenmai injection in the treatment of patients with chronic fatigue syndrome. *Modern Integrated Traditional Chinese and Western Medicine Journal* 2000;**9**(8): 684–685.

Pu 2002 *{published data only}*

* Pu YF, Zhang XL, Shen AH. Observation for the effect of Huangqi injection in the treatment of 43 patients with chronic fatigue syndrome. *Modern Journal of Integrated Traditional Chinese and Western Medicine* 2002;**11**(3):224.

Shu 1997 *{published data only}*

* Shu YQ, Zhang GL. Treating 30 cases of chronic fatigue syndrome with modified Buzhong Yiqi decoction. *Journal of Anhui College of TCM* 1997;**16**(5):11–12.

Wang 2004 *{published data only}*

* Wang N. Clinical analysis of Zhonghuichuanghuang liquid in the treatment of chronic fatigue syndrome. *Modern Journal of Integrated Chinese and Western Medicine* 2004;**13**(1):53–54.

Wang 2006 *{published data only}*

* Wang N, Dan YF. Clinical observation of Xianqi decoction in the treatment of chronic fatigue syndrome. *Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine* 2006;**6**(2):31–32,37.

Xiong 2000 *{published data only}*

* Xiong FL, Xiao YP. Acupoints shot by using Huangqi injection in the treatment of 32 patients with chronic fatigue syndrome. *Guangxi Journal of TCM* 2000;**23**(6):30–31.

Yuan 2006 *{published data only}*

* Yuan SG, Zhao CW. Observations on the curative effect of traditional Chinese medicine in the treatment of chronic fatigue syndrome. *Chinese Journal of Information on Traditional Chinese Medicine* 2006;**13**(8):57.

Zhang 2004 *{published data only}*

* Zhang SX, Zhou W. Buzhong Yiqi decoction in the treatment of 40 patients with chronic fatigue syndrome. *Journal of Primary Medicine and Pharmacology* 2004;**11**(5): 608.

Zhang R 2004 *{published data only}*

* Zhang R, Li J, Chen J, Zhang ZJ, Guo ZH. Clinical observation in the treatment of Shenqi Fuyuan decoction in the treatment of patient with chronic fatigue syndrome. *Chinese Journal of TCM Information* 2004;**11**(2):148.

Additional references

Afari 2003

Afari N, Buchwald D. Chronic fatigue syndrome: a review. *American Journal of Psychiatry* 2003;**160**:221–236.

Altman 2001

Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T. The revised CONSORT statement for reporting randomized controlled trials: explanation and elaboration. *Annals of Internal Medicine* 2001;**134**(8):663–694.

Becker 2000

Becker S. *A handbook of Chinese hematology*. Boulder, Colorado: Blue Poppy Press, 2000.

Bombardier 1996

Bombardier C, Buchwald D. Chronic fatigue, chronic fatigue syndrome, and fibromyalgia. Disability and health-care use. *Medical Care* 1996;**34**:924–930.

Buchwald 1994

Buchwald D. Defining chronic fatigue syndrome. In: Straus, S editor(s). *Chronic fatigue syndrome*. New York, NY: Marcel Dekker, Inc, 1994:46.

Carruthers 2003

Carruthers B, Jain A, De Meirleir K, Peterson D, Klimas N, Lerner A, et al.Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *Journal of Chronic Fatigue Syndrome* 2003;**11**:7–115.

Chalder 1993
Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al.Development of a fatigue scale. *Journal of Psychosomatic Research* 1993;**37**(6):147–53.

Chen 1999
Chen J, Yang W. Treatment of chronic fatigue syndrome with Chinese medicine. *Journal of Chronic Fatigue Syndrome* 1999;**5**:61–5.

Chen 2008
Chen R, Moriya J, Yamakawa J, Takahashi T, Kanda T. Traditional Chinese medicine for chronic fatigue syndrome. *eCAM* 2008. [DOI: 10.1093/ecam/nen017]

Cohen 2000
Cohen M, Gish R. *The hepatitis C help book: a groundbreaking treatment program combining western and eastern medicine for maximum wellness and healing*. New York, NY: St. Martin's Press, 2000.

