INPLASY PROTOCOL

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Conflicts of interest:
None.

Effect and safety of Huanglong Cough Oral Liquid for cough variant asthma _ A protocol for meta-analysis

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Review question / Objective: **P: Adults with a cough variant asthma ; I: Huanglong Cough Oral Liquid alone or in combination with conventional therapy and/or biological agents; C: no treatment, placebo, and conventional therapy alone. O: Frequency of asthma exacerbations during follow-up, Asthmatic symptoms by validated instruments; S: RCTs.**

Condition being studied: **Cough variant asthma (CVA), a phenotype of asthma and originally described as those patients with asthma and cough as the sole symptom, is the most common cause of chronic cough, which account for a higher proportion of patients with chronic cough in China than in Western countries .Though it shares some clinical and pathophysiological features with classic asthma with wheezing such as seasonal or nocturnal coughing, airway hyperresponsiveness, eosinophilic airway inflammation, and airway remodeling, CVA patients are more depressed and anxious than classic asthma patients.The etiology of CVA remains unclear. Lucky, Chinese medicine have good therapeutic effect on irritable bowel syndrome.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 08 December 2020 and was last updated on 08 December 2020 (registration number INPLASY2020120046).

INTRODUCTION

Review question / Objective: **P: Adults with a cough variant asthma ; I: Huanglong Cough Oral Liquid alone or in combination with conventional therapy and/or biological agents; C: no treatment, placebo, and conventional therapy alone. O: Frequency of asthma exacerbations during follow-up, Asthmatic symptoms by validated instruments; S: RCTs.**

Rationale: **Many people with cough variant asthma use Traditional Chinese Medicine Huanglong Cough Oral Liquid to help reduce symptoms. However there is no**

systematic reviews had promising its efficacy and safety for cough variant asthma.

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METHODS

Search strategy: #1 search "Cough Variant Asthma" [Title/Abstract], #2 Search "Huanglong Cough Oral Liquid" [Title/Abstract], #3 Search "RCT" [Title/Abstract] OR "randomized controlled trial" [Title/Abstract],#4 Search "Efficacy" [Title/Abstract] OR "safety" [Title/Abstract],#5 #1 and #2 and #3 and #4.

Participant or population: Participants were adults with a cough variant asthma.

Intervention: Interventions included Suhuang anti-tussive capsule alone or in combination with conventional therapy (CT) and/or biological agents for at least 2 weeks.

Comparator: The comparator included no treatment, placebo, and CT alone.

Study designs to be included: Randomized controlled trails will be included.

Eligibility criteria: Two authors independently complete the following process: according to the above search strategy to complete the process of document retrieval, import documents into EndNote X7 for centralized management. Then, according to the inclusion and exclusion criteria, fifilter the literature by reading the title and abstract. If it is not possible to determine whether the article meets the requirements based on the inclusion and exclusion criteria, then read the full text to select. In the entire literature screening process, if the 2 authors have different opinions, the third author joins the discussion to get a common opinion.

Information sources: The China National Knowledge Infrastructure, Wanfang Database, Chinese Science and Technology Periodical Database, Chinese Biomedical Literature Database, Pubmed, Embase, Web of Science, and the Cochrane library were searched for randomized clinical trials until 8st of December 8, 2020.

Main outcome(s): Frequency of asthma exacerbations during follow-up. Asthmatic symptoms by validated instruments (including symptom scores, Likert scale, visual analogue scale).

Additional outcome(s): Lung function (PEF,FEV1,FEV 1%,FEV1/FVC) or peak expiratory flow rate,Serum immunoglobulin E(IgE).Blood eosinophil count,Phlegm eosinophil count,Tumor necrosis factor-a (TNF-a),Interleukin-1b (IL-1b), Adverse effects (numbers of participants experiencing each adverse events).

Data management: The basic process of the included literatures will be determined by referring to the Cochrane Collaboration System Evaluator's Manual (5.1.0). Extracted data included participants (age, sex), interventions (Huanglong Cough Oral Liquid alone or in combination with CT), controls (type, frequency, and duration), outcomes (measures and time points), and study design (randomization, allocation concealment, blinding, and etc). If required information was not reported, we tried to request it from the corresponding author of the studies.

Quality assessment / Risk of bias analysis: Two researchers independently evaluated the risk of bias in randomized controlled trials in accordance with the Cochrane Handbook of Systematic Reviewers, including the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The quality of studies was classified as being at of high, unclear, or low risk of bias. After completion, they would recheck. In case of a disagreement, they would discuss. If no agreement could be reached, a decision would be made in consultation with researchers from the third party.

Strategy of data synthesis: Statistical analyses were performed using RevMan 5.3 software. Dichotomous data. The relative risk (RR) was calculated with 95% confidence intervals (CI). Continuous data. A fixed-effect mean difference (MD) with 95% CI was calculated for outcomes reported in the same scale and the standardized mean difference (SMD) with 95% CI was calculated for outcomes reported in difference scales.Assessment of heterogeneity: For the meta-analysis of non-significant heterogeneity, we applied a fixed-effect model (FEM), otherwise, Statistical heterogeneity was calculated using the I2 statistic and >50% was considered to be substantial. Subgroup analyses were performed to explore heterogeneity and a random-effects model applied.

Subgroup analysis: When heterogeneity is detected, we will judge the source of heterogeneity through subgroup analysis (e.g., different types of Chinese medicines therapies, research quality, publication age, participation population, length of treatment). In addition, we can also observe the relationship between effect values and grouping variables.

Sensibility analysis: In order to ensure the Credibility of the research results, we will conduct a sensitivity analysis of the included literature and will eliminate low quality literature.

Language: The language is limited to Chinese and English.

Country(ies) involved: China.

Other relevant information: This work is supported by Key R&D Project of China's Sichuan Province Science and Technology Plan (2017SZ0164)

Keywords: Cough variant asthma, meta-analysis, protocol, Huanglong Cough Oral Liquid.

Contributions of each author:
Author 1 - Yang Yuan - The author drafted the manuscript.
Author 2 - Xu Li - The author provided statistical expertise.
Author 3 - Bengang Wang - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Dong Tang - The author read, provided feedback and approved the final manuscript.
Author 5 - Fang Yuan - The author read, provided feedback and approved the final manuscript.
Author 6 - Rong Li - The author contributed to the development of the selection criteria.
Author 7 - Chengshi He - The author provide scientific research ideas and guidance.