Journal of Ethnopharmacology xxx (2011) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study

Jian-Sheng Li[a,b,*], Su-Yun Li[b], Xue-Qing Yu[b], Yang Xie[a], Ming-Hang Wang[b], Ze-Geng Li[c], Nian-Zhi Zhang[c], Su-Ju Shao[d], Yi-Jie Zhang[e], Lin Zhu[f], Lian-Xiang Guo[g], Yun-Ping Bai[a], Yan-Fang Wang[a]

[a] The Geriatric Department of Henan University of Traditional Chinese Medicine, No. 1 Jinshui Road, Jinshui District, Zhengzhou 450000, PR China
[b] Department of Respiratory, The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou 450000, PR China
[c] Department of Respiratory, The First Affiliated Hospital of Anhui College of Traditional Chinese Medicine, Hefei 230000, PR China
[d] Department of Acupuncture and Moxibustion, The Third Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou 450000, PR China
[e] Department of Respiratory, Huaihe Hospital of Henan University, Kaifeng 475000, PR China
[f] Department of Respiratory, Kaifeng Hospital of Traditional Chinese Medicine, Kaifeng 475000, PR China
[g] Department of Respiratory, The Second People's Hospital of Jiaozuo City, Jiaozuo 454150, PR China

ARTICLE INFO

Article history:
Received 28 March 2011
Received in revised form 23 August 2011
Accepted 25 August 2011
Available online xxx

Keywords:
Acupoint sticking therapy
Bu-Fei Yi-Shen granule
Chronic obstructive pulmonary disease
Clinical trials
Traditional Chinese medicine

ABSTRACT

Ethnopharmacological relevance: Bu-Fei Yi-Shen granule combined with acupoint sticking therapy has been used in the patients with stable chronic obstructive pulmonary disease (COPD) as major traditional interventions for the treatment of the disease.
Aim of the study: The objective of this study was to evaluate the efficacy and safety of traditional Chinese herbal medicine, the Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable COPD.
Methods: A 4-center, double-blinded, double-dummy and randomized controlled method was conducted. 244 patients who were divided into the trial group ($n = 122$, treated with Bu-Fei Yi-Shen granule combined with Shu-Fei Tie acupoint sticking therapy and oral placebo sustained-release theophylline) and the control group ($n = 122$, treated with oral sustained-release theophylline and placebo Bu-Fei Yi-Shen granule combined with placebo Shu-Fei Tie acupoint sticking therapy). The frequency and duration of acute exacerbation, lung function, clinical symptoms, six-minute walking distance, dyspnea grade and quality of life were observed during the 4-month treatment period, and for a further 6 months follow-up.
Results: Two hundred and twenty one patients fully completed the study, intent-to-treat (ITT) population was 234 and per-protocol (PP) population was 221. After treatment for 4 months and follow-up for 6 months, there were differences between the experimental and control group in frequency of acute exacerbation (ITT: $P = 0.007$, $P = 0.013$; PP: $P = 0.045$, $P = 0.046$); duration of acute exacerbation (ITT: $P = 0.030$, $P = 0.005$; PP: $P = 0.048$, $P = 0.006$); scores of symptoms (ITT: $P = 0.000$, $P = 0.000$; PP: $P = 0.000$, $P = 0.000$); six-minute walking distance (ITT: $P = 0.002$, $P = 0.001$; PP: $P = 0.002$, $P = 0.001$); dyspnea grade (ITT: $P = 0.014$, $P = 0.009$; PP: $P = 0.018$, $P = 0.012$); physiological aspects (ITT: $P = 0.003$, $P = 0.000$; PP: $P = 0.001$, $P = 0.000$); psychological aspects (ITT: $P = 0.007$, $P = 0.001$; PP: $P = 0.001$, $P = 0.000$) and environment aspects (ITT: $P = 0.003$, $P = 0.000$; PP: $P = 0.001$, $P = 0.000$) of the WHOQOL-BREF questionnaire. There were no differences between the experimental and control group in FVC, FEV1 and FEV1% and adverse events.
Conclusions: Bu-Fei Yi-Shen granule combined with acupoint sticking therapy showed beneficial effects for patients with stable COPD in the measured parameters over the 4-month treatment period and 6 months follow-up, with no relevant between-group differences in adverse events.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major serious disease threatening the public health. Its incidence, prevalence, mortality are increasing, and its economic burdens and harmful consequences are also rising steadily. Due to tobacco smoking,

* Corresponding author at: The Geriatric Department of Henan University of Traditional Chinese Medicine, No. 1 Jinshui Road, Jinshui District, Zhengzhou 450000, PR China. Tel.: +86 371 65676568; fax: +86 371 65944307.
E-mail address: li_js8@163.com (J.-S. Li).

0378-8741/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jep.2011.08.060

solid-fuel use and other reasons, between 2003 and 2033 an estimated 65 million people will die of COPD in China (Lin et al., 2008). Now, to strengthen the clinical study of prevention and treatment of COPD has become an important subject for research. At present, various methods have been used including the health education, the low-dose and slow-release theophylline, inhaled β2 agonists and corticosteroids, home oxygen therapy, and pulmonary rehabilitation exercise. However, it is difficult to help people keep their symptoms improving to some extent without suffering too many side effects or adverse events (Calverley et al., 2007).

The remarkable longevity and current popularity of Traditional Chinese Medicine (TCM) for COPD implies its potential advantages in improving symptoms, reducing the frequency of acute exacerbation, improving quality of life in the light of different syndromes and systems (Li et al., 2008, 2010a,b). Bu-Fei Yi-Shen granule is made from highly concentrated, selected Chinese herbs and produced in accordance to the traditional Chinese formula. The previous study shown Bu-Fei Yi-Shen granule can ameliorate the function of lung and kidney and be taken easily (Li et al., 2006). Acupoint sticking therapy, a treatment which externally applying herbal paste to acupoints, is used for many lung conditions in TCM practice. The paste is made from different formula according treatment propose. Acupoint sticking therapy is suitable for widely application in community due to its practical convenience and fewer side effects (Li et al., 2009). In routine medication, Chinese medicine herbal medicine combined with acupoint sticking therapy can improve the therapeutic effect of COPD. Therefore, a randomized, double-blind, double-dummy, active-controlled clinical study had been carried out to evaluate the efficacy and safety of the Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable COPD.

