Oral Chinese Herbal Medicine for Improvement of Quality of Life in Patients with Stable Chronic Obstructive Pulmonary Disease: A Systematic Review

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Abstract

Purpose: This study evaluates published clinical trials of Chinese herbal medicine (CHM) for chronic obstructive pulmonary disease (COPD) that employ a health-related quality of life (HRQoL) outcome measure.

Methods: Searches were conducted in April 2011 on MEDLINE®, Embase, the Cochrane Controlled Trials Register, CINAHL, Scopus, and Chinese databases (CNKI, CQVIP, WANFANG). Randomized controlled trials involving oral administration of CHM formulae or single herb, with or without blinding, compared to placebo, no treatment, routine pharmacotherapy control, or CHM plus routine pharmacotherapy versus routine pharmacotherapy, with a HRQoL questionnaire as an outcome measure were identified. The methodological quality was assessed using the Cochrane risk of bias assessment.

Results: A total of 27 studies involving 1966 patients were identified. St. George Respiratory Questionnaire (SGRQ) or Cai's QoLQ were used in 13 and 14 studies, respectively. Assessment of the Cochrane risk of bias revealed adequate sequence of generation in 10 studies and adequate allocation concealment in 1 study; double blinding was not described adequately in any studies. Seventeen (17) studies addressed incomplete outcome data, and 17 studies were free of selective reporting. The main results of meta-analysis showed improvement of total HRQoL scores (SGRQ and Cai's QoLQ) when CHM was compared to no treatment (−6.07 [−9.21, −2.93] and −0.20 [−32, −0.07], respectively) and for CHM plus routine pharmacotherapy versus routine pharmacotherapy (−5.15 [−7.26, −3.05]) and (−0.25 [−0.37, −0.13]).

Conclusions: While the results of CHM on HRQoL for stable COPD sufferers were promising, they need to be interpreted with caution due to methodological problems, which should be addressed in future trials.

Introduction

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) involves progressive deterioration of lung function which is characterized by airflow limitation that is not fully reversible. Morbidity and mortality associated with COPD is increasing and it is the fourth leading cause of death worldwide.¹ COPD causes impairment in health-related quality of life (HRQoL) of these patients. Even with optimal medical treatment, the HRQoL status inevitably worsens.² Therefore, new interventions that slow the decline in HRQoL are needed.

Pharmacologic treatments, as summarized in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the management of stable COPD include

bronchodilators (β_2 agonists and anticholinergics) and inhaled glucocorticosteroids.³ Other medications such as phosphodiesterase may be used for severe COPD.⁴ Some studies showed that these medications, whether used alone or in combination, seemed to be effective in improving HRQoL for patients with stable COPD.^{5–7} However, the optimal maintenance therapy has not yet been determined due to conflicting results regarding the effects and safety of these medications.²

There is a long history of using herbal medicine to treat disorders now classified as COPD, particularly in China, India, and their neighboring countries.^{8,9} A systematic review has indicated a promising benefit of ginseng, a commonly used Chinese herb, for the management of stable COPD.¹⁰ A number of randomized controlled trials (RCTs)

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have been conducted to evaluate various Chinese herbal medicines (CHM) formulae in the management of COPD.⁸ However, a comprehensive review of the current evidence for the effects of CHM on HRQoL is not available. This study systematically evaluates the results of RCTs investigating orally administered CHM in patients with stable COPD using HRQoL as an outcome measure.

Methods

Search strategy

Systematic searches were conducted in April 2011 of the following databases: MEDLINE®, Embase, the Cochrane Controlled Trials Register, Scopus, CINAHL, CNKI, CQVIP, and WANFANG. There was no restriction on the publication years. The search terms are available from the authors upon request.

Study selection

RCTs in English or Chinese involving oral administration of CHM formulae or single herbs in any form were considered. Inclusion criteria were the following: (1) RCTs with or without blinding; (2) CHM compared with placebo, no treatment, or routine pharmacotherapy (RP) as controls; (3) Oral administration of CHM formulae in any form (decoction, pill etc); (4) Patients must be aged 18 years or over, of any gender or ethnic origin; (5) Patients diagnosed with COPD in the stable stage as defined in the GOLD guideline.³ Stable was defined as no current infection and no exacerbation or hospitalization in the past month. Patients in the severe stage of COPD, but without respiratory failure or pulmonary hypertension or *cor pulmonale* were also included; (6) Only studies including a quality of life questionnaire as a key outcome measure were considered.

Exclusion criteria were the following: (1) Interventions that involved CHM but did not use oral administration, or used CHM in combination with acupuncture and/or acupressure; (2) Studies that included patients with acute COPD exacerbations or complications of severe COPD (see above).

Outcome measures

The St. George Respiratory Questionnaire (SGRQ) is a standardized, self-administered questionnaire for measuring impaired health and perceived HRQoL in airways diseases.²² It consists of 76 items and can be categorized into the three domains of “symptom,” “activity,” “impact,” plus “total score.” The “symptom” score assesses the patients’ perception of their recent (4 weeks) respiratory problems; the “activity” score measures the patients’ current disturbance in performing daily physical activities; the “impact” score evaluates the whole range of disturbances the patients currently experience in their life due to respiratory problems; and the “total” score sums and weighs all the former components. Scores can range from 0 (no impairment) to 100 (the worst impairment) for each component; higher scores denote greater distress and thus, worse HRQoL.¹¹ Cai’s Quality of Life Questionnaire (Cai’s QoLQ) is a SGRQ modified according to the specific conditions in China. It consists of 35 items, divided into the four domains of “activities of daily living,” “social activities,” “depression,” and “anxiety” as well as a total score. Cai’s calculation of the total score is different from that of the SGRQ, being the sum of

each item score divided by the number of items. Each item is graded from 1 (high QoL) to 4 (low QoL).

