

Review

Traditional Chinese Medicine for Chronic Fatigue Syndrome

Rui Chen^{1,2}, Junji Moriya², Jun-ichi Yamakawa², Takashi Takahashi² and Tsugiyasu Kanda²

¹Department of Traditional Chinese Medicine, Union Hospital Affiliated to Huazhong University of Science and Technology, Wuhan, China and ²Department of General Medicine, Kanazawa Medical University, Ishikawa, Japan

More and more patients have been diagnosed as having chronic fatigue syndrome (CFS) in recent years. Western drug use for this syndrome is often associated with many side-effects and little clinical benefit. As an alternative medicine, traditional Chinese medicine (TCM) has provided some evidences based upon ancient texts and recent studies, not only to offer clinical benefit but also offer insights into their mechanisms of action. It has perceived advantages such as being natural, effective and safe to ameliorate symptoms of CFS such as fatigue, disordered sleep, cognitive handicaps and other complex complaints, although there are some limitations regarding the diagnostic standards and methodology in related clinical or experimental studies. Modern mechanisms of TCM on CFS mainly focus on adjusting immune dysfunction, regulating abnormal activity in the hypothalamic-pituitary-adrenal (HPA) axis and serving as an antioxidant. It is vitally important for the further development to establish standards for 'zheng' of CFS, i.e. the different types of CFS pathogenesis in TCM, to perform randomized and controlled trials of TCM on CFS and to make full use of the latest biological, biochemical, molecular and immunological approaches in the experimental design.

Keywords: chronic fatigue syndrome – herbal therapy – traditional Chinese medicine

Introduction

Chronic fatigue syndrome (CFS) is defined by: (i) clinically unexplained, persistent or relapsing fatigue of at least 6 months' duration, and (ii) concurrent occurrence of at least 4 accompanying symptoms, such as significant impairment in memory/concentration and muscle pain (1). Factors causing this condition remain unclear. Thus, the diagnosis depends upon an evaluation of the self-reported symptoms while the pathophysiology remains uncertain.

As yet there is no definitive treatment, rather, therapy is directed toward relieving symptoms, which often cause different side-effects (2) (Table 1). Therefore, utilization of complementary and alternative medicine (CAM) has

been common in fatiguing illnesses (3). As a form of CAM, traditional Chinese medicine (TCM) has been reported to be useful and without any side-effects for CFS not only in China but also in other parts of the world (4–5). In this study, we explore the benefits that TCM can provide for CFS and its limitations. We also provide some suggestions for further development.

Ancient Records on the Treatment of 'fatigue syndrome' with TCM

In a search of the ancient literature of TCM, we did not find the term 'chronic fatigue syndrome'. On the other hand, the symptoms, etiology, pathogenesis and treatment for 'fatigue syndrome' have been recorded in detail.

Symptoms, Etiology and Pathogenesis

Nearly 70 types of symptoms were recorded in the chapter on 'fatigue syndrome' in *Zhubing Yuanhou Lun*,

For reprints and all correspondence: Prof. Tsugiyasu Kanda, Department of General Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920-0293, Japan. Tel: +81-76-286-2211 ext. 3841; Fax: +81-76-286-2702; E-mail: kandat@kanazawa-med.ac.jp

© 2008 The Author(s).

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/2.0/uk/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Table 1. Therapeutic effect and side-effects of Western medicines in the treatment of CFS

	Therapeutic effect	Side-effect
Antidepressant therapy	No beneficial effect 9 (44).	Greater than 15% patients with certain side-effects such as gastrointestinal complaints, headache, anxiety.
Steroid therapy	Short-term benefits with low-doses for hypoactivity of the HPA axis but no effect after withdrawal (45).	High doses associated with significant side-effects such as Cushing's syndrome, ulcers, acne, osteopenia, immunosuppression, etc.
Immunotherapy	Intravenous immunoglobulin therapy effectively relieves symptoms for CFS following an acute viral infection (46), while another study found no effect (47).	Of the subjects, 82% treated with IgG have intense side-effects such as gastrointestinal complaints, headache, arthralgia and sometimes worse fatigue.
Nutritional supplements	Benefits from nutritional supplements (48).	No side-effects reported.
NADH therapy	Efficacy observed only during the first trimester of the trial (49).	No severe adverse effects but mild effects included poor appetite, dyspepsia and abdominal distension.

NADH denotes reduced form of nicotinamide adenine dinucleotide.

Table 2. Comparison of the symptoms of CFS and 'fatigue syndrome' recorded in *Zhubing Yuanhou Lun*