2. Methods

2.1. Patients

Patients with stable COPD were recruited from 4 centers, which are The First Affiliated Hospital of Henan University of TCM, The First Affiliated Hospital of Anhui College of TCM, The Third Affiliated Hospital of Henan University of TCM and Kaifeng Hospital of Traditional Chinese Medicine.

2.1.1. Diagnostic criteria for COPD

Global Strategy for the Diagnosis, Management, and Prevention of COPD (2006) and Chinese Treatment Guidelines of Chronic Obstructive Pulmonary Disease (2007) (GOLD, 2006; COPD Study Group of Chinese Society of Respiratory Disease, 2007).

2.1.2. Inclusion criteria

(1) Patients met the diagnostic criteria; (2) patients met the patterns of deficiency of lung and kidney qi, according to who have the symptoms of dyspnea, short breath, weakness and spontaneous sweating, which can be aggravated with exertion; who have the symptoms of tinnitus, vertigo, frequent micturition, frequent urination at night, soreness and weakness of waist and knees (Li et al., 2010a,b); (3) patients should in the stable status of COPD and the severity grade of pulmonary function should be in a level of grade I–III; (4) age 40–80 years; (5) no experience with other clinical interventions research, one month prior to the recruitment; (6) patients should receive the treatment voluntarily and signed informed consent.

2.1.3. Exclusion criteria

(1) Patients with acute exacerbation of COPD and the severity grade of pulmonary function in a level of grade IV; (2) patients with confusion, dementia and all kinds of mental illness; (3) patients merged with bronchial asthma, or bronchiectasis, or active tuberculosis, or pulmonary embolism or diffuse panbronchiolitis; (4) patients with serious diseases such as tumor, heart failure, liver, kidney, or hematopoietic system diseases, etc.; (5) the cases with congenital or acquired immune deficiency; (6) patients participating in other clinical interventions research, allergic to treatment drugs, etc.

2.2. Study design

Design for a multi-center, randomized, double-blind, double-dummy, active-controlled study. The study was approved by the Ethical Research Committee of The First Affiliated Hospital of Henan University of Traditional Chinese Medicine. The batch number was YFYKTLL2008-06. The study was registered in Chinese Clinical Trial Register Center (ChiCTR-TRC-11001409).

2.2.1. Sample size

244 cases were divided into the trial group ($n = 122$) and the control group ($n = 122$). The frequency of acute exacerbation was considered as the primary outcome. From previous studies, the number of the exacerbation frequency decreased by 0.44 times every half year under the comprehensive interventions by TCM compared with the western medicine treatment (Zhou et al., 2006). Assume that there was promotional value only when the number of exacerbation frequency decreased by at least one time. The standard deviation was 1.25 times/year, the two-sided alpha level was 0.05, and beta level was 0.10. The formulae $(2(\mu_\alpha + \mu_\beta)^2\sigma^2/\delta^2)$ was based on a comparison between the equal numbers of two sample mean. Through calculation, the sample size in each group was 33. The sample size was inflated to allow for a 20% dropout rate over the course of the study ($n = 7$), therefore, 40 patients in each group. The severity of disease (I–III) was considered as the stratification factors, there were 120 patients in each group. The total sample size would increase to 240. Kaifeng Hospital is only one medium-sized hospital in four centers. Considering the recruitment process, four cases were added to Kaifeng Hospita center. Ultimately, the sample size was 244 cases.

2.2.2. Randomization

Stratified randomization is used. The number of total of seeds was 20090624 and samples was 244, the number of hierarchical level was 3 and the group was 4, the length of the block was 4, the number of the group was 2 and the distribution ratio was 1-to-1. Then the random number from 001 to 244 was generated by SAS 6.12 software. The random number was randomly divided into trial group and control group.

2.2.3. Double blinding

All drugs were blinded in unified packaging, appearance, weight, color, odor and taste in each group. Drug numbers were also blinded: neither patients nor clinical trial investigators knew the types of drugs.

2.3. Interventions

The patients were randomly divided into two groups: the trial group, in which patients took oral Bu-Fei Yi-Shen granule combined with acupoint sticking therapy and oral placebo of sustained-release theophylline; and control group, in which patients were given oral sustained-release theophylline and placebo of Bu-Fei Yi-Shen granule combined with acupoint sticking therapy.

Bu-Fei Yi-Shen granule, a compound preparation of traditional Chinese medicine (Table 1) was provided by Jiang Yin Tian Jiang Pharmaceutical Co. Ltd. with the authentication quality of Goods Manufacturing Practice (Approval Number: SU J0677), Jiangsu, PR

Please cite this article in press as: Li, J.-S., et al., Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study. J. Ethnopharmacol. (2011), doi:10.1016/j.jep.2011.08.060

Table 1
Composition and bioactive compounds of Bu-Fei Yi-Shen granule and Shu-Fei Tie ointment of acupoint sticking therapy.

Main composition	Main bioactive compounds	Amount (g)
Bu-Fei Yi-Shen granule		
Panax ginseng	Ginsenoside, panaxadiol, pseudoginsenoside saponin	9
Astragalus membranaceus (Fisch.) Bunge	Calycosin, astragaloside, glucuronic acid	15
Lycium barbarum L.	Polysaccharide, betaine, gyoscyamine	12
Cornus officinalis	Palmitic acid, benzyl cinnamate, isobutyl alcohol	12
Schisandra chinensis (Turcz.) Baill	Schizandrin, de-oxyschizandrin, neoschizandrin, schizan-drol	9
Epimedium brevicornum Maxim	Flavonoids compounds, icariin, icarisoside	9
Perilla frutescens (L.) Britt	Unsaturated fatty acid, linolenic acid, amino acid	9
Shu-Fei Tie ointment of acupoint sticking therapy		
Semen Brassicae	Mustard oil, ally isothiocyanate, isopropyl nitrate	10
Rhizoma corydalis	D-Corydaline, DL-tetrahydropalmatine, protopine	5
Rhizoma zingiberis	Zingiberone, β-bisabolene, α-curcumene, zingiberol	5
Asarum heterotropoides	α-Pinene, camphene, β-pinene, myrcene	5
Daphne genkwa	Genkwanin, hydroxygenkwain, yuenkanin	10

China, and its batch number was 0905302. The placebo of Bu-Fei Yi-Shen granule that was made up of dextrin, bitter agent and 10% dose of the Bu-Fei Yi-Shen composition were also prepared by the same company. The packaging specifications were 4.25 g/bag. The test results of drug quality were consistent with the required quality standards.