De Merlier 2003
De Mierleir K, McGregor N. Chronic fatigue syndrome guidelines. *Journal of Chronic Fatigue Syndrome* 2003;**11**: 1–5.

Deeks 2001
Deeks J, Altman D, Bradburn M. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger, M, Davey Smith, G, AltmanD editor(s). *Systematic reviews in health care*. 2nd Edition. London, UK: BMJ Books, 2001:300.

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal* 1997;**315**:629–634.

Flaws 1993
Flaws R. *Alternative medicine: the definitive guide*. Fife, WA: Future Medicine Publishing, 1993.

Flaws 2001
Flaws R. *The treatment of modern western diseases with Chinese medicine: a textbook & clinical manual*. Boulder, Colorado: New Poppy Press, 2001.

Fukuda 1994
Fukuda K, Straus S, Hickie I, Sharpe M, Dobbine J, Komaroff A, et al.The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Internal Medicine* 1994;**121**:953–959.

Gagnier 2006
Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Reporting randomized controlled trials of herbal interventions: an elaborated CONSORT statement. *Annals of Internal Medicine* 2006;**144**(5):364–367.

Higgins 2003
Higgins J, Thompson S, Deeks J, Altman D. Measuring inconsistency in meta-analyses. *British Medical Journal* 2003;**327**:557–560.

Holmes 1988
Holmes G, Kaplan J, Gantz N, Komaroff AL, Schonberger LB, Straus SE, Jones JF, Dubois RE, Cunningham-Rundles C, Pahwa S, Tosato G, Zegans LS, Purtilo DT, Brown N, Schooley RT, Brus I. Chronic fatigue syndrome: a working case definition. *Annals of Internal Medicine* 1988;**108**(3): 397–389.

Huizing 1995
Huizing A. *Acupuncture: an introduction to traditional Chinese medicine*. Edmonton, AB: Angie Huizing Publishing, 1995.

Jing 2009
Jing Z, Yang X, Ismail KMK, Chen X, Wu T. Chinese herbal medicine for premenstrual syndrome. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/ 14651858.CD006414.pub2]

Joyce 1997
Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. *Quarterly Journal of Medicine* 1997;**90**:223–233.

Krupp 1989
Krupp LB. The Fatigue Severity Scale: Application to patents with multiple sclerosis and systemic Lupus erythematosus. *Archives of Neurology* 1989;**46 46:1121-3.**: 1121–3.

Liu 2000
Liu JP, McIntosh H, Lin H. Chinese medicinal herbs for chronic hepatitis B. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD001940]

Liu 2002
Liu J, Kjaergard L, Gluud C. Misuse of randomization: a review of Chinese randomized trials of herbal medicines for chronic hepatitis B. *The American Journal of Chinese Medicine* 2002;**30**:173–176.

Lloyd 1990
Lloyd A, Hickie I, Boughton R, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. *Medical Journal of Australia* 1990;**153**(9): 522–528.

Maciocia 1994
Maciocia G. *The practice of Chinese medicine*. New York, NY: Churchill Livingstone, Inc, 1994.

Maciocia 2004
Maciocia G. *Diagnosis in Chinese medicine: a comprehensive guide*. New York, NY: Churchill Livingstone, Inc, 2004.

McCrone 2003
McCrone P, Darbishire L, Ridsdale L, Seed P. The economic cost of chronic fatigue and chronic fatigue syndrome in UK primary care. *Psychological Medicine* 2003;**33**:253–261.

McCulloch 2002
McCulloch M, Broffman M, Gao J, Colford Jr J. Chinese herbal medicine and interferon in the treatment of chronic hepatitis B: a meta-analysis of randomized, controlled trials. *American Journal of Public Health* 2002;**92**:1619–1627.

