

# Traditional Chinese medicine for restless legs syndrome

## A study protocol for a network meta-analysis

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### Abstract

**Background:** Restless legs syndrome (RLS) is a sensory motor disorder. It mainly manifests as indescribable pain in the lower limbs at night or at rest, and the symptoms are reduced after activity or beating, which seriously affects the patients sleep. Nowadays, a large number of randomized controlled clinical studies have shown that Chinese medicine has the advantages of good curative effect and high safety in the treatment of RLS. However, due to the various treatment methods of Chinese medicine, its relative effectiveness and safety have not been verified. Therefore, this study will use a network meta-analysis method to verify the effectiveness and safety of different types of TCM therapies in the treatment of RLS.

**Methods:** Computer retrieval was conducted in PubMed, Cochrane Library, Web of Science, Embase, SinoMed, CNKI, WanFang-database, VIP. The retrieval period was until September 9, 2020, and all randomized controlled trials of TCM treatment of RLS were collected. To avoid omissions, we will manually search relevant references and conference papers. According to the inclusion and exclusion criteria, we conduct quality assessment and risk assessment of all retrieved documents. Methodological quality assessment and risk of bias will be assessed using Cochrane bias risk tool. All data analysis will use Revman5.3, WinBUGS 1.4.3, and Stata14.2 software.

**Results:** This study will directly or indirectly compare the effectiveness of different interventions on RLS outcome indicators, and rank the effectiveness. The main outcome indicators include total effective rate (total effective rate = recovery + obvious effective + effective / total number of cases × 100%), International Restless Legs Syndrome Score Scale, secondary outcome indicators include visual analog scale, Pittsburgh sleep quality indicators and adverse events.

**Conclusion:** Provide a basis for evidence-based medicine, and provide a basis for clinical researchers to choose more effective Chinese medicine treatment of RLS.

**Abbreviations:** RCTs = randomized controlled trials, RLS = Restless legs syndrome, TCM = traditional Chinese medicine.

**Keywords:** traditional Chinese medicine, acupuncture, restless legs syndrome, network meta-analysis, protocol

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*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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## 1. Introduction

Restless legs syndrome (RLS) is a clinically common sleep-related sensorimotor disorder, the main clinical manifestations are indescribable paresthesia and discomfort in the lower limbs at rest or night sleep, and a strong desire to move the lower limbs. The symptoms are relieved after the activity and reappear after stopping.<sup>[1]</sup> RLS can be divided into 2 types: primary and secondary according to the presence or absence of primary disease. Primary may be genetically related, and secondary causes include spinocerebellar ataxia, Parkinsons disease, and iron deficiency anemia. Epidemiology shows that in the white adult population, the estimated range of prevalence is 7.2% to 11.5%. The prevalence of RLS increases with age, and women are more likely to be affected than men.<sup>[2]</sup> Western medicine treatment of this disease includes symptomatic treatments such as iron supplementation, improvement of lower limb blood circulation, and analgesia, dopamine receptor agonists are the first choice for the treatment of RLS.<sup>[3]</sup> However, some studies have shown that long-term high-dose dopamine agonists are prone to deterioration, often leading to treatment interruption.<sup>[4]</sup> Therefore, we urgently need to explore more effective and safe treatment methods.

As the traditional medicine of China, traditional Chinese medicine has been passed down to this day because of its

remarkable efficacy and high safety advantages. Traditional Chinese medicine has a history of thousands of years in China and has gradually been recognized by countries all over the world. Chinese medicine is believed to be effective in improving various diseases, including RLS. Traditional Chinese medicine believes that the etiology and pathogenesis of RLS are not single, so there are many corresponding treatment methods, such as traditional Chinese medicine, Chinese patent medicine, acupuncture, moxibustion, and massage. Studies have shown that acupuncture treatment of RLS can trigger the release of analgesic neuropeptides to relieve pain.<sup>[5]</sup> Chinese herbal medicine *Radix Paeoniae Alba* is one of the most commonly used Chinese medicines for the treatment of RLS. It has the functions of relaxing blood vessels, improving distal vascular circulation, regulating and improving blood circulation in extremities.<sup>[6]</sup> At present, some standard meta-analysis shows that TCM is definitely effective in the treatment of RLS,<sup>[7,8]</sup> But all of these are simply a traditional Chinese medicine method compared to a simple Western medicine, and it is impossible to compare multiple Chinese medicine methods. As we know, there are many treatment methods in traditional Chinese medicine, and the advantages of treatment are different, so the choice of which treatment method to use has brought troubles to clinical operators. The network meta-analysis can make positive comparisons of various interventions. Therefore, we will use network meta-analysis to systematically compare the effectiveness and safety of different TCM interventions, and provide evidence-based medicine for clinical researchers.