Shu-Fei Tie ointment of acupoint sticking therapy (Table 1) was produced by the First Affiliated Hospital of Henan University of TCM, batch number was 2004Z01386, 3.0 g/unit. Shu-Fei Tie ointment of acupoint sticking therapy and its preparation procedures had been applied for the National Patent (No. 200810049332.3). Its placebo was also produced by the same hospital. Placebos were same as the true drugs in their appearance, weight, color, odor and taste. The quality control of Shu-Fei Tie ointment of acupoint sticking therapy was completed by the Thin Layer Chromatography method, and its content of tetrahydropalmatine ($C_{21}H_{25}NO_4$) was required not to be less than 0.10 mg.

The sustained-release theophylline was provided by Hangzhou MinSheng Pharmaceutical Co. Ltd., batch number was C09F067; 0.1 g/tablet. The placebo of the theophylline was provided by the First Affiliated Hospital of Henan University of TCM.

Medication: Bu-Fei Yi-Shen granule (or its placebo) was administered orally with 3 bags each time and twice daily for 4 months; the ointment of acupoint sticking (or its placebo) was applied with 6–12 h each patching time and once every 7 days for 2 months; sustained-release theophylline (Zhou et al., 2006) and its placebo were given orally with 100 mg each time and twice daily for 4 months. 6-Month follow-up were studied.

The practitioner was required to provide a brief description of each adverse event (AE) and what action was taken, including details of any investigations and treatments. They were also asked to state whether, in their opinion, the event was related to the TCM therapy being administered.

2.4. Outcomes

2.4.1. Frequency and duration of acute exacerbation of COPD

The frequency and duration of acute exacerbation of COPD each time within the treatment was counted for 4 months and followed-up survey for 6 months. If the interval between two onsets of acute exacerbation within 1 week, it can be counted as one time of acute exacerbation. The date was observed and recorded before treatment, each month during the treatment period, and the time in the third month and the sixth month respectively during the follow-up period.

The frequency and duration of acute exacerbation of COPD (AECOPD): AECOPD refers to the patients' acute exacerbation on their original conditions of dyspnea, cough and (or) expectoration in the development of the disease, which exceeds the daily routine variation, and requires a change in treatment (Celli and MacNee, 2004; GOLD, 2006). Usually in the disease process, patients with short breath aggravation are often accompanied by dyspnea, chest tightness, worse cough, increased sputum volume, changes of the color, and (or) viscosity of sputum and fever. The patients can also show general malaise, insomnia, lethargy, fatigue, depression, mental disorders and other symptoms. The decrease of exercise tolerance, fever and (or) abnormalities of chest imaging may be signs of COPD exacerbation. The frequency of AECOPD: The interval between two acute exacerbations is at least one week. If the interval between two acute exacerbations is within one week, it should be counted as one acute exacerbation. The duration of AECOPD is measured from the beginning of the acute exacerbation to the symptoms the patient feels reduce significantly or restore to the level before acute exacerbation.

2.4.2. Lung function

The indicators of FVC, FEV1 and FEV1% (percentage of predicted value) were tested and recorded before and after treatment respectively.

2.4.3. Symptoms

Symptom including cough, sputum, shortness of breath, dyspnea, gasping, cyanosis, etc, were observed and recorded before treatment, each month during the treatment period, and the time in the third month and the sixth month respectively during the follow-up period. The Dyspnea Scale Questionnaire, which was firstly developed by the British Medical Research Council (MRC) (Mahler and Well, 1988), and later revised by the American Thoracic Society revised (MMRC), was observed and recorded before treatment, in the second month and fourth month during the treatment period, and the time in the sixth month respectively during the follow-up period.

2.4.4. Quality of life

The WHOQOL-BREF questionnaire (WHO, 2004) was adopted, and was observed and recorded before treatment, in the second month and fourth month during the treatment period, and the time in the third month and the sixth month respectively during the follow-up once respectively in the first, second and fourth month during the treatment period, and one time in the third month and the sixth month respectively during the follow-up period.

2.4.5. The six-minute walking distance (6MWD)

The 6MWD (American Thoracic Society, 2002) was observed and recorded once respectively before treatment, in the second month and fourth month during the treatment period, and the time the sixth month respectively during the follow-up period.

Please cite this article in press as: Li, J.-S., et al., Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study. J. Ethnopharmacol. (2011), doi:10.1016/j.jep.2011.08.060

2.4.6. Safety

The routine blood test, routine urine test, routine stool test, liver and kidney function test and ECG were examined before and after treatment respectively. Adverse events were observed and recorded at any time in the treatment period and follow-up period.

2.5. Statistical analysis

2.5.1. The statistical analysis set

(1) Intent-to-treat analysis set was used to analyze the baseline date, the clinical evaluation data of the cases who went through randomization and received treatments and got observation at least one related record on time point. The partially missing data of the clinical evaluation was carried forward with the principle of the last visit carried forward (LOCF). (2) Per-protocol analysis set was used to analyze the clinical evaluation data of the cases who fully completed the trial with better compliance.

2.5.2. Data processing and statistical analysis methods

(1) All P values were two-tailed and the α level of significance was set at 0.05. (2) Measurement data was described by mean and standard deviation ($\bar{x} \pm$ SD), median, interquartile range. The paired-sampled T test or signed rank sum test were used to compare the value differences between pre-treatment and post-treatment within one group. The analysis of variance was used to compare the value differences between trial group and control group. The analysis of covariance was used to compare the value differences of center effect. The repeated measures were used to compare the value differences of several continuous observations. (3) The numeration data was described by absolute frequency or constituent ratio. The Chi square test was used to compare the value differences between trial group and control group. (4) All statistical analyses were undertaken using Statistical Package for the Social Sciences (SPSS 19.0) (License number: 6f1d84c801f1e6010dc).

3. Results

3.1. Study population

Of 325 patients assessed for eligibility, 244 underwent randomization (Fig. 1). Based on the exclusion and off criteria, owing to withdrew consent, protocol noncompliance and entry criteria not met, 10 cases were excluded. Meanwhile, 13 patients who had adverse event, who were lost to follow up; who lacked of efficacy did not fully complete the study. 221 patients fully completed the study. 112 patients in trial group and 109 patients in control group. Therefore the number of per-protocol analysis set was 221. The clinical evaluation data of the 13 patients who did not fully complete the study, but received treatments at least one related record and also completed observation at least one related record on time point should be analyzed, 6 patients in trial group and 7 patients in control group. According to the principle of the last visit carried forward (LOCF), the data of them should be evaluated by intent-to-treat analysis. Therefore the number of intent-to-treat analysis set was 234. When patients received treatments, the safety of the treatments should be observed. In general, the number of the safety set was consistent with the number of the intent-to-treat set. Then the number of safety data set was 234.