	Symptoms of 'fatigue syndrome' described in <i>Zhubing Yuanhou Lun</i>	Symptoms of 'chronic fatigue syndrome' (1) (50–51)
General symptoms	Fatigue; asthenia; weak and lean; malaise; pseudo-heat; fever; puffiness; susceptible hidrosis; deficient night sweating; postmorbidity sweating; hyperhidrosis; irregular chills and fever; osteopyrexia and fever.	fatigue; post-exertional malaise lasting > 24h; unusually warm; abnormal sweating; sudden changes in skin color; tender cervical/axillary lymph nodes.
Nervous system symptoms	Insomnia; dream-disturbed sleep; headaches; decreased visual acuity; decreased acoustic sensibility; anxiety; depression.	Sleep disorders including periodic movement disorder, excessive daytime sleepiness, apnea and narcolepsy; impaired short-term memory or concentration; headaches; tinnitus; anxiety; depression.
Symptoms of the digestive system	Poor appetite; impairment of digestive function; intestinal obstruction; abdominal distention; abdominal pain; vomiting; dry mouth and excessive thirst; swollen tongue; profuse saliva; gingival bleeding; hematemesis; hemorrhinia; blood in stools; loose stool; diarrhea; constipation.	Fullness and bloating after a small meal; abdominal distension; nausea; loss of appetite; irritable bowel symptoms including abdominal pain, diarrhea, loose stools, etc; mouth sores; dry mouth; vague complaints of dysesthesia and dysgeusia.
Symptoms of the <i>musculoskeletal locomotor</i> system	Painful extremities; spasms; paralysis; ecdysis of the hands and feet; cold and soft knees; somatic feelings of heaviness; lumbago; joint pain and muscle pain; cool limbs.	Muscle pain; multi-joint pain without swelling or redness; pain in the facial and masticatory muscles; temporomandibular joint dysfunction; shivering hands; acrocyanosis, cool extremities.
Respiratory symptoms	Dry and painful pharynx; expectoration and excessive phlegm; uneven breathing; poor inspiratory effort.	Sore throat; hyperventilation.
Circulation system symptoms	Palpitation; irregular pulse.	Palpitation.
Symptoms of the genital system	Acyesis; contraction of the genital organs; spermocrasia; spermorrhea; hemospermia; impotence; premature ejaculation.	No related symptoms.
Symptoms of the urinary system	Edema; polyuria; dysuria; turbid urine; hematuria.	Edema.

a famous tract about the etiology and symptoms of disease written during the Sui Dynasty. The symptoms can be categorized into two groups: somatic symptoms including fatigue, a somatic sense of heaviness, cold knees, puffiness, headaches, somatic pain (joint pain and muscle pain) and so on; and psychological symptoms, such as depression, anxiety, restlessness and so on. For an explanation of TCM, the ultimate reasons for the symptoms described earlier are induced by deficiencies in five organs (including *qi*, blood, *yin* and *yang* deficiencies) caused by the invasion of an exogenous pathogen,

excessive physical strain (manual labor, mental labor and sexual intercourse), abnormal emotional states (elation, anger, worry, anxiety, sorrow, fear and terror) or an improper diet.

Obviously, although such symptoms do not exactly mimic the Centers for Disease Control and Prevention (CDC) research criteria for CFS, they are extremely similar to CFS, as Table 2 indicates. Certainly, the limitations of symptom-related records are also obvious. First, there were not criteria for the diagnosis of 'fatigue syndrome' in this text or even other ancient TCM texts.

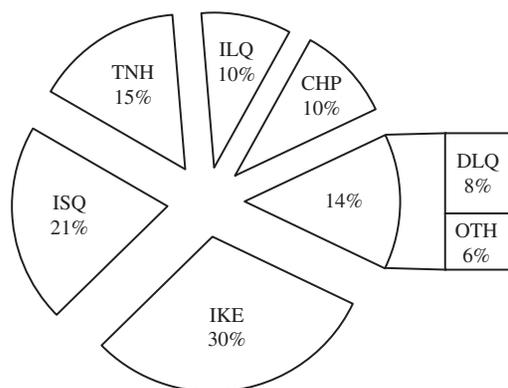


Figure 1. Different types of prescriptions for 'fatigue syndrome' in *Pujifang*. IKE, invigorating the kidney essence; ISQ, invigorating the Spleen *qi*; DLQ, dispersing the depressed liver *qi*; TNH, tranquilizing by nourishing the heart; ILQ, invigorating the lung *qi* and *yin*; CHP, clearing heat-pathogens; OTH, others.

Second, the characteristics of each symptom were not clearly described. For instance, no duration, no relieving or aggravating factors and no other characteristics were recorded about the symptom of 'fatigue'. Third, some symptoms are not consistent with CFS, such as the hemorrhage of different organs.

Treatment

We checked for the term 'fatigue syndrome' in more than 600 TCM e-books in the software of *Encyclopedia of Traditional Chinese Medicine*, published by Hunan Electronic Audio-Video Publishing House, including *Bencao Gangmu (Compendium of Materia Medica)*, *Pujifang* and so on, and found many records about its treatment.

Prescriptions

We searched for some prescriptions for 'fatigue syndrome' in *Pujifang*, the most monumental prescription book produced during the Ming Dynasty, in which there are about 975 items for 'fatigue syndrome'. According to the theory of TCM, most were used for repleting the body's deficiency, ameliorating sleep and abnormal emotion, and especially for invigorating kidney essence [the fundamental energy in the body (6)] and spleen *qi* [vital energy for maintaining normal digestive function and controlling blood in the blood vessels (6)] (Fig. 1). Some examples of the main prescriptions for 'fatigue syndrome' patients recorded in this book are Liu-Wei-Di-Huang-Wan (Rokumi-gan in Kampo), Bu-Zhong-Yi-Qi-Tang (Hochu-ekki-to in Kampo), Xiao-Chai-Hu-Tang (Sho-saiko-to in Kampo) and so on.

