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Comparative Effectiveness of Six Chinese Herb Formulas for Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Protocol for Systematic Review and Network Meta-analysis

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Comparative Effectiveness of Six Chinese Herb Formulas for Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Protocol for Systematic Review and Network Meta-analysis

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Abstract

Introduction

Chinese medicine is commonly used to combine with pharmacotherapy for the treatment of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Six Chinese herb formulas involving *Weijing* decoction, *Maxingshigan* decoction, *Yuebijiabanxia* decoction, *Qingqihuatan* decoction, *Dingchuan* decoction and *Sangbaipi* decoction are recommended in Chinese medicine clinical guideline or text book, to relieve patients with phlegm-heat according to Chinese syndrome differentiation. However, the comparative effectiveness among these six formulas has not been investigated in published randomized controlled trials. We plan to summarize the direct and indirect evidence for these six formulas combined with pharmacotherapy to determine the relative merits options for the management of AECOPD.

Methods and analysis

We will perform the comprehensive search for the randomized controlled trials to evaluate the effectiveness of six Chinese herbal formulas recommended in Chinese medicine clinical guideline or text book. The combination of pharmacotherapy includes bronchodilators, antibiotics and corticosteroids that are routinely prescribed for AECOPD. The primary outcome will be lung function, arterial blood gases and length of hospital stay. The data screening and extraction will be conducted by two different reviewers. The quality of RCT will be assessed according to the Cochrane handbook risk of bias tool. The Bayes of network meta-analysis will be conducted with winBUGS to compare the effectiveness of six formulas. We will also use the Surface Under the Cumulative Ranking Curve (SUCRA) to obtain the comprehensive rank for these treatments.

Ethics and dissemination

This review does not require ethics approval and the results of network meta-analysis will be submitted to a peer-review journal.

Protocol registration number: PROSPERO CRD42016052699

The strength and limitations of the study

This study will be the first meta-analysis to compare the Chinese herb formula combined with pharmacotherapy for AECOPD.

The results of this study will provide the additional evidence for the clinical guideline and help the clinical practitioners to make decision for the treatment of AECOPD.

Although the comprehensive search will be performed in our study, potential unpublished trials are inevitable. This will introduce some bias.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common respiratory disease characterized by persistent airflow limitation and abnormal inflammatory response in airways.[1] A recent survey reported that the estimated COPD prevalence was 6.2% in nine Asia-Pacific territories.[2] This condition has resulted in an economic and social burden with the substantial morbidity and mortality worldwide.[3 4] A survey estimates that COPD will become the third leading cause of death worldwide in 2030.[5] Acute exacerbation of COPD is defined as the sustain worsening of the patient's respiratory symptoms beyond normal day-to-day variations.[1] It has a considerable impact on the patients' health status, lung function and even increases the risk of death.[6-8] The clinical guideline recommended pharmacologic therapies for the management of acute exacerbation

including bronchodilators, antibiotics, corticosteroids and some other respiratory support. Despite the effectiveness of these therapies, acute exacerbation still occurs frequently and is significantly associated with morbidity and mortality.[9] Also, the clinical practice needs to be balanced against the potential harm of these pharmacotherapies.

Chinese herbal medicine is widely prescribed as an adjunct to western medicine to manage AECOPD in clinical guideline. Six Chinese herb formulas: *Weijing* decoction, *Maxingshigan* decoction, *Yuebijiabanxia* decoction, *Qingqihuatan* decoction, *Dingchuan* decoction and *Sangbaipi* decoction are representative recipes to treat AECOPD patients of phlegm-heat syndromes in Chinese medicine theory.[10-12] Despite the difference of herb ingredients, all these formulas can be prescribed to clear phlegm-heat symptoms for the patients. They also will be modified mildly according to additional clinical symptoms. Several systematic reviews synthesized the effectiveness of single formula.[13 14] However, the paucity of evidence from direct comparison between these six formulas posed a challenge for clinicians to find the more effective therapeutic option.

Network meta-analysis (NMAs), a newer statistical technique, compared with the traditional pairwise meta-analysis, can evaluate the relative efficacy of multiple treatment comparisons including both direct and indirect comparisons.[15-18] The combination of direct and indirect evidence may improve the precision for the estimated effect size.[15 19-21] The major value of NMAs is that it can provide the ranking of treatment options according to their effectiveness, which is important for clinicians to make the best treatment choice.