Demographic and baseline characteristics of the patients are shown in Table 2. There was no statistical difference between two groups in gender, age, the course of disease, body mass index (BMI), exacerbations, lung function, and severity grade of lung function.

3.2. Effect

3.2.1. Exacerbations

Frequency of acute exacerbation (1) Before treatment, there was no statistical difference between two groups (ITT: $P = 0.305$; PP: $P = 0.196$); after treatment for 4 months and follow-up for 6 months, there was difference in the trial group (ITT: $P = 0.007$, $P = 0.013$; PP: $P = 0.045$, $P = 0.046$), compared with control group. (2) As for trial group, there was difference in the frequency of acute exacerbation pre and post treatment and follow-up time (ITT: $P = 0.000$; PP: $P = 0.000$), however that was no difference in control group (ITT: $P = 0.397$; PP: $P = 0.454$). The results are shown in Fig. 2(A).

Duration of acute exacerbation (1) Before treatment, there was no statistical difference between two groups (ITT: $P = 0.265$; PP: $P = 0.260$); after treatment for 4 months and follow-up for 6 months, there was difference in the trial group (ITT: $P = 0.030$, $P = 0.005$; PP: $P = 0.048$, $P = 0.006$), compared with control group. (2) As for trial group, there was difference in the duration of acute exacerbation pre and post treatment and follow-up time (ITT: $P = 0.000$; PP: $P = 0.000$), however that was no difference in control group (ITT: $P = 0.245$; PP: $P = 0.481$). The results are shown in Fig. 2(B).

3.2.2. Lung function

Pre and post treatment, there was no statistical difference between two groups for FVC, FEV1, FEV1% ($P > 0.05$). The results are shown in Table 3.

3.2.3. Symptoms

(1) There was time effect with the change over time of the treatment and follow-up (ITT: $P = 0.000$; PP: $P = 0.000$). (2) Symptom scores between two groups were continued to drop with the change over time. The mean scores of trial group was lower than that of control group (ITT: $P = 0.000$; PP: $P = 0.000$). (3) From each time point, before treatment, there was no statistical difference between two groups (ITT: $P = 0.998$; PP: $P = 0.870$); after treatment and follow-up time points, there were differences between trial group and control group (ITT: $P = 0.000$, $P = 0.000$; PP: $P = 0.000$, $P = 0.000$). (4) There was interactions of two groups pre and post treatment and follow-up time (ITT: $P = 0.000$; PP: $P = 0.000$). The results are shown in Fig. 2(C).

3.2.4. 6MWD

(1) There was time effect with the change over time of the treatment and follow-up (ITT: $P = 0.000$; PP: $P = 0.000$). (2) 6MWD of two groups continued to increase with the change over time, and the mean index of trial group was higher than that of control group (ITT: $P = 0.021$; PP: $P = 0.022$). (3) From each time point, before treatment and in the second month for treatment, there was no statistical difference between two groups (ITT: $P = 0.372$; PP: $P = 0.360$); in the fourth month for treatment and follow-up time points, there was difference in trial group compared with control group (ITT: $P = 0.002$, $P = 0.001$; PP: $P = 0.002$, $P = 0.001$). (4) There was interactions of two groups pre and post treatment and follow-up time (ITT: $P = 0.000$; PP: $P = 0.000$). The results are shown in Fig. 2(D).

3.2.5. Dyspnea grade

There was no statistical difference between two groups before treatment (ITT: $P = 0.762$; PP: $P = 0.755$); after treatment and follow-up time points, there was difference of the improvement of dyspnea in the trial group compared with the control group (ITT: $P = 0.014$, $P = 0.009$; PP: $P = 0.018$, $P = 0.012$). There was difference of the comparison with centers (ITT: $P = 0.007$; PP: $P = 0.011$). The results are shown in Table 4.

Please cite this article in press as: Li, J.-S., et al., Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study. J. Ethnopharmacol. (2011), doi:10.1016/j.jep.2011.08.060

Table 2
Baseline characteristics of the patients.

Characteristics	Intent-to-treat analysis set				Per-protocol analysis set			
	Trial $n=118$	Control $n=116$	$t/\chi^2/Z$	P	Trial $n=112$	Control $n=109$	$t/\chi^2/Z$	P
Age (yr)	66.53 ± 9.65	66.44 ± 8.49	0.079	0.937	66.41 ± 9.43	66.02 ± 8.49	0.325	0.746
Course of disease[a]	222.60 ± 144.55	218.43 ± 153.80	−0.517	0.605	220.81 ± 146.19	225.85 ± 155.10	−0.510	0.610
BMI[b]	23.68 ± 4.29	23.12 ± 3.78	−0.828	0.408	23.71 ± 4.33	23.27 ± 3.81	−0.582	0.561
Exacerbation[c]								
Frequency (times)	3.00 ± 1.81	3.12 ± 3.19	−1.027	0.305	2.99 ± 1.83	2.92 ± 2.87	−1.292	0.196
Duration (days)	11.43 ± 8.67	10.05 ± 7.00	−1.115	0.265	11.51 ± 8.86	10.03 ± 7.12	−1.127	0.260
Lung function[d]								
FVC (l)	2.31 ± 0.88	2.29 ± 0.84	−0.257	0.797	2.32 ± 0.88	2.31 ± 0.84	−0.129	0.897
FEV1 (l)	1.29 ± 0.53	1.31 ± 0.55	−0.072	0.942	1.29 ± 0.53	1.33 ± 0.55	−0.259	0.796
FEV1%	49.93 ± 17.94	52.67 ± 18.43	−1.064	0.287	50.41 ± 17.95	52.91 ± 18.12	−0.992	0.321
Gender								
Male	76	71	0.138	0.665	73	67	0.187	0.665
Female	42	45			39	42		
Smoking status								
Current smoking	54	48	0.296	0.586	52	46	0.247	0.619
None-smoking	64	68			60	63		
Smoking (pack-yr)	14.15 ± 17.74	12.67 ± 17.01	−0.413	0.680	14.57 ± 18.00	12.84 ± 17.06	−0.588	0.556
Gold stage[e]								
I	7	13	−0.589	0.556	7	12	−0.623	0.534
II	47	42			46	42		
III	64	61			59	55		

[a] The course of disease was calculated in months.
[b] The body-mass index is the weight in kilograms divided by the square of the height in meters.
[c] Exacerbations during the 12 months before screening were self-reported.
[d] Clinical data are from visit 1 (the screening visit). FEV denotes forced expiratory volume in 1 s, and FVC forced vital capacity.
[e] Severity grades of lung function were determined by guidelines of COPD.