Drugs

We searched Chinese crude drugs that have a therapeutic effect on 'fatigue syndrome' in 50 ancient monographs

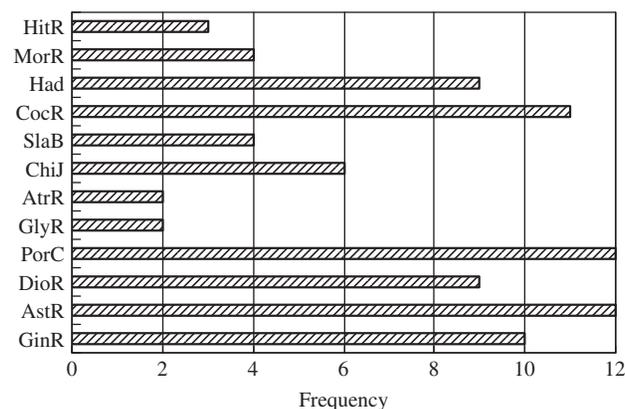


Figure 2. Frequency of invigorating *qi* and *yang* drugs for 'fatigue syndrome' in 50 famous ancient materia medica texts. GinR, Ginseng root; AstR, Astragalus root (*Astragalus membranaceus* Bge.); DioR, Dioscorea rhizome (*Dioscorea batatas* Decne.); PorC, Poria; GlyR, Glycyrrhiza root; AtrR, Atractylodes rhizome [*Atractylodes macrocephala* Koidz. (*A. ovata* A.P.DA.)]; ChiJ, Chinese Jujube (*Zizyphus jujuba* Mill); SlaB, Slenderstyle Acanthopanax Bark (*Acanthopanax gracilistylus* W.W.Smith.); CocR, Common Curculigo rhizome (*Curculigo orchoides* Gaertn.); HadH, Hairy Deer-horn (*Cervus elaphus* L.); MorR, Morinda root (*Morinda officinalis* How.); HitR, Himalayan Teasel root (*Dipsacus asper* Wall.).

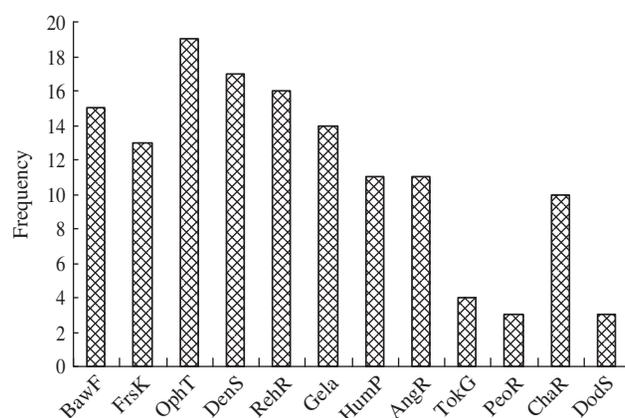


Figure 3. Frequency of nourishing *Yin* and Blood drugs for 'fatigue syndrome' in 50 famous ancient materia medica texts. BawF, Barbary Wolfberry fruit (*Lycium chinense* Mill.); FrsR, Fragrant Solomonseal rhizome (*Polygonatum officinale* All.); OphT, Ophiopogon tuber [*Ophiopogon japonicus* (Thunb.) Ker-Gaw]; DenS, Dendrobium nobile stems (*Dendrobium nobile* Lindl.); RehR, Rehmannia root; Gela: Gelatin (*Equus asinus* L.); HumP, Human placenta (*Placenta hominis*); AngR, Angelica root; TokG, Tokay Gecko (*Gekko gecko* Linnaeus); PeoR, Peony root; ChaR, Chinese Asparagus root [*Asparagus cochinchinensis* (Lour.) Merr.]; DodS, Dodder seed (*Cuscuta chinensis* Lam.).

of Chinese materia medica. Most treated 'fatigue syndrome' by invigorating *qi* and *yang* (Fig. 2), nourishing *yin* and blood (Fig. 3), adjusting abnormal sleep and emotion (Fig. 4) and clearing heat-pathogens (systemic or local febrile factors) (Fig. 5). At the same time, some beneficial meals for CFS were also found in these sources as displayed in Figure 6.

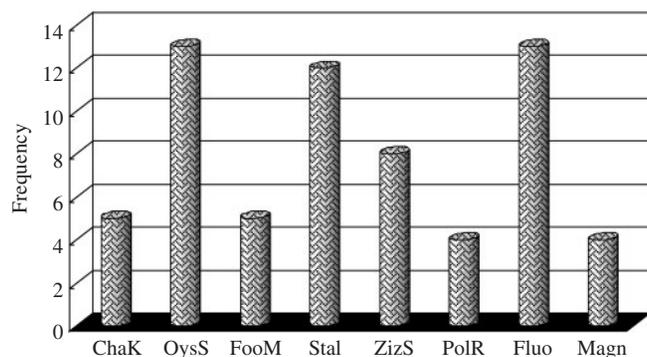


Figure 4. Frequency of adjusting abnormal sleep and emotion drugs for 'fatigue syndrome' in 50 famous ancient materia medica texts. ChaK, Chinese Arborvitae Kernel (*Biota orientalis* Endl.); OysS, Oyster shell (*Ostrea gigas* Thunb.); FooM, Fossilia Ossia Mastoidi; Stal, Stalactite; ZizS, Ziziphus seed (*Zizyphus spinosus* Hu.); PolR, Polygala root; Fluo, Fluorite; Magn, Magnetite.