Reeves 2005
Reeves WC, Wagner D, Nisenbaum R, Jones JF, Gurbaxani B, Solomon L, Papanicolaou DA, Unger ER, Vernon SD, Heim C. Chronic Fatigue Syndrome - a clinically empirical

approach to its definition and study. *BMC Medicine* 2005; **3**:19 doi:10.1186/1741-7015-3-19.

Reynolds 2004
Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The economic impact of chronic fatigue syndrome. *Cost Effectiveness and Resource Allocation* 2004;**2**:4 doi:10.1186/1478-7547-2-4.

Sharp 1998
Sharp S. Meta-analysis regression. *Stata Technical Bulletin*. Stata Press, 1998.

Sharpe 1991
Sharpe M, Archard L, Banatvala J, et al.Chronic fatigue syndrome: guidelines for research. *Journal of the Royal Society of Medicine* 1991;**84**:118–121.

Turnbull 2007
Turnbull N, Shaw EJ, Baker R, Dunsdon S, Costin N, Britton G, Kuntze S, Norman R. *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) in adults and children*. London: Royal College of General Practitioners, 2007.

Vickers 1994
Vickers E, Dharmananda S, Fruehauf H. Treatment of chronic fatigue immune deficiency syndrome with Chinese medicine. *International Journal of Oriental Medicine* 1994; **19**:143–159.

Wessely 1997
Wessely S, Chalder T, Hirsch S, Wallace P, Wright D. The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study. *American Journal of Public Health* 1997;**87**:1449–1455.

Wessely 1998
Wessely S, Hotopf M, Sharpe M. *Chronic fatigue and its syndromes*. Oxford, UK: Oxford University Press, 1998.

Wiebe 2006
Wiebe N, Vandermeer B, Platt R, Klassen T, Moher D, Barrowman N. A systematic review identifies a lack of standardization in methods for handling missing variance data. *Journal of Clinical Epidemiology* 2006;**59**:342–353.

Wu 2005
Wu T, Munro AJ, Guanjian L, Liu GJ. Chinese medical herbs for chemotherapy side effects in colorectal cancer patients. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD004540.pub2]

Wu 2006
Wu T, Li Y, Bian Z, Liu G, Li J, Zhang J, et al.Investigation for quality of claimed ' randomised controlled trials' published in China. Cochrane Colloquium, Dublin Ireland. Oxford: UKCC, 2006.

Zeng 2007
Zeng X, Yuan Y, Wu T, Yan L, Su H. Chinese herbal medicines for hyperthyroidism. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD005450.pub2]

Zhu 1998
Zhu YP. *Chinese Materia Medica: Chemistry, Pharmacology and Applications*. Boca Raton FL: CRC Press, 1998.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
de Ruyter 1995	Not an intervention study
de Sylva 1992	Not an intervention study
Jiao 2006	Invalid intervention - not a TCM herb
Lijue 2005	Invalid control
Meng 2006	Invalid intervention - not a TCM herb
Ni 2002	Invalid control
Ning 2002	Not an RCT - assigned based on patient choice
Peng 2000	Not an RCT - assigned based on order of entry
Pu 2002	Not an RCT - assigned based on order of entry
Shu 1997	Not an RCT - retrospective study
Wang 2004	Invalid control
Wang 2006	Invalid control
Xiong 2000	Invalid control
Yuan 2006	Invalid control
Zhang 2004	Not an RCT - retrospective study
Zhang R 2004	Not an RCT - assigned based on patient choice