Table 3
FVC, FEV1 and FEV1 (%) before and after treatment.

Variable	Intent-to-treat analysis set				Per-protocol analysis set			
	Trial group	Control group	t/Z	P	Trial group	Control group	t/Z	P
FVC ($\bar{x}$ ± SD)								
Before treatment	2.31 ± 0.88	2.29 ± 0.84	−0.257	0.797	2.32 ± 0.88	2.31 ± 0.84	−0.129	0.897
After treatment	2.21 ± 0.82	2.22 ± 0.84	−0.063	0.950	2.23 ± 0.81	2.24 ± 0.85	−0.075	0.940
			−1.087[a]	0.277[a]			−0.938[a]	0.348[a]
			−0.989[b]	0.323[b]			−0.989[b]	0.323[b]
Center comparison	$F=0.091$; $P=0.763$				$F=0.278$; $P=0.599$			
FEV1 ($\bar{x}$ ± SD)								
Before treatment	1.29 ± 0.53	1.31 ± 0.55	−0.072	0.942	1.29 ± 0.53	1.33 ± 0.55	−0.259	0.796
After treatment	1.25 ± 0.56	1.29 ± 0.65	−0.093	0.926	1.26 ± 0.56	1.30 ± 0.66	−0.019	0.985
			−0.690[a]	0.490[a]			−0.547[a]	0.584[a]
			−0.826[b]	0.409[b]			−0.826[b]	0.409[b]
Center comparison	$F=0.079$; $P=0.779$				$F=1.231$; $P=0.268$			
FEV1% ($\bar{x}$ ± SD)								
Before treatment	49.93 ± 17.94	52.67 ± 18.43	−1.064	0.287	50.41 ± 17.95	52.91 ± 18.12	−0.992	0.321
After treatment	50.85 ± 21.12	52.07 ± 23.67	−0.186	0.852	51.40 ± 21.24	52.28 ± 23.74	−0.109	0.913
			−0.368[a]	0.713[a]			−0.407[a]	0.684[a]
			−0.553[b]	0.580[b]			−0.553[b]	0.580[b]
Center comparison	$F=0.995$; $P=0.329$				$F=1.231$; $P=0.268$			

[a] Z and P values of the comparison of after-treatment with before-treatment in trial group.
[b] Z and P values of the comparison of after-treatment with before-treatment in control group.

Table 4
Dyspnea grade at time point (before treatment, 2 month, 4 month, and 6 month).

Time	Group	Intent-to-treat analysis set							Per-protocol analysis set						
		0 level	1 level	2 level	3 level	4 level	Z	P	0 level	1 level	2 level	3 level	4 level	Z	P
Before-treatment	Trial	2	43	43	27	3	−0.303	0.762	2	42	30	25	3	−0.312	0.755
	Control	4	35	48	27	2			4	33	46	24	2		
2 month	Trial	1	47	56	14		−2.100	0.036	1	47	52	12		−2.106	0.035
	Control	1	32	62	21				3	32	57	19			
4 month	Trial	4	54	44	16	0	−2.470	0.014	4	54	40	14	0	−2.376	0.018
	Control	1	35	63	14	3			1	35	60	12	1		
6 month	Trial	1	59	51	7	0	−2.631	0.009	1	58	47	6	0	−2.524	0.012
	Control	1	40	60	13	2			1	39	57	11	1		
Center comparison	$\chi^2=7.184$; $P=0.007$								$\chi^2=6.471$; $P=0.011$						

Please cite this article in press as: Li, J.-S., et al., Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study. J. Ethnopharmacol. (2011), doi:10.1016/j.jep.2011.08.060