Therefore, we plan to conduct this systematic review and NMAs to compare these six Chinese herb formulas combined with pharmacotherapy to determine their relative effectiveness and safety in the treatment of AECOPD.

Methods and analysis

Registration

The study protocol has been registered on international prospective register of systematic review (PROSPERO). The procedure of this protocol will be conducted according to the Preferred Reporting Item for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidance.[22]

Eligibility criteria

Type of study

We will include all the randomized controlled trials that investigated the effectiveness of six Chinese herb formulas combined with pharmacotherapy for the treatment of AECOPD.

Participants

Patients must be aged at least 18 years old and diagnosed as acute exacerbation chronic obstructive pulmonary disease with one or more following symptoms: increased cough frequency, increased sputum volume, increased dyspnea.[1] We will exclude studies of participants with other respiratory disease like asthma, bronchiectasia, pulmonary tuberculosis, etc.

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Interventions and comparators

Interventions involving the combination of Chinese herb formulas with conventional pharmacotherapy are eligible. The interested Chinese medicine therapies include the following six formulas: *Weijing* decoction, *Maxingshigan* decoction, *Yuebijiabanxia* decoction, *Qingqihuatan*

decoction, *Dingchuan* decoction and *Sangbaipi* decoction. The same conventional pharmacotherapy must be used in the comparator arm.

Outcome

The primary outcomes include: (1) lung function—forced expiratory volume in 1 second (FEV1); (2) arterial blood gases—partial pressure of oxygen (PaO2) and carbon dioxide (PaCO2); (3) length of hospital stay.

The secondary outcomes include: (1) Dyspnoea; (2) health related quality of life; (3) adverse events.

Search strategy

We will perform the comprehensive search in both English and Chinese database involving PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, AMED, Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP information (CQVIP) and Wanfang database, from their inceptions to December 2016. The following sources will also be searched to identify clinical trials which are in progress or completed: ClinicalTrials.gov and WHO clinical trials registry. The additional relevant studies will also be retrieved from the reference lists of systematic reviews and included studies. We will map search terms to controlled vocabulary if possible. In addition, the search strategy for selecting the fields of title, abstract or keyword will be different referring to the characteristics of databases. Search terms are grouped into three blocks (see table 1).

Study selection and data extraction

Literature retrieved citations will be managed by ENDNOTE X6 software. Two independent reviewers (JL and JZ) will assess the title and abstract of the literature after removing duplications. The further screening will be performed to select eligible articles by reviewing the full-text. Any disagreement between the reviewers will be resolved by discussion with a third person (JC). The selection process will be provided in a PRISMA flow chart (see Figure 1)

We will design the standardized database sheet for data extraction. Epidata software 3.1 (The EpiData Association, Odense, Denmark, 2003-2008) will be used to extract data and check the consistency of information. The data extraction items include: first author, publication year, diagnose information, disease duration, stage, sample size, age, details of intervention, control and outcomes, treatment duration and follow-up period, and adverse events.

Risk of bias assessment

The methodological quality of the eligible studies will be evaluated according to the Cochrane collaboration's risk of bias tool.[23] The assessment details include: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias. Each domain will be assessed as 'low risk' or high risk' or 'unclear risk' according to the description details of eligible studies. Any discrepancies will be further discussed with a third reviewer (YH).

Statistical analysis

Pairwise meta-analysis

The conventional pairwise meta-analysis will be performed using random-effects model by

Revman 5.3 software. Dichotomous data is presented as relative risk (RR) with 95% confidence interval (CI) and continuous data is reported as mean difference (MD) with 95%CI. The Chi-square test and I^2 test will be conducted to convey the potential heterogeneity.

Network meta-analysis

The network meta-analysis will be conducted in a Bayesian hierarchical framework using the Markov Chain Monte Carlo (MCMC) algorithm by WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK).[24] The statistical heterogeneity of entire NMAs will be investigated by the magnitude of heterogeneity variance ($\boldsymbol{\tau}^2$) estimated from the NMAs model.[25] If the direct evidence is available, the combined estimation will be provided for NMAs. There are several methods to evaluate the potential difference in treatment effect estimated by direct and indirect comparisons.[26-29] We will apply node splitting method to explore the inconsistency of the model. [26 30]The deviance information criterion (DIC) will be used to assess the model fitness by comparing the fixed and random effects model, and the lower DIC is preferred.[31] To rank the probabilities of the best intervention for various treatments, we will use SUCRA and the mean ranks.[32] SUCRA will be described with percentages, and larger values indicate the better ranks for the treatment. The generation of NMAs graphs and result figures will be performed by Stata software (version 12; Stata Corporation, College Station, Texas, USA). If the data are not available for quantitative analysis, we will describe and summarize the evidence.