## 2. Protocol registration

This system review program will strictly follow the system review and meta-analysis program (PRISMA-P) preferred report items for reporting.<sup>[9]</sup> The system review program has been registered on the INPLASY website (the registration number is INPLASY202090041), If there are any adjustments during the entire study period, we will promptly revise and update the detailed information in the final report.

## 3. Methods

### 3.1. Inclusion and exclusion criteria

**3.1.1. Study type.** RCTs based on different Chinese medicine treatments for restless legs syndrome, the language is limited to Chinese and English. Non-RCTs literature, such as conference reports, literature reviews will be excluded; Literatures on other folk remedies besides traditional Chinese medicine will be excluded; Literatures with unavailable data and full text will be excluded; Literatures that do not include the outcome indicators included in this study will be excluded. The most recent one shall be selected for repeated detection and repeated publication.

**3.1.2. Participants.** Patients diagnosed as RLS in accordance with the internationally recognized diagnostic criteria have clear curative effect standards, regardless of age, race, gender, and source of cases. However, the following patients will be excluded:

1. Patients who are unwilling to receive TCM treatment,
2. Patients with serious cardiovascular and cerebrovascular diseases and mental illnesses.
3. Pregnant or lactating women.

**3.1.3. Interventions.** The experimental group only uses traditional Chinese medicine, such as traditional Chinese medicine, proprietary Chinese medicine, acupuncture, moxibustion, and massage. The control group uses Western medicine alone. Both the experimental group and the control group can cooperate with conventional medical treatment.

**3.1.4. Outcome indicators.** The included outcome indicators include 1 or more of the following: The main outcome indicators include total effective rate (total effective rate=rocovery+obvious effective+effective/total number of cases×100%), International Restless Legs Syndrome Score Scale, secondary outcome indicators include visual analog scale, Pittsburgh sleep quality indicators And adverse events.<sup>[10–12]</sup>

## 3.2. Data sources and search strategies

Computer retrieval was conducted in PubMed, Cochrane Library, Web of Science, Embase, SinoMed, CNKI, WanFang-database, VIP. The retrieval period was until September 9, 2020, The search terms are:“traditional Chinese medicine”, “Chinese herbal medicine”, “ Chinese patent medicine”, “Chinese medicine decoction” “acupuncture”, “moxibustion”, “massage”, “Restless legs syndrome”. The search strategy is to combine search terms with subject words and free words. The data retrieval strategy is shown in Figure 1.

Search strategy used in PubMed database.	
NO	Search items
1	Restless legs syndrome
2	RLS
3	Periodic leg movement
4	1 or 2-3
5	Traditional Chinese medicine
6	Chinese herbal medicine
7	Chinese patent medicine
8	Chinese medicine decoction
9	TCM
10	Acupuncture
11	Needle knife
12	Needle scalpel
13	Acupotomy
14	Fire needling
15	Electroacupuncture
16	Massage
17	Tuina
18	Moxibustion
19	5 or 6-18
20	Randomized controlled trial
21	Clinical trial
22	RCT
23	Controlled clinical trial
24	20 or 21-23
25	4 and 19 and 24

Figure 1. Search strategy used in PubMed database.

### 3.3. Selection of studies and data extraction

The 2 evaluators (LTL and RFX) first screened independently according to the literature inclusion and exclusion criteria, and then cross-checked. If there is a difference, the third reviewer can make a decision. Establish a document information extraction table in EXCEL, and extract information including: author, publication time, number of cases, allocation method, intervention measures, treatment course, and outcome indicators, etc.