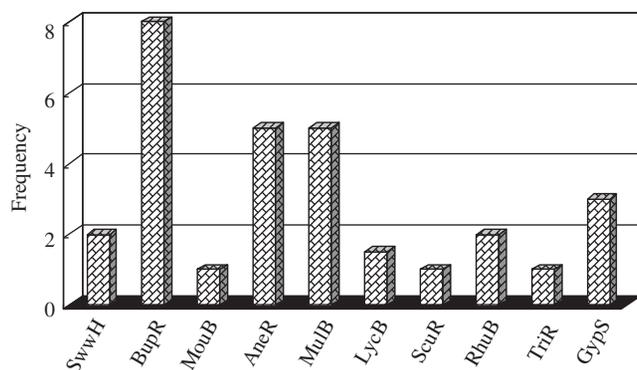


Figure 5. Frequency of clearing heat-pathogen drugs for 'fatigue syndrome' in 50 famous ancient materia medica texts. SwwH, Sweet Wormwood herb (*Artemisia apiacea* Hance); BupR, Bupleurum root (*Bupleurum scorzoneraefolium* Willd.); MouB, Moutan bark (*Paeonia suffruticosa* Andr.); AneR, Anemarrhena rhizome (*Anemarrhena asphodeloides* Bge.); MulB, Mulberry bark (*Morus alba* L.); LycB, Lycium bark (*Lycium chinense* Mill.); ScuR, Scutellaria root (*Scutellaria baicalensis* Georgi.); RhuB, Rhubarb (*Rheum tanguticum* Maxim. Et Rgl.); TriR, Trichosanthes root (*Trichosanthes kirilowii* Maxim.); Gyps, Gypsum.

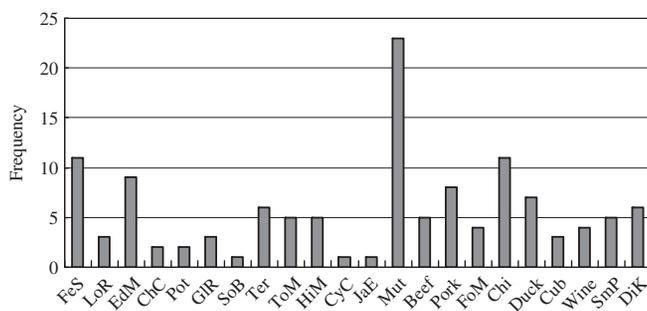


Figure 6. Frequency of meat, fishes, grains and other nutriments for 'fatigue syndrome' in 50 famous ancient materia medica texts. FeS, Fermented soybean; LoR, Lotus root; EdM, Edible mussel; ChC, Chinese chive; Pot, Potato; GiR, Glutinous rice; SoB, Soya bean; Ter, Terrapin; ToM, Tortoise meat; HiM, Hilsa herring meat; CyC, Cyprinus carpio; JaE, Japanese eel; Mut, Mutton; Beef, Beef; Pork, Pork; FoM, Fox meat; Chi, Chicken; Duck, Duck meat; Cub, Cubilose; Wine, Wine; Smp, Smoked plum; DiK, Diospyros kaki.

Present Evidence to Support the Efficacy of TCM in Treating 'fatigue syndrome'

Present Evidences

Some of the ancient prescriptions are also used in the modern clinic effectively. In a double-blinded, placebo-controlled trial, Liu-Wei-Di-Huang-Wan, a famous general herbal tonic for invigorating kidney essence (6), was proven able to accelerate the speed of information processing, enhance cognitive ability and benefit dementia patients or help the elderly recover from a cognitive defect, which is one of the most important clinical manifestations of CFS (7). A randomized trial of Bu-Zhong-Yi-Qi-Tang in combination with Xiao-Chai-Hu-Tang, which theoretically invigorates spleen *qi* (6) and smooths the liver *qi* [functional activities of vital energy and an emotion regulator (6)], in the treatment of 38 CFS patients showed that 18 patients were able to resume normal work and daily activity while the symptoms of 16 additional patients were relieved (8). Ren-Shen-Yang-Rong-Tang (Ninjin-yoei-to in Kampo), a prescription for invigorating *qi* and nourishing the blood, was used in the management of 134 CFS patients and of these, 98 patients returned to work or school (9). Shi-Quan-Da-Bu-Tang (Juzen-taiho-to in Kampo) can also lessen fatigue and other symptoms caused by cancer or anti-cancer treatment in carcinoma patients (10). Prescriptions of smoothing the liver *qi* (6) have often been used to treat the psychological symptoms, which are the main complaints of CFS patients. Yi-Gan-San can improve the psychological symptoms of dementia and activities of daily living in a randomized, observer-blind, controlled trial (11). Sleep disorders are one of the main symptoms of CFS. Suan-Zao-Ren-Tang is the most commonly used over-the-counter sleeping drug in Hong Kong (12).

Chinese crude drugs that can improve the symptoms of CFS have already been studied for a long time, especially drugs with the effect of invigorating *qi* and *yang*. At present, Ginseng root (*Panax ginseng* C.A. Mey.) has been the most widely researched herb for fatigue or CFS. However, the results of studies on Ginseng's antifatigue activity are conflicting. Some showed no difference between Ginseng and placebo on relieving fatigue (13). On the other hand, in a randomized controlled trial of Ginseng for chronic fatigue, fatigue severity and duration were significantly improved in response to Ginseng and treatment was effective at 2 months for 45 subjects who had less severe fatigue among the group of 76 patients studied (14). In addition, Ginseng's ability to enhance cognitive performance in CFS patients was proven in a double-blind, placebo-controlled study (15). Yet, Ginseng was no different from placebo for improving a sleep dysfunction despite Ginseng's benefits for increasing alertness, relaxation, appetite and quality of life in Wiklund's controlled trial (16).