Data collection process

Study characteristics including trial design, sample size, mean and standard deviation of participants’ age and history of COPD, severity of COPD, differentiation of syndrome, methodological quality, intervention, outcome measures, treatment duration and follow-up period, and adverse events were extracted to a predefined form and checked by a second reviewer.

Risk of bias in individual studies

The methodological quality of the included studies was independently assessed by 2 authors using the Cochrane risk of bias.¹² Assessment of Cochrane risk of bias consists of six domains: (1) adequate sequence generation; (2) allocation concealment; (3) blinding; (4) incomplete outcome data addressed; (5) selective reporting; and (6) other sources of bias (defined as baseline data comparability). For each domain, evaluation was by denoting: “yes”—adequate (low risk of bias); “no”—inadequate (high risk of bias); or “unclear”—unclear or not used (uncertain risk of bias) according to the descriptions of the method in each study. Any disagreement was resolved by discussion with a third reviewer.

Data analysis

Meta-analysis was performed using Review Manager Software (RevMan 5.0). For continuous data, studies were pooled to yield mean differences (MD) and reported using 95% confidence intervals (CI); for categorical data, risk ratios were calculated. Heterogeneity was tested using χ^2 with significance being set at $p < 0.10$.

Results

Results of searches

A total of 1713 potential articles were initially identified. Further screening of abstracts and full texts identified 27 studies as meeting the inclusion criteria (Fig. 1, flow diagram).

Study characteristics

The main characteristics of the individual studies (study location, study design, sample size, gender, average age of patients, severity of COPD, Chinese medicine syndrome differentiation, and average years of COPD) are summarized in Table 1.

The 27 included studies were all conducted in China. They involved 1966 participants. The average ages ranged from 59.4 to 72.0 years across the studies. All participants were in the stable stage and diagnosis was based on the GOLD guideline modified by the Chinese Society of Respiratory Diseases (CSR D).¹³ There were dropouts during the treatment period in five studies totaling 52 participants, but intention-to-treat analysis was not applied.^{14–18} In 20 studies, the severity of COPD in individual patients was described as four stages: I—mild, II—moderate, III—severe, IV—very severe,^{14–17,19–34} which was in accord with the guidelines by CSR D.¹³ Severity of COPD was not described in seven studies.^{18,35–40} Chinese medicine differentiation of

FIG. 1. Flow diagram for study selection process. CHM, Chinese herbal medicines; QoLQ, Cai's Quality of Life Questionnaire; RCTs, randomized controlled trials.

syndromes was described in 20 studies.^{20–22,25,27,32,35,37,39,40} Sixteen (16) studies reported the average number of years patients had suffered from COPD.^{17,21–23,26–30,32,33,35,37–40}

CHM was compared with placebo alone in one study,³¹ with no treatment control in seven studies,^{14–16,18,22,33,39} and with RP in one study.³⁴ In one study, CHM plus RP was compared with placebo plus RP.³⁷ The remaining studies compared CHM plus RP with RP alone. Duration of treatment was up to 2 months in 6 studies,^{17,29,31,37,39,40} 2–4 months in 6 studies,^{16,19–21,23,32} and 6 months in 15 studies.^{14,15,18,22,24–28,30,33–36,38} A follow-up period was mentioned in four studies.^{15,17,22,36}

The RP used was variable. It mainly involved bronchodilators such as the β_2 agonists salbutamol and salmeterol, anticholinergics (e.g. ipratropium bromide) or theophylline. These were used alone or in combination.^{17,20,26,28–30,37,40} Five (5) studies used inhalation of a β_2 agonist or an anticholinergic alone or a combination of β_2 agonist and anticholinergic.^{19,24,25,27,34} Inhalation of a β_2 agonist with oral theophylline was used in three studies.^{26,37,40} One study used inhalation of a β_2 agonist plus a glucocorticosteroid (Becotide).¹⁷ Oral theophylline was used alone in two studies.^{28,30} CHM alone versus inhalation of ipratropium bromide aerosol was used in one study.³⁴ One (1) study mentioned that

the RP included antibiotics, expectorants, and bronchodilators but provided no further detail.²⁹ Five (5) studies did not provide information on the RP used.^{21,23,29,32,35,36,38}

CHM formulae were in the form of pills, capsules, granules, syrups, or decoctions (Table 2). The individual formulae comprised 1–17 different herbs. Two (2) studies used syndrome differentiation according to CHM principles to select the most appropriate of four CHM treatment interventions. Both of these studies used very similar designs and formula selection.^{35,38} Another two studies investigated almost identical formulae.^{20,21} Two (2) studies investigated modified versions of formulas of the same name (*Zhoufeitang*).^{14,15} Eighty-three (83) different herbs were used in the studies. The five most commonly used herbs were the following:

- *Huangqi* (*Astragalus membranaceus* [Fisch.] Bge. var. *mongolicus* (Bge.) Hsiao (root) in 14 studies^{18–24,26,27,29,32,33,35,38};
- *Baizhu* (*Atractylodes macrocephala* Koidz [rhizome]) in 13 studies^{16,17,19,22,23,26,27,30,32,33,35,38,40};
- *Dangshen* (*Codonopsis pilosula* [Franch.] Nannf. (root) in 12 studies^{14–16,19,27,29–33,35,38};
- *Fuling* (*Poria cocos* [Schw.] Wolf (sclerotium) in 12 studies^{16–19,23,27,28,30,33,35,38,40}; and
- *Wuweizi* (*Schisandra chinensis* [Turcz.] Baill (fruit) in 10 studies.^{14,15,19,22,29,30,34,35,37,38}

Quality control data on the herbal ingredients were not provided in any of the studies.