Sensitivity analysis and subgroup analysis

The strategies employed to address the heterogeneity of pair-wise meta-analysis also can be used in network analysis to tackle inconsistency.[15] If the heterogeneity or inconsistency among the studies was detected, subgroup analysis will be conducted according to the effect modifiers, including sample size, severity of COPD, treatment duration et al. Also, the network meta-regression will be performed to explore the possible sources of inconsistency.[33] We will perform the sensitivity analysis to explore the robust conclusions of primary outcomes if feasible. Different levels of the methodological quality of studies will influence the overall effects. Sensitivity analysis will be conducted by removing trails that report the non-random sequence generation.

Publication bias

Egger's regression test will be performed to assess the publication bias of the included studies. If feasible, we will also convey whether the small study effects exist in a network of interventions by the statistical model.[34]

Quality of evidence

We will also assess the quality of evidence for the main outcomes with the GRADE approach (the Grading of Recommendations Assessment, Development and Evaluation).[35] The five items will be investigated, including limitations in study design, inconsistency, imprecision, indirectness and publication bias.

Ethics and dissemination

This review doesn't require the ethical approval since the study bases on the published evidence. The results of network meta-analysis will be reported according to the PRISMA extension

statement for reporting of systematic reviews incorporating network meta-analysis, and submitted to a peer-review journal. [36]

Contributors

SL, XG and LW conceived and designed this study. SL and JC drafted the protocol. JL and JZ will conduct the search, data screening and extraction. SL, JC, YH, LW, LY and XG have critically reviewed the manuscript and approved it for publication.

Conflicts of interest

None declared

Provenance and peer review

Not commissioned; externally peer reviewed

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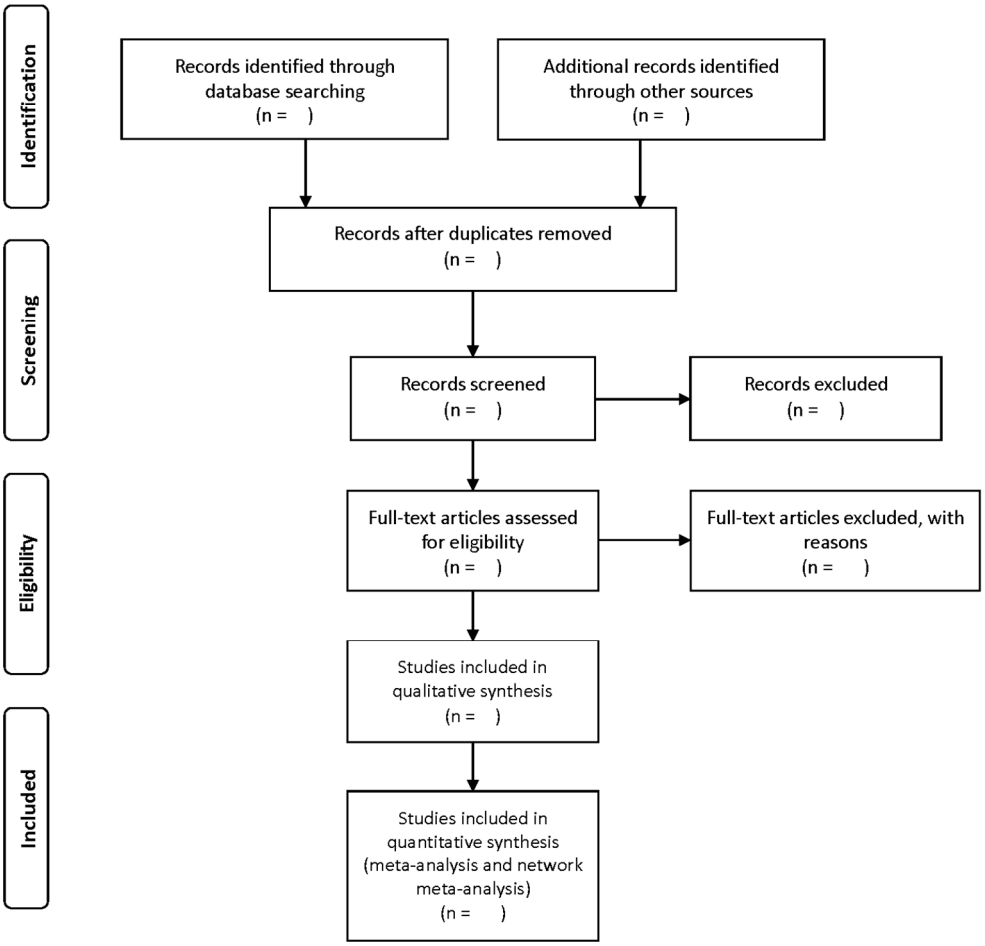
Table 1 Search terms