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Search methods: MEDLINE

Search terms
MEDLINE Search Strategy
1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS/
4. RANDOM ALLOCATION/
5. DOUBLE BLIND METHOD/
6. SINGLE-BLIND METHOD/
7. or/1-6
8. ANIMAL/ not HUMAN/
9. 7 not 8
10. CLINICAL TRIAL.pt.
11. exp CLINICAL TRIALS/
12. (clin$ adj25 trial$).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14. PLACEBOS/
15. placebo$.ti,ab.
16. random$.ti,ab.
17. RESEARCH DESIGN/
18. or/10-17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY/
22. exp EVALUATION STUDIES/
23. FOLLOW UP STUDIES/
24. PROSPECTIVE STUDIES/
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. acupressure/
31. exp acupuncture therapy/
32. “channels and collaterals”.tw.
33. qi.mp.
34. qi/
35. (chinese adj1 (diagnos$ or extract$ or formula$ or herb$)).tw.
36. (Chinese adj2 (medical or medicin$)).tw.
37. (cupping adj1 (treatment or therapy)).tw.
38. Drugs, Chinese Herbal/
39. Huang qi.tw.
40. Medicine, kampo/

Table 1. Search methods: MEDLINE (*Continued*)

41. Medicine, Chinese traditional/
42. medicine, oriental traditional/
43. Meridian doctrine.tw.
44. Moxibustion/
45. moxabustion.tw.
46. Oriental massage.tw.
47. qigong.tw.
48. tai ji/
49. tai chi.tw.
50. five element theory.tw.
51. Tongue diagnosis.tw.
52. (Traditional Chinese adj (medicine or medical)).tw.
53. Tuina.tw.
54. vital energy.tw.
55. Yang deficiency/
56. Yin deficiency/
57. yin-yang.tw.
58. Shenmai.tw.
59. pulse.tw.
60. tcm.tw.
61. or/30-60
62. (phyto$ or plant$ or herb$).mp.
63. idiopathic chronic fatigue.mp.
64. unexplained chronic fatigue.mp.
65. exp Fatigue Syndrome, Chronic/
66. exp Fatigue/
67. (FATIGUE$ or APATH$ or ASTHENIA or EXHAUST$ or LANGUOR$ or LASSITUDE or LETHARG$ or MALAISE or TIRED$).mp.
68. chronic fatigue.mp.
69. fatigue syndrome.mp.
70. chronic fatigue immune dysfunction syndrome.mp.
71. (chronic fatigue and immune dysfunction syndrome).mp.
72. exp NEURASTHENIA/
73. neurasthenia.mp.
74. myalgic encephalomyelitis.mp.
75. post-viral fatigue syndrome.mp.
76. post-infective fatigue syndrome.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
77. chronic Epstein-Barr virus infection.mp.
78. chronic Epstein-Barr virus syndrome.mp.
79. chronic Epstein-Barr virus infection syndrome.mp.
80. chronic mononucleosis.mp.
81. Iceland disease.mp.
82. Royal Free disease.mp.
83. exp Neurocirculatory Asthenia/
84. effort syndrome.mp.
85. Soldier s Heart.mp.
86. Da Costa's syndrome.mp.
87. immun$ deficiency syndrome.mp.

Table 1. Search methods: MEDLINE (*Continued*)

88. CFIDS.mp.
89. CFS.mp.
90. ICF.mp.
91. ME.mp.
92. EBV syndrome.mp.
93. or/63-92

Table 2. Search Strategy: Chinese Dtabse

Search terms
Chinese Database Search Strategy
#1 fatigue
#2 chronic fatigue
#3 chronic fatigue syndrome
#4 1-3/or
#5 traditional Chinese medicine
#6 herbs
#7 herbal medicine
#8 acupuncture
#9 electronic acupuncture
#10 acupressure
#11 tuina
#12 tai ji
#13 qi gong
#14 moxibustion
#15 huo guan
#16 6-15/or
#17 random
#18 random$ control$
#19 control$
#20 17-19/or
#21 #4 AND #16 AND #20

APPENDICES

Appendix 1. Methods to be used in future updates of the review

Data extraction and management

Data will be extracted independently by two review authors using a standardised data extraction form; disagreement will be resolved by discussion.