Assessment of methodological quality

Assessment of the Cochrane risk of bias revealed that there was adequate sequence generation in nine studies,^{20–22,25,28,32,34,39,40} and one study provided information on allocation concealment.³⁹ Seven (7) studies were not blinded since they compared CHM with no treatment.^{14–16,18,22,33,39} Blinding was not described adequately in the two single-blind studies,^{23,37} and blinding was not mentioned in the remaining 19 studies. Incomplete outcome data were addressed in 17 studies^{21–23,25–36,38,39}; and 17 studies were judged as free of selective reporting.^{14,16,18–20,22–24,27–29,31–33,35,37,39} All but one of the studies were free of other bias (baseline data incomparability)^{14–18,20–40} (Fig. 2).

Outcome measures for QoL

SGRQ was used in 10 studies,^{16–19,23,24,31,32,34,36} and a modified SGRQ was used in 3 studies.^{20,21,27} The remaining 14 studies used Cai's QoLQ.^{14,15,22,25,26,28–30,33,35,37–40}

The 27 included studies were grouped into four types according to the study design. Three (3) studies did not report data suitable for meta-analysis.^{20,21,37}

Data extracted from 24 studies for QoL were pooled and analyzed in RevMan 5. The total score and scores in the subcategories for both SGRQ and Cai's QoLQ for the treatment and control groups were analyzed to determine any differences between scores at baseline and at the end of treatment. The results for the studies in each type are summarized below.

CHM versus placebo ($n=2$)

One (1) study compared CHM with placebo and used SGRQ as an outcome ($n=60$).³¹ CHM was significantly better

TABLE 1. CHARACTERISTICS OF INCLUDED STUDIES

First author, date	Location, design (duration/follow-up)	Out-/in-patients	No. subjects (R/A)	M/F	Age mean SD (years)	Severity of COPD: no. subjects	CM syndrome differentiation	COPD history (years)
Chen, 2009	Fujian, China RCT (3 mths/NS)	Outpatients	T: 30/30 C: 30/30	29/31	70.1	III & IV: NS	NS	NS
Fang, 2008	Guangdong, China RCT (6 mths /NS)	NS	T: 35/30 C: 35/26	T: 26/4 C: 23/3	T: 68.0±5.70 C: 68.0±4.96	T: I 8, II 22 C: I 6, II 20	NS	NS
Feng, 2005	Beijing, China RCT (3 mths/NS)	Outpatients	T: 35/35 C: 37/37	T: 16/19 C: 18/19	T: 60.59±8.99 C: 56.57±8.81	T: 0 8, I 9, II 9, III 9 C: 0 8, I 12, II _A 9, III 8	Qi deficiency & blood stasis	NS
Feng, 2007	Beijing, China RCT (3 mths/NS)	Outpatients	T: 46/46 C: 30/30	T: 25/21 C: 14/16	T: 63.37±8.99 C: 62.26±8.72	T: II 24, III 22 C: II 16, III 14	Qi deficiency & blood stasis	T: 6.15±1.71 C: 6.23±1.59
Feng, 2008	Hebei, China RCT (6 mths/NS)	NS	T: 60/60 C: 60/60	NS	63.0±5.0	NS	Lung & Spleen & Kidney deficiency	14.0±5.0
Hong, 2005	Fujian, China RCT (6 mths/6 mths)	NS	T: 20/20 C: 18/18	T: 17/3 C: 16/2	T: 67.7±5.68 C: 66.89±5.57	T: II 5, III 15 C: II 4, III 14	Lung & Spleen & Kidney deficiency	T: 15.05±5.54 C: 14.33±7.28
Huang, 2005	Guangdong, China RCT (3 mths/NS)	Outpatients	T: 32/32 C: 31/31	T: 21/11 C: 23/8	T: 69.5±11.8 C: 68.8±10.6	T: II 17, III 15 C: II 18, III 13	NS	T: 8.5±3.2 C: 8.3±3.5
Jia, 2007	Jiangsu, China RCT (6 mths/NS)	NS	T: 30/30 C: 25/25	T: 23/7 C: 17/8	T: 61.6±6.1 C: 63.2±5.3	T: I 5, II 18, III 7 C: I 3, II 17, III 5	NS	NS
Jian, 2008	Guangdong, China RCT (6 mths/NS)	Out-/In patients	T: 23/23 C: 22/22	T: 18/5 C: 16/6	T: 71±9.6 C: 69±8.9	T: I 7, II 16 C: I 7, II 15	Lung & Kidney deficiency	NS
Lang, 2010	Shanghai, China RCT (6 mths/6 mths)	NS	T: 30/30 C: 30/30	NS	NS	NS	NS	NS
Liang, 2009	Guangxi, China RCT (6 mths/NS)	Outpatients	T: 32/32 C: 33/33	T: 20/12 C: 22/11	T: 69.73±NS C: 70.69±NS	T: IIA13, III 12, IV 7 C: IIA 15, III 12, IV 6	NS	T: 17.32±NS C: 17.02±NS
Liu, 2005	Guangdong, China RCT (6 mths/6 mths)	NS	T: 30/26 C: 30/25	T: 22/4 C: 23/2	T: 68.0±5.70 C: 68.0±4.96	T: I 4, II 22 C: I 5, II 20	NS	NS
Liu, 2006	Guangdong, China RCT (6 mths/NS)	Out-/In patients	T: 30/30 C: 30/30	T: 25/5 C: 23/7	T: 67.37±6.03 C: 67.27±5.75	T: I 4, II 26 C: I 5, II 25	NS	T: 3.62±2.07 C: 3.62±2.07
Liu, 2010	Shanghai, China RCT (6 mths/NS)	Outpatients	T: 30/30 C: 30/30	T: 18/12 C: 16/14	T: 65.12±5.36 C: 64.12±7.36	T: 0 5, I 9, II 16 C: 0 6, I 10, II 14	Qi deficiency and Phlegm stasis	T: 17.32±2.36 C: 16.12±2.06