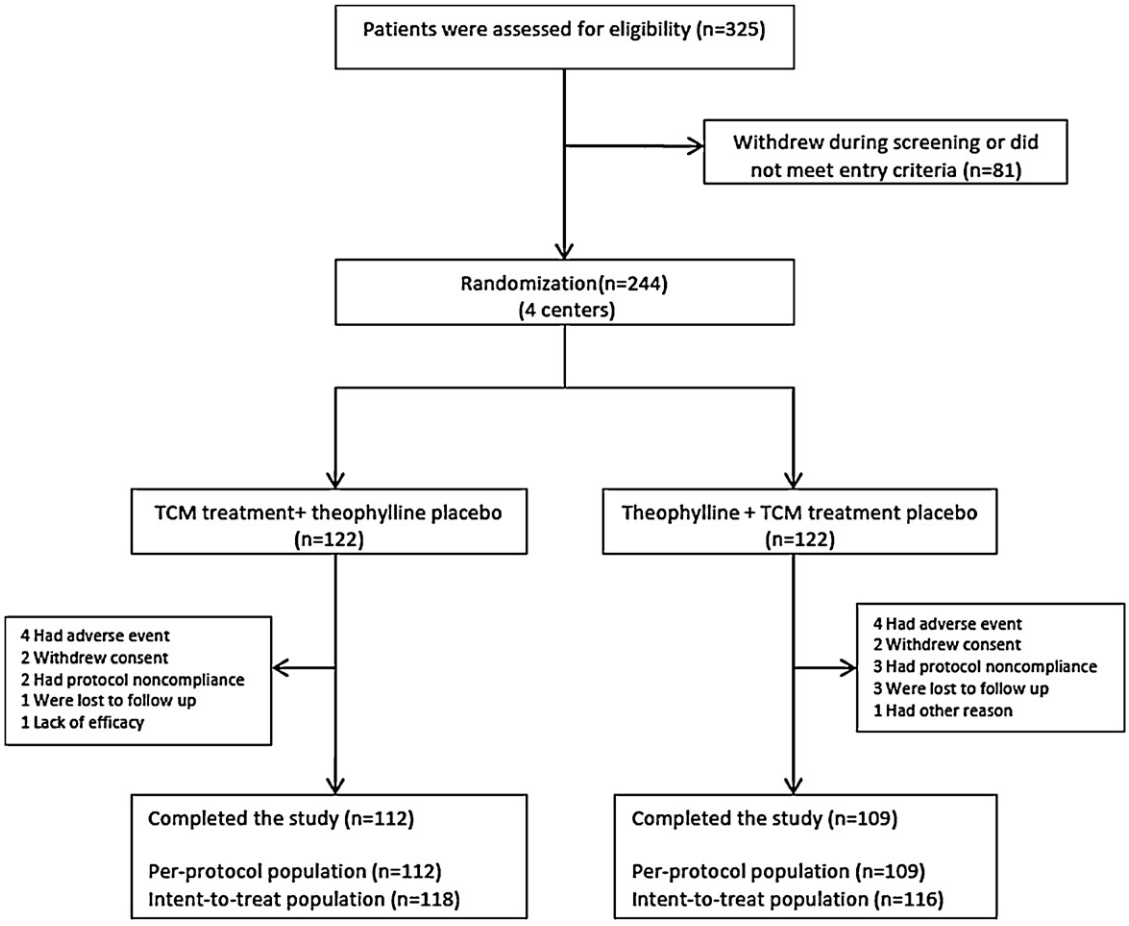

Fig. 1. Enrollment of patients and completion of the study.

3.2.6. Quality of life

Scores of physiological field (1) There was time effect with the change over time of the treatment and follow-up (ITT: $P = 0.000$; PP: $P = 0.000$). (2) Scores of two groups were continued to increase with the change over time, and the mean scores of trial group was higher than those of the control group (ITT: $P = 0.002$; PP: $P = 0.000$). (3) From each time point, before treatment, there was no statistical difference between two groups (ITT: $P = 0.395$; PP: $P = 0.397$); after treatment and follow-up time points, there was difference in the trial group compared with the control group (ITT: $P = 0.003$,

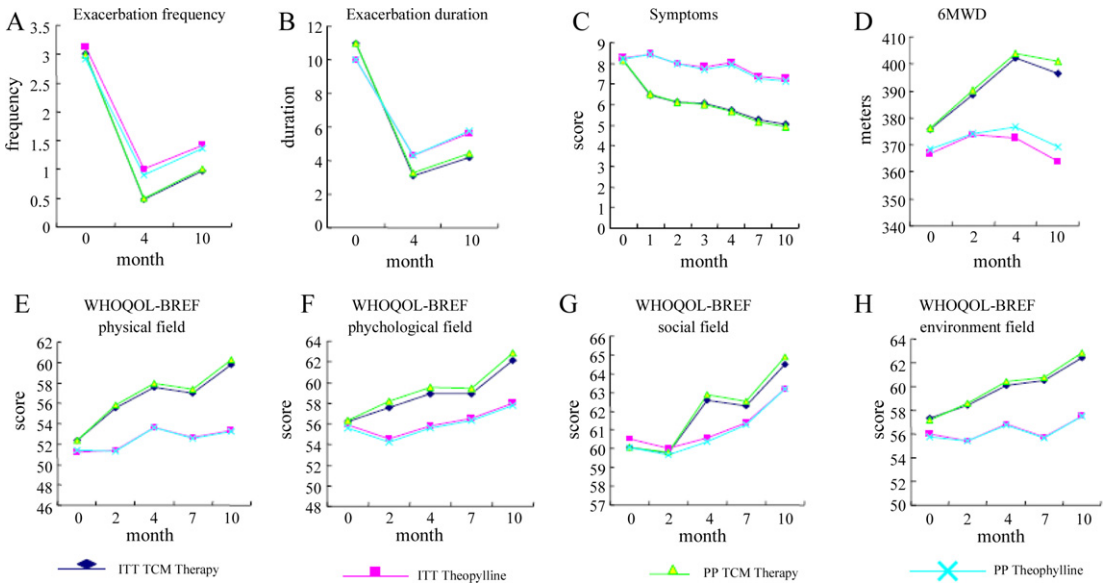

Fig. 2. Exacerbation frequency, exacerbation duration, symptoms, six-minute walking distance, WHOQOL-BREF physiological field, WHOQOL-BREF psychological field, WHOQOL-BREF social field, and WHOQOL-BREF environment field.

Please cite this article in press as: Li, J.-S., et al., Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study. J. Ethnopharmacol. (2011), doi:10.1016/j.jep.2011.08.060

$P = 0.000$; PP: $P = 0.001$, $P = 0.000$). (4) There was interactions of the two groups pre and post treatment and follow-up time (ITT: $P = 0.018$; PP: $P = 0.009$). The results are shown in Fig. 2(E).

Scores of psychological field (1) There was time effect with the change over time of the treatment and follow-up (ITT: $P = 0.000$; PP: $P = 0.000$). (2) Scores of two groups continued to increase with the change over time and the mean scores of trial group were higher than those of the control group (ITT: $P = 0.006$; PP: $P = 0.000$). (3) From each time point, before treatment, there was no statistical difference between two groups (ITT: $P = 0.779$; PP: $P = 0.545$); after treatment and follow-up time points, there was difference in the trial group compared with the control group (ITT: $P = 0.007$, $P = 0.001$; PP: $P = 0.001$, $P = 0.000$). (4) There was no interaction of two groups pre and post treatment and follow-up time (ITT: $P = 0.086$; PP: $P = 0.047$). The results are shown in Fig. 2(F).

Scores of social field (1) There was statistical difference of time effect with the change over time of the treatment and follow-up (ITT: $P = 0.000$; PP: $P = 0.000$) while the others had no statistical difference ($P > 0.05$). The results are shown in Fig. 2(G).

Scores of environment field (1) There was time effect with the change over time of the treatment and follow-up (ITT: $P = 0.000$; PP: $P = 0.000$). (2) Scores of the two groups continued to increase with the change over time, showing the mean scores of trial group higher than those of the control group (ITT: $P = 0.000$; PP: $P = 0.000$). (3) From each time point, there was no statistical difference between two groups (ITT: $P = 0.360$; PP: $P = 0.314$) before treatment; after treatment and follow-up time points, there was difference in the trial group compared with the control group (ITT: $P = 0.003$, $P = 0.000$; PP: $P = 0.001$, $P = 0.000$). (4) There was interaction of the two groups pre and post treatment and follow-up time (ITT: $P = 0.044$; PP: $P = 0.009$). The results are shown in Fig. 2(H).