Search block	Search terms
Participants	Pulmonary Disease, Chronic Obstructive OR Bronchitis, Chronic OR Pulmonary Emphysema OR Emphysema OR COPD OR Chronic Obstructive Pulmonary OR COAD OR Chronic Obstructive Airway OR Chronic Obstructive Lung OR Chronic obstructive bronchopulmonary OR Chronic obstructive respiratory OR Chronic Airflow Obstruction OR Chronic Airflow Obstructive OR Chronic bronchitis OR Pulmonary emphysema OR Lung emphysema OR Chronic Airflow limitation.
Intervention	wejing decoction OR wejing tang OR sangbaipi decoction OR sangbaipi tang OR maxingshigan decoction OR maxingshigan tang OR yuebijiabanxia decoction OR yuebijiabanxia tang OR dingchuan decoction OR dingchuan tang OR qingqihuatan decoction OR qingqihuatan tang OR qingqihuatan pill
Study design	Randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups



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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page#
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	6
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	6
Sponsor	5b	Provide name for the review funder and/or sponsor	6
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	6
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2-3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3-4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	4
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	4-5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	4-5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Protocol registration number: PROSPERO CRD42016052699

The strength and limitations of the study

This study will be the first meta-analysis to compare the Chinese herb formula combined with pharmacotherapy for AECOPD.

The results of this study will provide the additional evidence for the clinical guideline and help the clinical practitioners to make decision for the treatment of AECOPD.

Although the comprehensive search will be performed in our study, potential unpublished trials are inevitable. This will introduce some bias.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common respiratory disease characterized by persistent airflow limitation and abnormal inflammatory response in airways.[1] A recent survey reported that the estimated COPD prevalence was 6.2% in nine Asia-Pacific territories.[2] This condition has resulted in an economic and social burden with the substantial morbidity and mortality worldwide.[3 4] A survey estimates that COPD will become the third leading cause of death worldwide in 2030.[5] Acute exacerbation of COPD is defined as the sustain worsening of the patient's respiratory symptoms beyond normal day-to-day variations.[1] It has a considerable impact on the patients' health status, lung function and even increases the risk of death.[6-8] The clinical guideline recommended pharmacologic therapies for the management of acute exacerbation

including bronchodilators, antibiotics, corticosteroids and some other respiratory support. Despite the effectiveness of these therapies, acute exacerbation still occurs frequently and is significantly associated with morbidity and mortality.[9] Moreover, these therapies have been associated with some side effects such as tremor, hyperglycaemia, candidiasis and antibiotic resistance.[9] Clinicians should balance the effectiveness and safety of these pharmaceutical interventions for patients.