(continued)

TABLE 1. (CONTINUED)

First author, date	Location, design (duration/follow-up)	Out-/in-patients	No. subjects (R/A)	M/F	Age mean SD (years)	Severity of COPD: no. subjects	CM syndrome differentiation	COPD history (years)
Mai, 2009	Guangdong, China RCT (2 mths/NS)	Outpatients	T: 40/40 C: 40/40	T: 22/18 C: 24/16	T: 67.70±6.80 C: 66.89±5.87	T: II 12, III 28 C: II 10 III 30	NS	T: 13.05±6.84 C: 14.53±6.05
Ni, 2008	Shanghai, China RCT (2 mths/NS)	Outpatients	T: 34/34 C: 34/34	T: 19/15 C: 20/14	T: 64.35±6.77 C: 64.62±7.05	NS	Kidney deficiency	T: 11.24±5.02 C: 10.50±4.56
Shan, 2007	Guangdong, China RCT (6 mths/NS)	Out-/inpatients	T: 28/28 C: 27/27	T: 24/4 C: 24/3	T: 66.75±5.95 C: 66.89±6.18	T: I 5, II 23 C: I 6, II 21	NS	T: 17.32±7.23 C: 16.15±6.18
Shi, 2009	Tianjin, China RCT (6 mths/6 mths)	NS	T: 90/90 C: 90/90	103/87	63.0±5.0	NS	NS	14.0±5.0
Sun, 2009	Tianjin, China RCT (1 mth/NS)	Outpatients	T: 30/30 C: 30/30	T: 21/9 C: 22/8	T: 60.97±8.97 C: 59.54±10.87	II & III: NS	NS	NS
Tang, 2009	Guangdong, China RCT (2 mths/NS)	Out-/inpatients	T: 30/30 C: 30/30	T: 27/3 C: 26/4	T: 63.2±NS C: 65.5±NS	NS	Lung Qi & Kidney Qi deficiency	T: 7.2±NS C: 7.5±NS
Tang, 2010	Shanghai, China RCT (3 mths/NS)	Outpatients	T: 34/34 C: 35/35	T: 23/11 C: 26/9	T: 72.18±10.78 C: 71.00±10.53	T: I-II 8, III-IV 26 C: I-II 8, III-IV 27	Lung & Spleen & Kidney deficiency	T: 14.53±9.15 C: 15.46±10.89
Wang, 2009	Zhejiang, China RCT (2 mths/NS)	Inpatients	T: 30/30 C: 32/32	T: 24/6 C: 25/7	T: 70.5±NS C: 69.8±NS	NS	Lung Qi & Spleen Qi deficiency	T: 7.3±NS C: 6.8±NS
Wu, 2007	Guangdong, China RCT (4 mths/NS)	NS	T: 71/63 C: 62/59	T: 49/14 C: 43/16	T: 61.5±NS C: 61.9±NS	T: I 15, II 29, III 19 C: I 14, II 27, III 18	NS	NS
You, 2008	Hunan, China RCT (2 mths/1 year)	Outpatients	T: 32/30 C: 32/30	T: NS C: NS	T: 59.43±11.56 C: 56.23±10.69	I & II: NS	NS	T: 6.15±1.71 C: 6.23±1.59
Zhang, 2006	Guangdong, China RCT (6 mths/NS)	NS	T: 24/24 C: 22/22	T: 18/6 C: 17/5	T: 66.70±6.60 C: 67.89±4.57	T: II 5, III 14 C: II 4, III 18	NS	T: 14.05±6.54 C: 15.33±5.0
Zhang, 2009	Guangdong, China RCT (6 mths/NS)	Outpatients	T: 60/56 C: 60/48	NS	68.4±NS	NS	NS	NS
Zhu, 2007	Guangdong, China RCT (6 mths/NS)	Out-/inpatients	T: 35/35 C: 32/32	T: 16/19 C: 15/17	T: 72.0±10.3 C: 71.7±9.5	T: I 22, II 13 C: I 20, II 12	NS	NS

R, number subjects randomized; A, number subjects analyzed; SD, standard deviation; COPD, chronic obstructive pulmonary disease; mths, months; CM, Chinese medicine; RCT, randomized controlled trial; NS, not specified; T, treatment; C, control.