3.3. Safety evaluation

There was no statistical difference in the routine blood test, routine urine test, routine stool test, liver and kidney function test and ECG in both groups before and after treatment. There was also no statistical difference in adverse events during the trial period ($P = 0.836$). In the case of adverse events, 10 cases were in the trial group. And 8 cases of them may be caused by drug-related effect of Bu-Fei Yi-Shen granule and acupoint sticking therapy. Among 8 cases, 5 cases had nausea, vomiting, abdominal distension and other had stomach discomfort (2 cases withdrew); 1 case has diarrhea (1 case withdrew); 1 case was with palpitation, and 1 case with severe erythema. For the control group, there were 8 cases with adverse events, and 7 cases of them may be caused by drug-related effect of sustained-release theophylline. Among 7 cases, there were 2 cases with palpitations and chest tightness (2 cases exited), 2 cases with diarrhea (1 case exited), 2 cases with skin rash and 1 case with severe erythema.

4. Discussions

Current therapy for COPD has limitations. Alternative approaches are therefore required in some patients with COPD. There is limited evidence concerning TCM comprehensive interventions for the patients with stable COPD. And the results are poor comparability and less scientific evidence, and it is difficult to fully reflect the efficacy, characteristics and advantages of TCM (Zhang and Zhang, 2007). Therefore, based on TCM theory of lung and kidney deficiency and previous study of Chinese Bu-Fei Yi-Shen granule and Shu-Fei Tie acupoint sticking therapy (Li et al., 2006, 2009), this study was conducted in order to evaluate the efficacy and safety of the combination therapy.

Sustained-release theophylline was selected as active control drug for the reason of its efficacy: low-dose, slow-release oral theophylline is effective and well-tolerated in the long term treatment of stable COPD (Molfino and Zhang, 2006; Zhou et al., 2006). Considering the influence of seasonal factors on COPD and time requirements of traditional acupoint sticking therapy which need applied in summer dog-days, the therapeutic course was in summer and autumn, and follow-up period was in winter and spring. The variation of the exacerbation frequency in different seasons was taken into account. Whether the frequency of acute exacerbation can be reduced by comprehensive TCM Interventions in winter and spring was also observed.

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a main factor in deterioration. Thus the prevention of AECOPD can delay the progression of the disease, and have an important impact on long-term prognosis of patients. Therefore, the reductions of the frequency and duration of acute exacerbation were a major goal of the treatment and also a key indicator for evaluating the treatment of patients with stable COPD (Li and Wang, 2007). Our results showed the frequency and the duration of acute exacerbation of the trial group were significantly lower and shorter than the control group. In the trial group, the frequency of acute exacerbation decreased by about 1.0 times, and the days of acute exacerbation reduced about 4.23 days. In the control group, 0.15 times and 1.15 days respectively. The interventions of Bu-Fei Yi-Shen granule combined with acupoint sticking therapy can reduce the frequency and duration of acute exacerbation.

COPD is a disease characterized by restricted airflow that is not fully reversible and progressive developing. It was reported by different articles that FVE1 decline rate of patients with COPD decreased from 47 to 69 ml/year (Lung Health Study Research Group, 2000). According to the results of UPLIFT Trial, the FEV1 decline rate of patients with COPD in the placebo group was 55 ml/year, in the salmeterol group was 42 ml/year, the fluticasone group was 42 ml/year, and in the combination group was 39 ml/year. According to the results of TORCH Trial, the FVE1 decline rate of patients with COPD in tiotropium group decreased by about 41 ml/year, and that decreased by about 42 ml/year in the control group (Zhou et al., 2006; Calverley et al., 2007; Donald et al., 2008). Based on our results, after treatment the FVE1 decline rate of patients in the trial group decreased by about 20 ml, and that decreased by about 25 ml in the control group. Our results are consistent with those of large trials reported in the world. However, as a shorter observation time, there was no significant difference between the groups. The trials need further researching.

Exertional dyspnea is the main clinical symptoms of COPD. Yet in an early stage and stable state, it is not obvious and often be overlooked by patients and physicians. Thus evaluation of the degree of breathing difficulty is important to understand the severity of the disease, the health status of patients and to evaluate clinical intervention effects (Li et al., 2007a,b). Our study group uses the Dyspnea Scale Questionnaire, which was firstly developed by the British Medical Research Council (MRC) and later revised by the American Thoracic Society (MMRC), to assess the influence of shortness of breath on daily activities and clinical symptoms. In addition, six-minute walking distance (6MWD) is the comprehensive evaluation of functional status of the body with moderate or severe disease (Montes et al., 2005), which stresses on exercise capacity closely related to the clinical symptoms. The results showed there were more reduction of dyspnea and more improvement of the 6MWD in the trial group than that in the control group. The interventions of Bu-Fei Yi-Shen granule combined with acupoint sticking therapy can improve exercise capacity of patients with COPD, lower dyspnea grade of patients with COPD, and reduce the symptoms of patients with breathing difficulties.

Please cite this article in press as: Li, J.-S., et al., Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study. J. Ethnopharmacol. (2011), doi:10.1016/j.jep.2011.08.060

Currently, quality of life becomes an indispensable indicator and assessment tool, and is emphasized and widely used in the world. As quality of life is subjective experience, questionnaire is an important tool for the assessment of it. There are many kinds of effective and reliable health related quality of life (HRQL) questionnaires on chronic respiratory diseases (Li et al., 2007a,b; Wang and Wen, 2008). Our group adopted WHOQOL-BREF questionnaire with good reliability and validity to evaluate the quality of life of patients with COPD. The results showed that after treatment – followed up time, there were more improvement in the scores of the physiological, psychological and environment field in the trial group than that in the control group. For the improvement of quality of life of patients with COPD, the interventions of Bu-Fei Yi-Shen granule combined with acupoint sticking therapy have better effect than sustained-release theophylline.

In view of the results from this trial, Bu-Fei Yi-Shen granule combined with acupoint sticking therapy is safe and effective for treatment of patients with stable COPD. The curative effect lied in reducing the frequency of acute exacerbation, ameliorating symptoms, improving quality of life. The interventions are easily operated and not limited by medical equipments and clinical conditions, and thus suitable for widely application. However, there are some limitations of the study. On the one hand, single Bu-Fei Yi-Shen granule group and single acupoint sticking were not set, the relative contribution of either the granule or the acupoint therapy singly in relieving the features of COPD patients cannot be evaluated. The observed beneficial effects are solely due to the combination of the two therapies. On the other hand, the observation time and follow-up time of the interventions was not long enough to reflect the change of lung function.