Evidence about other herbs for invigorating *qi* and *yang* on CFS have also been reported, but these have been vague and sporadic. Poria (*Poria cocos* Wolf.) was reported to possess antineurasthenia activity (17) and to improve sleep (18). Cistanche Deserticola [*Cistanche salsa* (C.A. Mey) G. Beck] is able to prolong the duration of swimming (19) and hexobarbital-induced sleeping time (20). Glycyrrhiza root (*Glycyrrhiza uralensis* Fisch.) is a herb with the property of corticosteroids which can improve the symptoms of CFS (21).

Crude drugs that nourish *yin* and blood have also been used for CFS or its main symptoms not only in this clinic but also in animal experiments. Angelica root [*Angelica sinensis* (Oliv.) Diels] markedly alleviated the sleep disturbances and fatigue of menopausal women (22). Aatalpol, an iridoid glycoside isolated from Rehmannia root [*Rehmannia glutinosa* Libosch. f. *hueichingensis* (Chao et Schih) Hsiao], can treat cognitive impairment via enhancing endogenous antioxidant enzymatic activities and inhibiting free radical generation (23). In animal experiments, treatment with Peony root (*Paeonia lactiflora* Pall.) inhibits 5-HT synthesis and tryptophan hydroxylase expression, which may reduce fatigue, both during exercise and the resting state (24). One of the active components of Peony root, paeoniflorin, has also been reported to be able to reverse or alleviate behavioral and cognitive impairments (25).

Adjusting abnormal sleep patterns and emotion is another evidence-based way of possibly employing crude drugs for CFS or its main symptoms. The active component tenuifoliside B, 3,6'-disinapoysucrose (26) and BT-11 (27) in Polygala root (*Polygala tenuifolia* Willd.) has cognition-improving effects. In mice, an 80% methanol extract of Fossilia Osis Mastoidi elicited GABA receptor-mediated anxiolysis, potentiation of pentobarbital sleeping time, reduced locomotor activity and anticonvulsive activity (28). Magnetite has been associated with a significant improvement in muscle fatigability (29). It is also able to reduce the threshold dose of pentobarbital sodium and shorten a rodent's incubation period for falling asleep (30).

Limitations of Ancient Records and Present Related Evidence

First, some recorded drugs do not attenuate the symptoms of CFS and may even aggravate such symptoms. For example, the mineral drug fluorite was recorded as possessing an antifatigue activity, but evidence-based studies have shown that cerebral impairment occurs with its use due to exposure to its main component (fluoride), and that it causes general malaise and fatigue (31). Second, some crude drugs may improve some of the symptoms of CFS such as fatigue, sleep disorders and so on, but this does not mean that they are effective for CFS. Third, there is no proof in recent studies

to clarify the activity of crude drugs that can eliminate heat-pathogens. Crude drugs that can eliminate heat-pathogens were often used for viral or bacterial infections. Perhaps they are beneficial for the initial microbial infections of CFS. However, there currently is no evidence to support this hypothesis.

Clinical Benefits of TCM in the Treatment of CFS Patients Nowadays

Two kinds of therapeutic methods are often applied in a TCM clinic. One is treatment for the symptoms and the other is for the TCM pathogenesis. The former is called '*Bianbing Lunzhi*'. The latter is named '*Bianzheng Lunzhi*' which the treatment is based on the TCM pathogenesis summarized from the systemic symptoms and signs. In the CFS clinic, the two methods are widely utilized.

Bianbing Lunzhi

The effect of a single prescription or single crude drug on CFS often has been observed in the clinic that mirrored the scientific evidence for the ancient texts presented earlier. Most belong to '*Bianbing Lunzhi*'. Hence, unnecessary details will not be repeated here.

Bianzheng Lunzhi

The key point of this type of treatment is '*zheng*', also known as TCM's view of pathogenesis. The TCM's view of the pathogenesis of CFS recently has become diverse. The following five items are universally accepted and treatment based upon them can often be clinically effective (4).

1. *Qi*-deficiency of the spleen (6), characterized by lassitude of the limbs, poor appetite, a pale tongue with white coating and a thready pulse. Gui-Pi-Tang (Kihito in Kampo) is often used (6).
2. Incoordination between the liver and spleen (6), characterized by mental depression, sighing, fatigue, decreased food intake, abdominal distention, a pale tongue with a white coating and a strong pulse. Jia-Wei-Xiao-Yao-San (Kamishoyo-san in Kampo) is often prescribed.
3. Blood stasis due to *qi* deficiency, characterized by poor spirit, lassitude, somatic pain, insomnia, a pale dim tongue with a white coating and unsmooth-feeble pulse. Xue-Fu-Zhu-Yu-Tang is often selected.
4. *Yin*-deficiency of the liver and kidney (6), characterized by weakness, forgetfulness and insomnia, and soreness and weakness of the waist and knee joints, tinnitus, dry throat and mouth, dysphoria with feverish sensations in the chest, palms and soles, night sweating, a red tongue with little coating and

a thready-rapid pulse. Liu-Wei-Di-Huang-Wan is the best choice for this.