TABLE 2. INTERVENTIONS, CONTROLS, AND ADVERSE EVENTS FOR INCLUDED STUDIES

First author, date	Intervention			Adverse events
	Formula name (form): Dose, ingredients	Plus RP	Control	
Chen, 2009	Qixueiduiqitang (decoction): 250 mL bid Shanzhuoyu, Shanyao, Shudihuang, Mudanpi, Zexie, Fuling, Wuweizi, Huangqi, Dangshen, Baizhu	Salmeterol 50 µg & fluticasone 500 µg inhaled bid	Salmeterol 50 µg & fluticasone 500 µg inhaled bid	No
Fang, 2008	Zoufei granule: 10 g tid Dangshen, Guizhi, Ziyuan, Kuandonghua, Wuweizi, Xingshen, Taoren, Chenxiang, Zishiying	No	No treatment	NS
Feng, 2005	Yiqihuoxuehuatan Formula (decoction): 1 packet per day Huangqi, Shuizhi, Beimu, Guangdulong, etc. or Feikang granule: 10 g daily Huangqi, Shuizhi, Huangjing, Danggui, Chenpi, etc. + Bailing capsule: 0.8 g tid, extract of Dongchongxiacao	Stage 0: No treatment Stage 1: Bronchodilators (short-acting as needed) Stage 2: Bronchodilators or glucocorticoids (inhaler) Routine medication	Stage 0: No treatment Stage 1: Bronchodilators (short-acting as needed) Stage 2: Bronchodilators or glucocorticoids (inhaler) Routine medication	NS
Feng, 2007	Yiqihuoxuehuatan Formula (decoction): 1 packet per day Huangqi, Shuizhi, Banxia, Guangdulong etc. or Feikang granule: 3 g daily. Huangqi, Shuizhi, Huangjing, Danggui, Chenpi etc. + Bailing capsule: 4 caps tid, extract of Dongchongxiacao	Routine medication	Routine medication	NS
Feng, 2008 ^a	Bufeitang (decoction): 1 packet per day, in 2 doses (morning & night) Dangshen, Huangqi, Baizhu, Shanyao, Wuweizi, Maidong, Yuzhu, Zhimu, Jiegeng, Chenpi, Baibu, Zhigancao or Qixueiduiqitang + Shengnaisan (decoction): as above Shudi, Shanzhuoyu, Shengshanyao, Fuling, Dampi, Gouji, Wuweizi, Taizishen, Maidong, Nozhenzi, Hanliancao or Jinguishenqituan (decoction): as above Shudi, Shanzhuoyu, Chaoshanyao, Fuling, Shufuzi, Rougui, Lujiaojiao, Tusizi, Dangshen, Baizhu, Danshen, Huainiuxi, Yiyiren or Suzijiangqitang (decoction): as above Zisuzi, Banxia, Qianlu, Houpo, Danggui, Chenpi, Rougui, Gancao	Routine medication	Routine medication	NS
Hong, 2005	Yufening pill: 6 g bid Renshen, Huangqi, Baizhu, Fangfeng, Zilheche, Hetaorou, Tusizi, Shanzhuoyu, Wuweizi, Xingren, Gualou, Danshen, Taoren	No	No treatment	No
Huang, 2005	Yupingfeng granule: 5 g tid Huangqi, Fangfeng, Baizhu + Jianpiyifei granule: 10 g tid Renshen, Baizhu, Fuling, Maidong, Sangbaipi, Huangqi. + Bailing capsule: 1 g tid, extract of Dongchongxiacao	Routine medication	Routine medication	Yes
Jia, 2007	Yiqihuoxue formula (decoction): 1 packet per day Huangqi, Dilong, Xuanshen, Danshen, Taizishen, Danggui, etc.	Anticholinergics (ipratropium bromide inhaler)	Anticholinergics (ipratropium bromide inhaler)	NS

(continued)

TABLE 2. (CONTINUED)