5. Conclusions

Bu-Fei Yi-Shen granule combined with acupoint sticking therapy is safe and effective for treatment of patients with stable COPD. The curative effects lied in reducing the frequency and duration of acute exacerbation, ameliorating symptoms, improving quality of life. Though this study demonstrates that TCM combination treatment is an effective option for patients with stable COPD, further studies are required to determine the optimal patient population as well as dosing regimen and therapy duration for this approach.

Acknowledgments

This study was supported jointly by Specific research in the TCM industry of State Administration of Traditional Chinese Medicine (200707018) and National Key Technology R&D Program during the 11th Five-Year Plan Period (2008BA153B069).

The authors acknowledge Professor Sui-Qing Chen and Associate Professor Yong-Yan Jia for the great assistance in the preparation and quality control of Shu-Fei Tie ointment of acupoint application.

References

ATS, 2002. American Thoracic Society statement: guidelines for the six-minute walk test. American Journal of Respiratory and Critical Care Medicine 166, 111–117.
Calverley, P.M., Anderson, J.A., Celli, B., Ferguson, G.T., Jenkins, C., Jones, P.W., Yates, J.C., Vestbo, J., 2007. Satmeterol and flutieasene propionate and survival in chronic obstructive pulmonary disease. New England Journal of Medicine 356, 775–789.
Celli, B.R., MacNee, W., 2004. Standards for the diagnosis and treatment of patients with COPD: a summary the ATS/ERS position paper. European Respiratory Journal 23, 932–946.
COPD Study Group of Chinese Society of Respiratory Disease, 2007. Treatment guidelines of chronic obstructive pulmonary disease (2007). Chinese Journal of Tuberculosis and Respiratory Diseases 1, 8–17.
Donald, P., Tashkin, Bartolome, C., Stephen, S., Deborah, B., Steven, K., Shailendra, M., Marc, D., 2008. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. New England Journal of Medicine 359, 1543–1554.
GOLD, 2006. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Revised 2006, http://goldcopd.com/index. 2007-01-22.
Li, J.S., Wang, M.H., 2007. The clinical significance of acute exacerbation of chronic obstructive pulmonary disease. Chinese Critical Care Medicine 9, 572–573.
Li, S.Y., Zhou, Q.W., Wang, M.H., Wang, H.F., Wu, J.Z., 2006. Effect of bufeiyishen granule on pulmonary ventilation function and immunological function of patients with chronic obstructive pulmonary disease in remission phase: a randomized grouping and placebo controlled study. Chinese Journal of Clinical Rehabilitation 7, 145–147.
Li, J.S., Li, S.Y., Wang, M.H., 2007a. Appraisal investigating progression of chronic obstructive pulmonary dyspnea. Journal of Chinese Medicine 129, 79–80.
Li, J.S., Li, S.Y., Wang, M.H., 2007b. Functional status and living quality change of chronic obstructive pulmonary diseases. Journal of Chinese Medicine 1, 19–22.
Li, J.S., Wang, Z.W., Yu, X.Q., Wang, M.H., Li, S.Y., 2008. Systemic evaluation of TCM for COPD in the acute stage of exacerbation. Tianjin Journal of Traditional Chinese Medicine 5, 428–431.
Li, S.Y., Li, J.S., Yu, X.Q., Zhou, Q.W., Wang, X.Y., 2009. The observation of Shu Fei Tie acupoint sticking therapy for treatment of patients with chronic obstructive pulmonary disease. Shaanxi Journal of Traditional Chinese Medicine 4, 391–392.
Li, J.S., Wang, Z.W., Yu, X.Q., Wang, M.H., Li, S.Y., 2010a. Clinical efficacy and safety of TCM for COPD at stable phase: a systematic review. Liaoning Journal of Traditional Chinese Medicine 2, 229–232.
Li, J.S., Wang, Z.W., Li, S.Y., Yu, X.Q., Wang, M.H., Cao, E.X., Wang, Y.Y., 2010b. Syndrome diagnostic criteria of TCM of chronic obstructive pulmonary disease (draft). The internal medicine branch of China Association for Traditional Chinese Medicine. In: The Proceedings of the fourteenth National Traditional Chinese Medicine conference of Pulmonary Disease, pp. 428–431.
Lin, H.H., Megan, M., Ted, C., Caroline, C., Majid, E., 2008. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. Lancet 372, 1473–1483.
Lung Health Study Research Group, 2000. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. New England Journal of Medicine 343, 1902–1909.
Mahler, D.A., Well, C.K., 1988. Evaluation of clinical methods for rating dyspnea. Chest 93, 580–586.
Molfino, N.A., Zhang, P., 2006. A meta-analysis on the efficacy of oral theophylline in patients with stable COPD. International Journal of COPD 1, 261–266.
Montes, M., Torres, S.H., Gonzalez, Y., Romero, E., Hernandez, N., Tolamo, C., 2005. Changes in exercise tolerance, health related quality of life, and peripheral muscle characteristics of chronic obstructive disease patients pulmonary after 6 weeks' training. Archivos de Bronconeumologia 8, 413–418.
Wang, X., Wen, F.Q., 2008. Appraisal investigating progression of quality of life of chronic obstructive pulmonary disease. Medical Journal of West China 3, 635–637.
WHO, 2004. The World Health Organization Quality of Life (WHOQOL-BREF). The WHOQOL Group, Programme on Mental Health. World Health Organization.
Zhang, W.J., Zhang, Y.P., 2007. Recent research in chronic obstructive pulmonary disease treated by TCM. Journal of Beijing University of Traditional Chinese Medicine (Clinical Medicine) 5, 39–41.
Zhou, Y.M., Wang, X.P., Zeng, X.Y., Qiu, R., Xie, J.F., Liu, S.M., Zheng, J.P., Zhong, N.S., Ran, Y.X., 2006. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for l year. Respirology 5, 603–610.

Please cite this article in press as: Li, J.-S., et al., Bu-Fei Yi-Shen granule combined with acupoint sticking therapy in patients with stable chronic obstructive pulmonary disease: A randomized, double-blind, double-dummy, active-controlled, 4-center study. J. Ethnopharmacol. (2011), doi:10.1016/j.jep.2011.08.060