5. *Yang*-deficiency of the spleen and kidney (6), characterized by cold limbs, listlessness, cold and pain in the waist and knee joints, a pale tongue with a white coating and a deep-thready pulse. Shen-Qi-Wan (Hachimi-jio-gan in Kampo) is often applied.

Limitations

Although CFS can be diagnosed using international standards, there are somewhat different from the symptoms and signs of the 'zheng', which are quite difficult to standardize. In addition, anecdotal clinic trials and no randomized trials constitute a very large proportion of the publications on the TCM treatment of CFS, which lack scientific rigor and are less persuasive.

Modern Mechanisms of TCM on CFS

Adjusting the Immune Dysfunction of CFS by TCM drugs

Immune system dysfunction and its close interactions with the nervous and endocrine systems have been clearly reported in recent years as playing a role in the development of CFS (32). Hence, maintaining an efficient and equilibrated immune system is a reasonable approach to prevent certain chronic illnesses.

Drugs that invigorate *qi* and tonify the spleen (6) has been used most frequently for CFS patients and have shown outstanding effects in improving their immune situation. In animal experiments, Bu-Zhong-Yi-Qi-Tang significantly enhanced running activity in a *Brucella abortus* induced mouse model of CFS by decreasing the organ weight of spleen and interleukin (IL)-10 mRNA expression in the spleen (33). It can also significantly inhibit tumor necrosis factor- α , IL-6, IL-10 and transforming growth factor- β 1 production in CFS patients (34). Kuibitang (identical to Chinese Gui-Pi-Tang, Japanese Kihito) markedly inhibits lipopolysaccharide-induced tumor necrosis factor- α , IL-10 and transforming growth factor- β 1 production and increases interferon- γ production in the peripheral blood mononuclear cells of CFS patients (35). Ren-Shen-Yang-Rong-Tang can ameliorate lower NK cell activity, which is an important immune characteristic of CFS patients (9). Furthermore, extracts of Ginseng can also boost natural killer cell function and the cellular immunity of patients with CFS (36). In short, the TCM therapeutic approach of invigorating *qi* and tonifying the spleen (6) can improve the function of immune organs and immune cells as well as alter the expression of immune molecules which are abnormal in CFS patients and experimental animals.

Regulating the Abnormal Activity of the HPA Axis of CFS by TCM Drugs

Subtle dysregulation of the HPA axis has been proposed as an underlying pathophysiological mechanism in CFS (37). There is evidence for a hypofunction of the HPA axis in a proportion of the patients with CFS, despite the negative studies and methodological difficulties (38,39). Several underlying mechanisms have been proposed. Main findings include mild hypocortisolism, blunted adrenocorticotropin response to stressors and enhanced negative feedback sensitivity to glucocorticoids (39).

Ito reported that a type of Japanese Kampo named Koso-san (Xiang-Su-San in Chinese medicine) had antidepressant-like effects due to its suppression of the hyperactivity of the HPA axis in a mouse model of depression. It can reduce the increased levels of corticotropin-releasing hormone mRNA expression in the hypothalamus and proopiomelanocortin mRNA expression in the pituitary, and reverse the decreased glucocorticoid receptor protein expression in the hypothalamus paraventricular nucleus to normal (40).

Antioxidant Effect

A number of studies have shown that oxidative stress may be involved in the pathogenesis of CFS pathogenesis, and, therefore, CFS should be treated with specific antioxidants (41). Some specific natural antioxidants from herbs, such as *Withania somnifera*, Quercetin and *Hypericum perforatum* L. have been used for the treatment of CFS with the intent of reducing lipid peroxidation, restoring the glutathione levels and increasing the superoxide dismutase levels in the brains of CFS mice (42). *Ginkgo biloba* and *Vaccinium myrtillus* (bilberry) have also been reported to possess beneficial antioxidants for CFS (43).

Recommendations for the Further Study of TCM in Treating CFS

Herbal medicines are used by an increasing number of CFS patients primarily because of their perceived advantages such as being natural, effective and safe. Nevertheless, in order to further develop their use, ways to overcome their limitations must be explored and promoted.

First, more evidence-based clinical trials and animal experiments should be performed to demonstrate the efficacy of Chinese crude drugs and prescriptions in the ancient texts for the treatment of CFS, especially regarding the drugs that diminish heat-pathogens which may be the initial infection of CFS, since there currently are no data in this area.

Second, it is vitally important to establish standards for the 'zheng'. As a first step, the clinical data collected from

CFS patients should be quantitated with the help of modern apparatuses. Then, we can formulate definitive TCM classification guidelines for CFS.

Third, large randomized, controlled clinical trials are required to confirm the effect of TCM on CFS. Modern statistical methods should be used in the design of every clinical trial. If performed in this manner, reliable and persuasive results can be obtained and published in high impact journals.

Fourth, full use should be made of the latest biological, biochemical, molecular and immunological techniques. Experiments should be designed in consideration of the most current hypotheses regarding the pathogenesis of CFS and should explore the mechanisms by which TCM alleviate CFS.

Acknowledgements

This study was supported in part by a grant for promotion research from Kanazawa Medical University (S2004-2 and S2005-5), a grant for project research from the High-Technology Center of Kanazawa Medical University (H2004-7), a research grant from the Grant-in-Aid for Scientific Research (C), the Ministry of Education, Science and Culture of Japan (No. 17590767) and the science research promotion fund of the Promotion and Mutual Aid Corporation for Private Schools of Japan.