Chinese herb medicine is widely prescribed as an adjunct to western medicine to manage AECOPD in clinical guideline. Although CHM is not the mainstream for treating COPD, it has become increasingly accepted as a form of complementary or alternative medicine in western countries.[10] Chinese herb formulas combined with routine pharmacotherapy have showed the promising benefits on lung function, arterial blood gases, St George's Respiratory Questionnaire (SGRQ) scoring, and 6-Minute Walk Test (6MWT) when compared with routine pharmacotherapy alone.[11 12] Six Chinese herb formulas: *Weijing* decoction, *Maxingshigan* decoction, *Yuebijiabanxia* decoction, *Qingqihuatan* decoction, *Dingchuan* decoction and *Sangbaipi* decoction are representative recipes to treat AECOPD patients of phlegm-heat syndromes in Chinese medicine theory.[13-15] Despite the difference of herb ingredients, all these formulas can be prescribed to clear phlegm-heat symptoms for the patients. They also will be modified mildly according to additional clinical symptoms. These formulas or active compounds of herb ingredients also show the effects on anti-inflammation, anti-oxidative stress and improve immune function which may shorten recovery time and reduce recurrence of AECOPD.[16-21] Several systematic reviews synthesized the effectiveness of single formula.[12 22] However, the paucity of evidence from direct comparison between these six formulas posed a challenge for clinicians to find the more effective therapeutic option.

Network meta-analysis (NMAs), a newer statistical technique, compared with the traditional pairwise meta-analysis, can evaluate the relative efficacy of multiple treatment comparisons including both direct and indirect comparisons.[23-26] The combination of direct and indirect evidence may improve the precision for the estimated effect size.[23 27-29] The major value of NMAs is that it can provide the ranking of treatment options according to their effectiveness, which is important for clinicians to make the best treatment choice.

Therefore, we plan to conduct this systematic review and NMAs to compare these six Chinese herb formulas combined with pharmacotherapy to determine their relative effectiveness and safety in the treatment of AECOPD.

Methods and analysis

Registration

The study protocol has been registered on international prospective register of systematic review (PROSPERO). The procedure of this protocol will be conducted according to the Preferred Reporting Item for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidance.[30]

Eligibility criteria

Type of study

We will include all the randomized controlled trials that investigated the effectiveness of six Chinese herb formulas combined with pharmacotherapy for the treatment of AECOPD.

Participants

COPD should be confirmed according to the standard diagnostic criteria including the Global Initiative for Chronic Obstructive Lung Disease [GOLD];[1] the British Thoracic Society, the American Thoracic Society, the European Respiratory Society or Chinese COPD guideline.[31]

Patients must be aged at least 18 years old and diagnosed as acute exacerbation chronic obstructive pulmonary disease with one or more following symptoms: increased cough frequency, increased sputum volume, increased dyspnea.[1] We will exclude studies of participants with other respiratory disease like asthma, bronchiectasia, pulmonary tuberculosis, etc.

Interventions and comparators

Interventions involving the combination of Chinese herb formulas with conventional pharmacotherapy are eligible. The interested Chinese medicine therapies include the following six formulas: *Weijing* decoction, *Maxingshigan* decoction, *Yuebijiabanxia* decoction, *Qingqihuatan* decoction, *Dingchuan* decoction and *Sangbaipi* decoction. The same conventional pharmacotherapy must be used in the comparator arm.

Outcome

The primary outcomes include: (1) lung function—forced expiratory volume in 1 second (FEV1); (2) arterial blood gases—partial pressure of oxygen (PaO2) and carbon dioxide (PaCO2); (3) length of hospital stay.

The secondary outcomes include: (1) Dyspnoea; (2) health related quality of life; (3) hospital readmission for acute exacerbation; (4) effective rate;[32] (5) adverse events.

Search strategy

We will perform the comprehensive search in both English and Chinese database involving PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, AMED, Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP information (CQVIP) and Wanfang database, from their inceptions to December 2016. The following sources will also be searched to identify clinical trials which are in progress or completed: ClinicalTrials.gov and WHO clinical trials registry. The additional relevant studies will also be retrieved from the reference lists of systematic reviews and included studies. We will map search terms to controlled vocabulary if possible. In addition, the search strategy for selecting the fields of title, abstract or keyword will be different referring to the characteristics of databases. Search terms are grouped into three blocks (see table 1).

Table 1 Search terms

Search block	Search terms
Participants	Pulmonary Disease, Chronic Obstructive OR Bronchitis, Chronic OR Pulmonary Emphysema OR Emphysema OR COPD OR Chronic Obstructive Pulmonary OR COAD OR Chronic Obstructive Airway OR Chronic Obstructive Lung OR Chronic obstructive bronchopulmonary OR Chronic obstructive respiratory OR Chronic Airflow Obstruction OR Chronic Airflow Obstructive OR Chronic bronchitis OR Pulmonary emphysema OR Lung emphysema OR Chronic Airflow limitation.