The following information will be extracted: author; year, country and language of publication; funding source; objectives; study design; participant characteristics including age, gender, ethnicity, number of participants who were eligible, enrolled and completed the study; diagnostic criteria and procedures; presence of intention-to-treat analysis; presence and method of randomization, blinding and allocation concealment; numbers and reasons for withdrawals and dropouts; details of TCM and SOC treatments including number and length of treatment, dose of herbal; type of control; qualifications of practitioners; presence of co-morbid disorders or concurrent medication; details of each outcome measured as well as assessment tool(s) and assessor(s); measure of treatment effect; measure of compliance; and adverse events.

If necessary, principal authors will be contacted for further details of each study.

Assessment of risk of bias in included studies

Methodological quality will be independently assessed by two review authors, using the Cochrane Collaboration 'risk of bias' tool, which assesses sources of bias including methods of sequence generation, allocation concealment, blinding, and collection and reporting of outcomes. Disagreement will be resolved by discussion.

Measures of treatment effect

Dichotomous data will be presented as relative risk (of improvement), along with corresponding 95% confidence intervals. The number needed to treat (for improvement) and number needed to harm (for adverse events) will also be determined for statistically significant outcomes.

Continuous data will be presented as weighted mean differences (for common measurement units) or standardized mean differences (for differing measurement units and different scales), along with corresponding 95% confidence intervals.

Unit of analysis issues

For studies with comparable treatment groups, data for studies with more than one active treatment arm will be entered separately into the meta-analysis and the control arm data will be evenly divided as much as possible between entries.

Dealing with missing data

In instances where information appears to be missing, study authors will be asked to provide the information. In cases where SDs are unavailable and not appropriated from the authors, SDs will be obtained using a method appropriate to the situation, as outlined in Wiebe et al (Wiebe 2006). For studies that report only per protocol analyses, and where sufficient information is available, intention to treat (ITT) analyses will be conducted. For missing dichotomous data, in sensitivity analyses best/worst case scenarios will be calculated in order to determine minimum effects.

Assessment of heterogeneity

Heterogeneity will be quantified with the I^2 statistic (Higgins 2003). The I^2 statistic describes the proportion of variance due to between-study variance (rather than within-study variance). Where there are eight or more studies included in a comparison, meta-regression, performed in Stata, will be carried out (Sharp 1998). In the event of less than eight studies per sub-group, Deek's Chi-square test for heterogeneity will be used (Deeks 2001).

Assessment of reporting bias

Publication bias will be assessed visually using funnel plots, and quantitatively assessed using weighted regression (Egger 1997).

Data synthesis

Random effects models will be used for the primary analyses, as a more conservative estimate of effect than fixed effect models.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be carried out on the following categories:

1. subtype of chronic fatigue (ICF versus CFS)
2. age (paediatric versus adult)
3. severity of fatigue before treatment
4. duration of fatigue before treatment
5. primary investigator's diagnostic or inclusion criteria
6. outcome measurement tool

Sensitivity analysis

Subgroup analyses will be carried out on study quality score. In a further sensitivity analysis, we will apply intention-to-treat principles with loss to follow-up data.

FEEDBACK

Feedback, 23 January 2009

Summary

None submitted

Reply

None

Contributors

None

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 4, 2009

Date	Event	Description
10 September 2008	Amended	Converted to new review format.
13 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Denise Adams has designed and prepared the protocol and led all aspects of the review except Chinese-language database searching and screening.

Taixiang Wu led Chinese-language database searching and screening.

Xunzhe Yang acted as a second reviewer for the Chinese databases.

Shusheng Tai provided TCM content expertise and acted as a second reviewer for screening and data extraction of the English databases.

Sunita Vohra provided editing and methodological guidance.

DECLARATIONS OF INTEREST

None known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

Chronic Disease; Drugs, Chinese Herbal [*therapeutic use]; Fatigue [*drug therapy]; Fatigue Syndrome, Chronic [*drug therapy]

MeSH check words

Humans