First author, date	Intervention			Adverse events
	Formula name (form): Dose, ingredients	Plus RP	Control	
Jian, 2008	Pingchuan capsule: 4 capsules tid Renshen, Gejie, Tianqi, etc.	Iprratriptium inhaler, 2 puffs, bid	Iprratriptium inhaler, 2 puffs, bid	NS
Lang, 2010	Baibuyangfei Syrup: NS Baibu, etc.	Routine medication	Routine medication	No
Liang, 2009	Donggingtang (powder in decoction): 1 packet per day Dongchongxiacao, Huangqi, Baizhu, Fangfeng	Stage 1: Salmeterol inhaler, 200 µg up to tid Stage 2: Theophylline tablets: 0.1–0.2 g tid or terbutaline sulfate tablets 2.5 mg bid or salmeterol inhaler, 200 µg up to qid (if dyspnea severe) Stage 3: Theophylline tablets: 0.1–0.2 g tid or terbutaline sulfate tablets 2.5 mg tid or salmeterol inhaler, 200 µg up to 6 times/day (if dyspnea severe)	Stage 1: Salmeterol inhaler, 200 µg up to tid Stage 2: Theophylline tablets: 0.1–0.2 g tid or terbutaline sulfate tablets 2.5 mg bid or salmeterol inhaler, 200 µg up to qid (if dyspnea severe) Stage 3: Theophylline tablets: 0.1–0.2 g tid or terbutaline sulfate tablets 2.5 mg tid or salmeterol inhaler, 200 µg up to 6 times/day (if dyspnea severe) No treatment	Liang, 2009
Liu, 2005	Zoufeitang (decoction): 200 mL bid Dangshen, Gejie, Taoren, Wuweizi, Guizhi, Ziyuan, Kuandonghua, Hutaoren, Wuweizi, Kuxingren, Chenxiang, Yangfei	No		NS
Liu, 2006	Huatanhuoxue formula (decoction): 1 packet per day Chenpi, Fabanxia, Laifuzi, Zisuzi, Zhebeimu, Xingren, Taoren, Fuling, Maodongqing, Baijiezi, Gancao	Theophylline 0.2 g bid	Theophylline 0.2 g bid	NS
Liu, 2010	Yiqihuoxuehuatanlongluo Formula (decoction): 1 packet per day 100 mL bid Huangqi, Dangshen, Fuling, Baizhu, Chuanbeimu, Dilong, Damshe, Xixin, Baijiezi, Zishiyong, Hongjingtian + Bailing capsule: 1–2 g daily, extract of Dongchongxiacao or Jinsuibao capsule: 1.65 g daily Extract of Dongchongxiacao	Salbutamol inhaler 1 or 2 puffs daily or salbutamol tablet 10 g daily	Salbutamol inhaler 1 or 2 puffs daily or salbutamol tablet 10 g daily	NS
Mai, 2009	Bufeitang + Renshengjietang (decoction): 200 mL per day Dangshen, Huangqi, Shudihuang, Wuweizi, Ziyuan, Sangbaipi, Gejie, etc.	Routine medication (antibiotics, expectorants, bronchodilators)	Routine medication (antibiotics, expectorants, bronchodilators)	NS
Ni, 2008	Bushennaqi granule: 10 g tid Buguzhi, Yinyanghuo, Fupenzi, Wuweizi	Salbutamol inhaler, theophylline, prednisone	Placebo (<i>Shanzhu</i> granule) + salbutamol inhaler, theophylline, prednisone	NS
Shan, 2007	Peitushengjiantang (decoction): 1 packet per day Dangshen, Wuzhualong, Fuling, Baizhu, Shanyao, Wuweizi, Kuandonghua, Xingren, Taoren, Suzi, Jineijin	Theophylline tablets 0.2 g bid	Theophylline tablets 0.2 g bid	NS
Shi, 2009 ^a	Bufeitang (decoction): 1 packet per day, in 2 doses (morning & night)	Routine medication	Routine medication	NS

(continued)

TABLE 2. (CONTINUED)

First author, date	Intervention			Control	Adverse events
	Formula name (form): Dose, ingredients	Plus RP			
Sun, 2009	Huangqi, Dangshen, Baizhu, Jiegeng, Chenpi, Zhigancao, Chaoshanyao, Zhimu, Wuweizi, Maidong, Yuzhu, Zhibaihu or Qiweiduqiwán + Shengmaisan (decoction): as above Shudi, Shanyurou, Shengshanyao, Gouji, Maidong, Nvzhenzi, Hanliancao, Fuling, Danpi, Wuweizi, Taizishen or linguisheqiwán (decoction): as above Shudi, Danshen, Yiyiren, Shanyurou, Chaoshanyao, Fuling, Dangshen, Baizhu, Huaminxi, Shufuzi, Tusizi, Rougui, Lujiaojiao or Suzijiangqitang (decoction): as above Zisuzi, Banxia, Qianhu, Houpo, Chenpi, Danggui, Rougui, Gancao	No	Placebo	No	No
Tang, 2009	Buwei granule: 16 g bid Dangshen, Shudihuang, Danggui, Shanzhuyu, Mahuang, Sangbaipi, Chenpi, Ziyuan Bailing capsule: 3 capsules tid Extract of Dongchongxiacao	No routine medication but medical support provided as required Smoking cessation + routine medication	No routine medication but medical support provided as required Smoking cessation + routine medication	NS	NS
Tang, 2010	Jianpiyishen formula (decoction): 1 packet per day Huangqi, Dangshen, Baizhu, Shashen (Nan), Shashen (Bei), Buguzhi, Baijitian, Danggui, etc.	Salbutamol inhaler: 200 µg tid or theophylline tablets or if dyspnea more severe: theophylline 0.25 g + 0.9% NSal, Gsol (250–500 mL) IV drip 15 drip/min Erythromycin 100 g bid (to relieve airway inflammation)	Salbutamol inhaler: 200 µg tid or theophylline tablets or if dyspnea more severe: theophylline 0.25 g + 0.9% NSal, Gsol (250–500 mL) IV drip 15 drip/min No treatment	NS	NS
Wang, 2009	Sanshenjinfaitang (decoction): 1 packet per day Taizishen, Danshen, Shashen, Fuling, Baizhu, Honghua, Danggui, Taoren, Jiegeng, Chishao, Tianhuafen, Zhibanxia, Shenggancao, Sharen, Xiangfu, Juhong, etc.	Salbutamol or beclomethasone dipropionate (Becotide) inhaler & theophylline tablets	Salbutamol or beclomethasone dipropionate (Becotide) inhaler & theophylline tablets	NS	NS
Wu, 2007	Liuqunzhitang (decoction): 100 mL bid Dangshen, Baizhu, Fuling, Chenpi, Zhibanxia, Gancao	No	No treatment	NS	NS
You, 2008	Yifei mixture (decoction): 100 mL bid Yinyanghuo, Xianmao, Renshen, Fuling, Baizhu, Danshen, Fabanxia, Zhuru, Gualoupi, Houpo, Zhiqiao	No	No treatment	NS	NS
Zhang, 2006	Jiapiyifeibushen formula (decoction): 1 packet per day Huangqi, Dangshen, Baizhu, Fuling, Maidong, Shashen, Buguzhi, Tusizi, Nvzhenzi, Gejie, Xingren, Gualou, Beimu, Danshen, Chuanxiong	No	No treatment	NS	NS
Zhang, 2009	Yifeiyangjintang (decoction): 300 mL bid Baile, Shengdihuang, Shudihuang, Chuanbei, Jiegeng, Zhiqiao, Maidong, Baishao, Danggui, Shashen, Huaishanyao, Fuling, Huangqi, Shenggancao	No routine medication but medical support as required + Smoking cessation	No routine medication but medical support as required + smoking cessation	NS	NS
Zhu, 2007	Tianlongkechuanling capsule: 4 capsules, tid Qingtiankui, Kuandonghua, Fabanxia, Shufuzi, Wuweizi, etc.	No	Salbutamol + beclomethasone dipropionate inhaler 2 puffs, qid	NS	NS