References

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Int Med* 1994;121:953–59.
2. Afari N, Buchwald D. Chronic fatigue syndrome: a review. *Am J Psychiatry* 2003;160:221–36.
3. Jones JF, Maloney EM, Boneva RS, Jones AB, Reeves WC. Complementary and alternative medical therapy utilization by people with chronic fatiguing illnesses in the United States. *BMC Complement Altern Med* 2007;7:12.
4. Zhao LJ. Acupuncture and Chinese patent drugs for treatment of chronic fatigue syndrome. *J Tradit Chin Med* 2005;25:99–101.
5. Mears T. Acupuncture in the treatment of post viral fatigue syndrome—a case report. *Acupunct Med* 2005;23:141–45.
6. Ehling D. Oriental medicine: an introduction. *Altern Ther Health Med* 2001;7:71–82.
7. Park E, Kang M, Oh JW, Jung M, Park C, Cho C, et al. Yukmijihwang-tang derivatives enhance cognitive processing in normal young adults: a double-blinded, placebo-controlled trial. *Am J Chin Med* 2005;33:107–15.
8. Yang SH, Gao M, Yang XW, Chen DQ. Clinical observation of the treatment of chronic fatigue syndrome by using Bu-Zhong-Yi-Qi decoction in combination with Xiao-Chai-Hu decoction. *J Beijing Univ TCM* 2004;2:87–9.
9. Ogawa R, Toyama S, Matsumoto H. Chronic fatigue syndrome-cases in the Kanebo Memorial Hospital. *Nippon Rinsho* 1992;50:2648–52.
10. Zee-Cheng RK. Shi-quan-da-bu-tang (ten significant tonic decoction), SQT. A potent Chinese biological response modifier in cancer immunotherapy, potentiation and detoxification of anticancer drugs. *Methods Find Exp Clin Pharmacol* 1992;14:725–36.
11. Iwasaki K, Satoh-Nakagawa T, Maruyama M, Monma Y, Nemoto M, Tomita N, et al. A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. *J Clin Psychiatry* 2005;66:248–52.
12. Chung KF, Lee CK. Over-the-counter sleeping pills: a survey of use in Hong Kong and a review of their constituents. *Gen Hosp Psychiatry* 2002;24:430–5.
13. Morris AC, Jacobs J, Kligerman TM. No ergogenic effect of ginseng extract ingestion. *Med Sci Sports Exerc* 1994;26:S6.
14. Hartz AJ, Bentler S, Noyes R, Hoehns J, Logemann C, Sinift S, et al. Randomized controlled trial of Siberian ginseng for chronic fatigue. *Psychol Med* 2004;34:51–61.
15. Reay JL, Kennedy DO, Scholey AB. Effects of *Panax ginseng*, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks. *J Psychopharmacol* 2006;20:771–81.
16. Wiklund I, Karlberg J, Lund B. A double-blind comparison of the effect on quality of life of a combination of vital substances including standardized ginseng G115 and placebo. *Curr Ther Res* 1994;55:32–42.
17. Tang W, Gao Y, Chen G, Gao H, Dai X, Ye J, et al. A randomized, double-blind and placebo-controlled study of a *Ganoderma lucidum* polysaccharide extract in neurasthenia. *J Med Food* 2005;8:53–8.
18. Chu QP, Wang LE, Cui XY, Fu HZ, Lin ZB, Lin SQ, et al. Extract of *Ganoderma lucidum* potentiates pentobarbital-induced sleep via a GABAergic mechanism. *Pharmacol Biochem Behav* 2007;86:693–8.
19. Han LC, Hou JF. Effects of *Cistanche deserticola* Y.C. Ma on serum creatine kinase and ultrastructures of skeletal muscles in mice. *Zhongguo Zhong Yao Za Zhi* 1993;18:743–5.
20. Lu MC. Studies on the sedative effect of *Cistanche deserticola*. *J Ethnopharmacol* 1998;59:161–5.
21. Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA* 1995;274:961–7.
22. Kupfersztain C, Rotem C, Fagot R, Kaplan B. The immediate effect of natural plant extract, *Angelica sinensis* and *Matricaria chamomilla* (Climex) for the treatment of hot flushes during menopause. A preliminary report. *Clin Exp Obstet Gynecol* 2003;30:203–6.
23. Zhang XL, Jiang B, Li ZB, Hao S, An LJ. Catalpol ameliorates cognition deficits and attenuates oxidative damage in the brain of senescent mice induced by d-galactose. *Pharmacol Biochem Behav* 2007;88:64–72.
24. Hong JA, Chung SH, Lee JS, Kim SS, Shin HD, Kim H, et al. Effects of *Paeonia radix* on 5-hydroxytryptamine synthesis and tryptophan hydroxylase expression in the dorsal raphe of exercised rats. *Biol Pharm Bull* 2003;26:166–9.
25. Xiao L, Wang YZ, Liu J, Luo XT, Ye Y, Zhu XZ. Effects of paeoniflorin on the cerebral infarction, behavioral and cognitive impairments at the chronic stage of transient middle cerebral artery occlusion in rats. *Life Sci* 2005;78:413–20.
26. Karakida F, Ikeya Y, Tsunakawa M, Yamaguchi T, Ikarashi Y, Takeda S, et al. Cerebral protective and cognition-improving effects of sinapic acid in rodents. *Biol Pharm Bull* 2007;30:514–9.
27. Park CH, Choi SH, Koo JW, Seo JH, Kim HS, Jeong SJ, et al. Novel cognitive improving and neuroprotective activities of *Polygala tenuifolia* Willdenow extract, BT-11. *J Neurosci Res* 2002;70:484–92.
28. Ha JH, Lee MG, Chang SM, Lee JT. In vivo characterization of sedative activities of *Fossilia Mastodi* OSSIS. *Biol Pharm Bull* 2006;29:1414–7.
29. Brutsaert TD, Hernandez-Cordero S, Rivera J, Viola T, Hughes G, Haas JD. Iron supplementation improves progressive fatigue resistance during dynamic knee extensor exercise in iron-depleted, nonanemic women. *Am J Clin Nutr* 2003;77:441–8.
30. Wang R, Huang Y, Zhu W, Zhang H, Sun S. Pharmacological study on magnetite. *Zhongguo Zhong Yao Za Zhi* 1997;22:305–7.
31. Spittle B. Psychopharmacology of fluoride: a review. *Int Clin Psychopharmacol* 1994;9:79–82.
32. Gerrity TR, Papanicolaou DA, Amsterdam JD, Bingham S, Grossman A, Hedrick T, et al. Immunologic aspects of chronic fatigue syndrome. *Neuroimmunomodulation* 2004;11:351–57.
33. Wang XQ, Takahashi T, Zhu SJ, Moriya J, Saegusa S, Yamakawa J, et al. Effect of Hochu-ekki-to (TJ-41), a Japanese