Intervention	wejing decoction OR wejing tang OR sangbaipi decoction OR sangbaipi tang OR maxingshigan decoction OR maxingshigan tang OR yuebijiabanxia decoction OR yuebijiabanxia tang OR dingchuan decoction OR dingchuan tang OR qingqihuatan decoction OR qingqihuatan tang OR qingqihuatan pill
Study design	Randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups

Study selection and data extraction

Literature retrieved citations will be managed by ENDNOTE X6 software. Two independent reviewers (JL and JZ) will assess the title and abstract of the literature after removing duplications. The further screening will be performed to select eligible articles by reviewing the full-text. Any disagreement between the reviewers will be resolved by discussion with a third person (JC). The selection process will be provided in a PRISMA flow chart (see Figure 1)

We will design the standardized database sheet for data extraction. Epidata software 3.1 (The EpiData Association, Odense, Denmark, 2003-2008) will be used to extract data and check the consistency of information. The data extraction items include: first author, publication year, diagnose information, disease duration, stage, sample size, age, details of intervention, control and outcomes, treatment duration and follow-up period, and adverse events.

Risk of bias assessment

The methodological quality of the eligible studies will be evaluated according to the Cochrane collaboration's risk of bias tool.[33] The assessment details include: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias. Each domain will be assessed as 'low risk' or high risk' or 'unclear risk' according to the description details of eligible studies. Any discrepancies will be further discussed with a third reviewer (YH).

Statistical analysis

Pairwise meta-analysis

The conventional pairwise meta-analysis will be performed using random-effects model by Revman 5.3 software. Dichotomous data is presented as relative risk (RR) with 95% confidence interval (CI) and continuous data is reported as mean difference (MD) with 95%CI. The Chi-square test and I^2 test will be conducted to convey the potential heterogeneity.

Network meta-analysis

The network meta-analysis will be conducted in a Bayesian hierarchical framework using the Markov Chain Monte Carlo (MCMC) algorithm by WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK).[34] The statistical heterogeneity of entire NMAs will be investigated by the magnitude of heterogeneity variance (τ^2) estimated from the NMAs model.[35] If the direct evidence is available, the combined estimation will be provided for NMAs. There are several methods to evaluate the potential difference in treatment effect estimated by direct and indirect comparisons.[36-39] We will apply node splitting method to explore the inconsistency of the model. [36 40]The deviance information criterion (DIC) will be used to assess the model fitness by comparing the fixed and random effects model, and the lower DIC is preferred.[41] To rank the

probabilities of the best intervention for various treatments, we will use SUCRA and the mean ranks.[42] SUCRA will be described with percentages, and larger values indicate the better ranks for the treatment. The generation of NMAs graphs and result figures will be performed by Stata software (version 12; Stata Corporation, College Station, Texas, USA). If the data are not available for quantitative analysis, we will describe and summarize the evidence.

Sensitivity analysis and subgroup analysis

The strategies employed to address the heterogeneity of pair-wise meta-analysis also can be used in network analysis to tackle inconsistency.[23] If the heterogeneity or inconsistency among the studies was detected, subgroup analysis will be conducted according to the effect modifiers, including sample size, severity of COPD, treatment duration. Also, the network meta-regression will be performed to explore the possible sources of inconsistency.[43] We will perform the sensitivity analysis to explore the robust conclusions of primary outcomes if feasible. Different levels of the methodological quality of studies will influence the overall effects. Sensitivity analysis will be conducted by removing trails that report the non-random sequence generation.

Publication bias

Egger's regression test will be performed to assess the publication bias of the included studies. If feasible, we will also convey whether the small study effects exist in a network of interventions by the statistical model.[44]

Quality of evidence

We will also assess the quality of evidence for the main outcomes with the GRADE approach (the Grading of Recommendations Assessment, Development and Evaluation).[45] The five items will be investigated, including limitations in study design, inconsistency, imprecision, indirectness and publication bias.