^aUse of syndrome differentiation in selection of Chinese Medicine formula.
RP, routine pharmacotherapy; NS, not stated; Nsal, normal saline; Gsol, glucose solution.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Chen, 2009	?	?	?	?	+	+
Fang, 2008	?	?	+	+	+	+
Feng, 2005	+	?	?	+	+	+
Feng, 2007	+	?	?	+	+	+
Feng, 2008	?	?	?	+	+	+
Hong, 2005	+	?	+	+	+	+
Huang, 2005	?	?	+	+	+	+
Jia, 2007	?	?	?	?	+	+
Jian, 2008	+	?	?	+	+	+
Lang, 2010	?	?	?	+	+	+
Liang, 2009	?	?	?	+	+	+
Liu, 2005	?	?	+	+	+	+
Liu, 2006	+	?	?	+	+	+
Liu, 2010	?	?	?	+	+	+
Mal, 2009	?	?	?	+	+	+
Ni, 2008	?	?	+	?	+	+
Shan, 2007	?	?	?	+	+	+
Shi, 2009	?	?	?	+	+	+
Sun, 2009	?	?	?	+	+	+
Tang, 2009	+	+	+	+	+	+
Tang, 2010	+	?	?	+	+	+
Wang, 2009	+	?	?	+	+	+
Wu, 2007	?	?	+	+	+	+
You, 2008	+	?	?	+	+	+
Zhang, 2006	?	?	+	+	+	+
Zhang, 2009	?	?	+	+	+	+
Zhu, 2007	+	?	?	+	+	+

FIG. 2. Methodological quality summary. Review authors' judgments about each methodological quality item for each included study.

than placebo in improving QoL: (MD): -8.60 , 95% CI $(-14.54, -2.66)$ (Fig. 3). Further analysis was conducted of the individual domains of SGRQ: symptoms (MD): -3.20 , 95% CI $(-6.13, -0.27)$; activity (MD): -1.23 , 95% CI $(-2.78, -0.32)$; and impact (MD): -4.47 , 95% CI $(-7.02, -1.92)$, all of which showed significant improvement. Another one used Cai's QoLQ ($n=64$) that showed significant improvement of QoL when comparing CHM to placebo (both groups plus RP) (MD: -5.91 , 95% CI $[-7.78, -4.04]$); however the reported data are not suitable for meta-analysis.³⁷

CHM versus no treatment ($n=7$)

Pooling of data for the two studies using SGRQ ($n=226$) found a significant improvement in total scores in the CHM group compared with no treatment (MD -6.07 , 95% CI $[-9.21, -2.93]$)^{16,18} (Fig. 3). The five studies using Cai's QoLQ ($n=251$) were pooled and a significant improvement in total scores again was found (MD: -0.20 95% CI $[-0.32, -0.07]$).^{14,15,22,33,39} The two studies using SGRQ did not report information on the scores for individual domains. Further analysis of individual domains of Cai's QoLQ showed significant improvement of activities of daily living (MD: -0.16 , 95% CI $[-0.30, -0.01]$); depression (MD -0.28 , 95% CI $[-0.51, -0.06]$); and anxiety (MD -0.28 , 95% CI $[-0.47, -0.09]$) but not in social activities (MD: -0.11 , 95% CI $[-0.36, 0.13]$)^{14,15,39} (Fig. 4).

CHM versus RP ($n=1$)

One (1) study with 67 participants compared CHM alone versus RP using SGRQ. Analysis revealed a significant improvement in total score (MD: -7.05 , 95% CI $[-13.55, -0.55]$) (Fig. 3) and in the individual domains of symptoms (MD: -12.76 , 95% CI $[-18.02, -7.50]$) and activity (MD -7.18 , 95% CI $[-12.70, -1.66]$) but not for impact (MD: 0.77 , 95% CI $[-4.29, 5.83]$).³⁴

CHM plus RP versus RP ($n=17$)