### 3.4. Risk assessment of bias

Refer to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions to evaluate the risk of bias in the literature finally included in this study. The evaluation criteria include 7 items: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The evaluation results are evaluated in terms of "high risk", "low risk" and "unclear risk".<sup>[13,14]</sup>

### 3.5. Statistical analysis

Using Revman 5.3 software for bias assessment and standard Meta analysis, the outcome indicators were the ratio Ratio (or) of count data, the mean difference (MD) of measurement data, and the 95% confidence interval (95% CI) for the effect. Using WinBUGS 1.4.3 and Stata 14.2 for network meta analysis,<sup>[15,16]</sup> In WinBUGS software, use the Markov Chain Monte Carlo (MCMC) method for Bayesian network Meta analysis. The simulation is carried out through 4 chains, the number of iterations is set to 50,000, among which the first 20,000 times are annealed to eliminate the influence of the initial value, and the step size is set to 10.<sup>[17]</sup> At the same time, the potential scale reduction factor (potential scale reduction factor, PSRF) is used to evaluate the convergence of the results, When the PRSF is close to or equal to 1.00 ( $1.00 \leq \text{PSRF} \leq 1.05$ ), it indicates that the results have good convergence and the obtained results are highly reliable.<sup>[18]</sup> At the same time, Stata software is used to calculate the SUCRA (surface under the cumulative ranking curves, SUCRA) value and the area under the SUCRA curve in order to rank the efficacy of various interventions. The value range is 0 to 100. The larger the value and the larger the area under the curve, the better the effect of the intervention.

### 3.6. Assessment of inconsistency

Since this study involves many intervention measures, in the evidence network of each outcome indicator, the closed loop formed by the research with direct evidence and indirect evidence needs to be tested for inconsistency through Stata software. Calculate the inconsistency factor (IF), and judge whether there is inconsistency through the IF value and the P value.<sup>[19]</sup> If IF is close to 0, 95%CI starts at 0, and  $P > .05$ , it is considered that the results of direct comparison and indirect comparison are consistent. At the same time, the node-split model is used to determine whether each node has local inconsistencies.<sup>[20]</sup> If  $P > .05$ , the consistency model is adopted, otherwise, the inconsistency model is adopted. For the results obtained from the consistency model analysis, the stability of the results can be checked through the inconsistency model, when the inconsistency factors include 0 and the inconsistency standard deviation

includes 1, and the random standard deviation of the consistent effect model is approximately equal to the standard deviation of the inconsistency model, the consistency model results are more stable and reliable.<sup>[21,22]</sup>

### 3.7. Heterogeneity, subgroup analysis, sensitivity analysis

The heterogeneity between trials is quantified by  $I^2$  and  $P$  values.<sup>[23]</sup> For test results with obvious heterogeneity, the source of the heterogeneity should be analyzed. According to the different sources of heterogeneity, subgroup analysis can be carried out, such as treatment time, course of disease, underlying disease, race, gender, age, etc. If there is no clear source of heterogeneity, only descriptive analysis can be performed. The purpose of sensitivity analysis is to eliminate low-quality studies and different statistical models.<sup>[24]</sup> Observe the heterogeneity of different experiments, observe whether the combined results change after different treatments, and analyze the strength, reliability and stability of the results.

### 3.8. Assessment of publication bias

If the outcome indicators include in study  $\geq 10$ , We will use a funnel chart to assess publication bias.<sup>[25]</sup> If the funnel chart appears asymmetry or the distribution is different, it indicates publication bias or small sample effect.

### 3.9. Ethics and dissemination

Since this is a protocol for systematic reviews and network meta-analysis, all data in this study comes from published studies and does not involve patients, so ethical approval is not required. The results of this research will be distributed to peer-reviewed journals and published in relevant conferences.

## 4. Discussion

In recent years, with the continuous development and improvement of the TCM career, more and more clinical randomized controlled trials have shown that TCM treatment of RLS has the characteristics of significant efficacy and low side effects, indicating that TCM treatment of RLS has accumulated rich experience and achieved certain results. Standard meta-analysis can only make a single comparison, while network meta-analysis can compare multiple interventions in pairs. We will use the method of network meta-analysis to compare several different traditional Chinese medicine interventions to get a ranking of effectiveness and safety, so as to provide evidence-based medicine for clinical decision-makers.

### Author contributions

**Conceptualization:** Liting Liu.  
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**Writing – original draft:** Liting Liu.  
**Writing – review & editing:** Chunhua Huang, Liting Liu.

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