- herbal medicine, on daily activity in a Murine model of chronic fatigue syndrome. *Evid Based Complement Altern Med* 2004;1:203–6.
34. Shin HY, Shin CH, Shin TY, Lee EJ, Kim HM. Effect of bojunggikki-tang on lipopolysaccharide-induced cytokine production from peripheral blood mononuclear cells of chronic fatigue syndrome patients. *Immunopharmacol Immunotoxicol* 2003;25:491–501.
 35. Shin HY, An NH, Cha YJ, Shin EJ, Shin TY, Baek SH, et al. Effect of Kuibitang on lipopolysaccharide-induced cytokine production in peripheral blood mononuclear cells of chronic fatigue syndrome patients. *J Ethnopharmacol* 2004;90:253–9.
 36. See DM, Broumand N, Sahl L, Tilles JG. In vitro effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. *Immunopharmacology* 1997;35:229–35.
 37. Racciatti D, Guagnano MT, Vecchiet J, De Remigis PL, Pizzigallo E, Della Vecchia R, et al. Chronic fatigue syndrome: circadian rhythm and hypothalamic-pituitary-adrenal axis impairment. *Int J Immunopathol Pharmacol* 2001;14:11–5.
 38. Cevik R, Gur A, Acar S, Nas K, Sarac AJ. Hypothalamic-pituitary-gonadal axis hormones and cortisol in both menstrual phases of women with chronic fatigue syndrome and effect of depressive mood on these hormones. *BMC Musculoskelet Disord* 2004;5:47–53.
 39. Tanriverdi F, Karaca Z, Unluhizarci K, Kelestimur F. The hypothalamo-pituitary-adrenal axis in chronic fatigue syndrome and fibromyalgia syndrome. *Stress* 2007;10:13–25.
 40. Ito N, Nagai T, Yabe T, Nunome S, Hanawa T, Yamada H. Antidepressant-like activity of a Kampo (Japanese herbal) medicine, Koso-san (Xiang-Su-San), and its mode of action via the hypothalamic-pituitary-adrenal axis. *Phytomedicine* 2006;13:658–67.
 41. Manuel y Keenoy B, Moorkens G, Vertommen J, De Leeuw I. Antioxidant status and lipoprotein peroxidation in chronic fatigue syndrome. *Life Sci* 2001;68:2037–49.
 42. Singh A, Naidu PS, Gupta S, Kulkarni SK. Effect of natural and synthetic antioxidants in a mouse model of chronic fatigue syndrome. *J Med Food* 2002;5:211–20.
 43. Logan AC, Wong C. Chronic fatigue syndrome: oxidative stress and dietary modifications. *Altern Med Rev* 2001;6:450–9.
 44. Vercoulen JH, Swanink CM, Zitman FG, Vreden SG, Hoofs MP, Fennis JF, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet* 1996;347:858–61.
 45. Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. *Lancet* 1999;353:455–8.
 46. Kawamura Y, Kihara M, Nishimoto K, Taki M. Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Infect Dis* 2003;36:e100–6.
 47. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, Tymms K, Wakefield D, Dwyer J, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med* 1997;103:38–43.
 48. Werbach MR. Nutritional strategies for treating chronic fatigue syndrome. *Altern Med Rev* 2000;5:93–108.
 49. Santaella ML, Font I, Disdier OM. Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. *P R Health Sci J* 2004;23:89–93.
 50. Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, et al. (International Chronic Fatigue Syndrome Study Group). Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Serv Res* 2003;3:25–34.
 51. Burnet RB, Chatterton BE. Gastric emptying is slow in chronic fatigue syndrome. *BMC Gastroenterol* 2004;4:32–5.

Received March 8, 2007; accepted February 8, 2008



Hindawi
Submit your manuscripts at
<http://www.hindawi.com>