Fifteen (15) of the 17 studies that compared CHM plus RP with RP alone reported data suitable for analysis. Seven (7) studies used SGRQ ($n=427$). Significant improvements were found for total score (MD -5.15 , 95% CI $[-7.26, -3.05]$) (Fig. 3).^{17,19,23,24,27,32,36} Four studies also reported data on the individual domains of: symptoms (MD -5.53 , 95% CI $[-6.22, -4.84]$); activity (MD -5.21 , 95% CI $[-5.86, -4.57]$), and impact (MD -5.73 , 95% CI $[-6.35, -5.12]$)^{17,24,32,36}; Eight (8) studies used Cai's QoLQ ($n=664$). For Cai's QoLQ, only six studies reported total scores ($n=364$).^{25,26,28-30,40} A significant

FIG. 3. Comparison of Chinese herbal medicines (CHM) versus placebo, no treatment, routine pharmacotherapy, or CHM plus routine pharmacotherapy versus routine pharmacotherapy in patients with stable chronic obstructive pulmonary disease for the effect on total St. George Respiratory Questionnaire score at the end of treatment. SD, standard deviation; CI, confidence interval.

change in the total score was found (MD 0.25, 95% CI [-0.37, -0.13])^{25,26,28-30,40} (Fig. 4). In the eight studies ($n = 664$) that reported data for individual domains, there were significant changes in activities of daily living (MD -0.30, 95% CI [-0.42, -0.19]); social activities (MD -0.36 95% CI [-0.57, -0.15]); depression (MD -0.38, 95% CI [-0.55, -0.21]); and anxiety (MD -0.39, 95% CI [-0.56, -0.23]).^{25,26,28-30,35,38,40}

Two studies used a modified SGRQ^{20,21} and reported significant differences for CHM plus RP versus RP alone for total scores as well as the individual scores for symptoms, activity, and impact. The actual scores were not available for these studies, even after contacting the authors. Therefore, data for these studies were not included in the meta-analyses.

Adverse events

Adverse events were reported in five studies. In four of these, no adverse events were observed.^{19,22,31,36} In one study (63 participants), 2 subjects in the CHM treatment group reported dry mouth, mild stomach bloating, and 1 subject in the control group reported reduced appetite.²³ There was no mention of adverse events in the remaining studies^{14-18,20,21,24-30,32-35,37-40} (Table 2).

Discussion

This systematic review includes all RCTs of CHM for stable COPD available at the time of searching that included outcome measures of the quality of life of participants. All of the included studies were conducted and published in China from 2000 to 2010. Two (2) of these were also indexed in MEDLINE.^{20,22}

Meta-analysis indicated most studies showed that CHM improved the health status of patients with stable COPD when compared with no treatment, placebo, RP, or when CHM was combined with RP. Considerable heterogeneity was evident in comparisons 3.4, 4.1, and 4.2 (Figs. 3 and 4). The variation in COPD severity in patients and consequently the wide range in HRQoL scores is a likely source. Overall, methodological quality was problematic. Only two studies used a placebo in the control and no study satisfied all of the methodological criteria included in the Cochrane risk of bias, so the findings of the meta-analyses should be considered with caution. The absence of severe adverse events suggests that the CHMs were well tolerated.

Meta-analyses (Figs. 3 and 4) suggest that the combination of CHM and RP is better at promoting HRQoL in patients with stable COPD compared to RP alone. However, the

FIG. 4. Comparison of Chinese herbal medicines (CHM) versus no treatment or CHM plus routine pharmacotherapy versus routine pharmacotherapy in patients with stable chronic obstructive pulmonary disease for effect on total Cai's Quality of Life Questionnaire score at the end of treatment. SD, standard deviation; CI, confidence interval.

effects of the RPs used in the included studies may not have been optimal. According to the GOLD guidelines, theophylline in the management of stable COPD is controversial.³ Also, a recent review suggested that newer long-acting β_2 agonists and long-acting anticholinergic medications are better than the combination of salbutamol and ipratropium bromide for moderate and severe COPD.⁴¹ In future studies, the RP should be standardized to international best practice.

COPD is a chronic disease with progressive development that requires long-term therapy, so the 15 studies that lasted 6 months are the most relevant. Of these, the largest were Shi 2009 ($n=180$), Feng 2008 ($n=120$), and Zhang 2009 ($n=120$). Feng 2008 and Shi 2009 included the five most commonly used herbs, whereas Zhang 2009 included two of them (*huangqi* and *fuling*). For each of the five most commonly used herbs, there is additional evidence for bioactivity related to the respiratory system. Experimental studies on extracts of *huangqi* in mice found that airway hyperresponsiveness was inhibited by astragaloside IV⁴² and an aqueous extract decreased inflammatory infiltration and mucus secretion in lung tissues.⁴³ There is human experimental evidence to suggest that *dang-shen* can improve respiratory symptoms in acute altitude sickness.⁴⁴ Extracts of *baizhu* were found to have anti-inflammatory effects in acute and chronic animal models⁴⁵ and on rat lung cells.⁴⁶ *Fuling* has been shown to have anti-inflammatory effects.⁴⁷⁻⁴⁹ *Wuweizi* is considered an "adaptogen" with stress-protective effects,⁵⁰ and its constituent schisandrin demonstrated anti-inflammatory activity in mice.⁵¹ These herbs appear to warrant further investigation.

Conclusions

CHM appears to be a well-tolerated addition to pharmacotherapy for stable COPD and may confer an additional

benefit in terms of improving HRQoL of these patients. Such potential benefits need to be further evaluated through trials that address the identified methodological deficiencies and provide quality-control data for the CHM interventions. Trials should employ a randomized double-blind method using standard outcome instruments. Comparisons should be with placebo or a routine pharmacotherapy that reflects current best practice.

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