Discussion

Chinese medicine has been used more than thousands of years for the treatment of respiratory condition. Nowadays, Chinese herb formula is commonly used as adjuvant therapy for the management of AECOPD in China. Multiple Chinese herb formulas are recommended in clinical guideline or textbook, whilst different formulas for each Chinese syndrome. Although few studies have reviewed the effective of the individual formula, the relative therapeutic effect differences among these formulas are still uncertain. Therefore, we plan to conduct NMA to evaluate the comparative effectiveness of different Chinese herb formulas. This will be the first review to compare the effectiveness of six most commonly used Chinese herb formulas for the treatment of AECOPD. We hope that the results of our study will provide the clinical recommendation for patients with AECOPD in Chinese medicine clinical practice, and promote evidence-based for clinical Chinese medicine.

Ethics and dissemination

This review doesn't require the ethical approval since the study bases on the published evidence. The results of network meta-analysis will be reported according to the PRISMA extension

statement for reporting of systematic reviews incorporating network meta-analysis, and submitted to a peer-review journal. [46]

Contributors

SL, XG and LW conceived and designed this study. SL and JC drafted the protocol. JL and JZ will conduct the search, data screening and extraction. SL, JC, YH, LW, LY and XG have critically reviewed the manuscript and approved it for publication.

Conflicts of interest

None declared

Provenance and peer review

Not commissioned; externally peer reviewed

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Figure legends

Figure 1. Flowchart of searching and screening studies.

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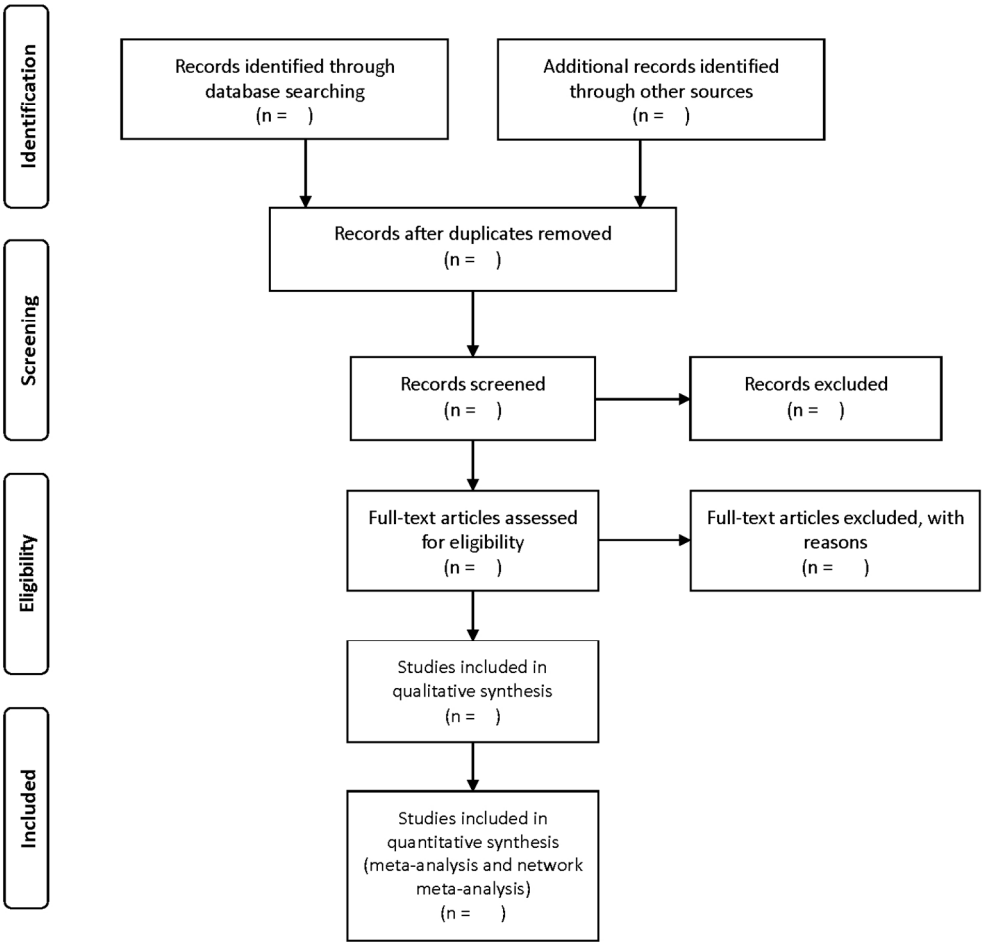

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page#
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	7
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	7
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	2-3
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3-4
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	4
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4-5

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	5
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5-6
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5-6
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	6

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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