Efficacy and safety of Shaoyao Gancao Tang for restless leg syndrome: A systematic review and meta-analysis

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Abstract

Restless leg syndrome (RLS) is a common and chronic neurological disease characterized by an irresistible and overwhelming urge to move the legs. In recent years, a growing body of clinical trials has demonstrated that traditional Chinese herbal medicine Shaoyao Gancao Tang (SG-Tang) may improve RLS. However, a critical examination of the available evidence is warranted. This study aimed to evaluate the efficacy and safety of SG-Tang in the treatment of RLS. The protocol of this study was registered and published at International Prospective Register of Systematic Reviews (PROSPERO; CRD42020173520). Randomized clinical trials (RCTs) on the efficacy and safety of SG-Tang in the treatment of RLS were identified by searching the Cochrane Library, PubMed, EMBASE, Web of Science, the Chinese Biological Medicine Database, China National Knowledge Infrastructure, Wanfang Database, and VIP Information Database from inception to February 14, 2022. The primary outcome measurements were the total effective rate, and the secondary outcome measurements included the International Restless Legs Syndrome Study Group Rating Scale for Severity of Restless Legs Syndrome (IRLS), the Pittsburgh Sleep Quality Index (PSQI), and the incidence of adverse events. The Review Manager 5.3 software was utilized to conduct quantitative synthesis according to the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Six eligible RCTs were included in this meta-analysis. Compared to conventional medications, SG-Tang intervention showed significant improvements in the total effective rate (risk ratio [RR] = 1.22, 95% confidence interval [CI] (1.09,1.36), \( P = 0.004 \)), the IRLS (mean difference [MD] = −4.74, 95% CI (−8.65, −0.83), \( P = 0.02 \)), and the PSQI (MD = −2.54, 95% CI (−4.34, −0.74), \( P = 0.006 \)) with less incidence of adverse events (RR = 0.21, 95% CI (0.09, 0.31), \( P = 0.0005 \)). SG-Tang may be effective and safe as a complementary and alternative treatment to relieve RLS. However, the results need to be interpreted with caution because of limited data and the undesirable methodological quality of the included studies. More well-designed, large-scale, high-quality, and multi-center RCTs are required to be performed for further verification.

Keywords: restless leg syndrome; natural products; Shaoyao Gancao Tang; effectiveness; safety
Introduction

Restless legs syndrome (RLS, also known as Willis–Ekbom disease [WED]) was first described by Sir Thomas Willis in 1672 as “...so great a Restlessness and Tossing of their Members ensue, that the diseased are no more able to sleep, than if they were in a Place of the greatest torture” (Ekbom, 1960). It is a chronic and neurological disorder characterized by an irresistible urge and restlessness to move the legs. Its clinical symptoms commonly occur and exacerbate in evening and night or at rest, and are temporarily alleviated upon movement (Gossard et al., 2021). Epidemiological studies have demonstrated the commonality of RLS affecting approximately 5–14.3% of the general population, and the prevalence increases with age (Ohayon et al., 2012; Rubi, 2018; Wijemanne and Ondo, 2017). Compelling evidence has demonstrated that RLS impairs sleep quality and quantity, triggers anxiety and depression, and is associated with hypertension, cardiovascular disorders, and cerebrovascular diseases (Trenkwalder et al., 2018). It significantly impairs patients’ health-related quality of life with the loss of work productivity; therefore, just as Dr. Ekbom wrote in 1960 “…the syndrome is so common and causes such suffering that it should be known to every physician.”

The explicit pathogenesis of RLS is still ambiguous but has been well-recognized as a complex condition attributed to predisposing genetic factors, iron deficiency, dysfunctional dopaminergic and nociceptive systems, altered adenosine and glutamatergic pathways, environmental factors, and such comorbidities as renal disease and diabetes mellitus (Vellieux and d’Ortho, 2020). Currently, its therapeutic options include iron preparations, opioids, and dopamine agonists, such as pramipexole, ropinirole, and rotigotine (Wijemanne and Ondo, 2017). However, potential side effects, including sleepiness, fatigue, dizziness, and augmentation risks with dopaminergic medications, reduce their compliance (Anguelova et al., 2020), yielding a therapeutic field sorely in need of innovation. Consequently, in recent years, increasing attention has been paid to natural products.

Shaoyao Gancao Tang (SG-Tang; to date also known as Jakjakgamcho-tang in South Korea and Shakuyaku-kanzo-to in Japan) has a time-honored history of treating RLS that can be dated back to over 1,800 years when Dr. Zhongqiing Zhang (150–219 AD) recorded his clinical thoughts and experiences of halting restlessness, spasms, and cramps in legs in his works Treatise on Cold Damage (Shanghan Lun, also known as the “Bible” of traditional Chinese medicine [TCM]). SG-Tang consists of Paeoniae Radix Alba and Glycyrrhizae Radix et Rhizoma in a ratio of 1:1, and is reported to exert desirable effects on RLS because of its multiple well-documented pharmacological actions, including spasmolysis, analgesic effect, anti-inflammatory, sedation, and neuroprotection (Chen et al., 2018; Lee et al., 2013). Moreover, its component Glycyrrhizae Radix et Rhizoma (also named glycyrrhiza or “Gan-Cao” in China and licorice or liquorice in Europe) is of a food and medicine continuum, and in 2002, Paeoniae Radix Alba was listed by the Ministry of Health of China as a Chinese material medica that can be used to prepare food for health preservation (Heinrich et al., 2021; National Health Commission of the People’s Republic of China, 2002).

In recent years, a growing body of randomized controlled trials (RCTs) has been performed to investigate the effectiveness and safety of SG-Tang in the treatment of RLS.

However, systematic reviews and meta-analyses that summarized and assessed the relevant evidence remain unreported. Consequently, this study aimed to evaluate systematically the effectiveness and safety of SG-Tang in RCTs for treating RLS, hopefully providing useful information for the patients and physicians with an evidence-based approach.

Methods

The protocol of this review was registered and published on International Prospective Register of Systematic Reviews (PROSPERO; CRD42020173520; Chen et al., 2020). This meta-analysis was performed with RevMan (version 5.3) (The Cochrane Collaboration, NCC, Copenhagen, Denmark) by following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2009).

Search strategy

Two reviewers (Ying Xiong and Rong Li) independently searched Cochrane library, PubMed, EMBASE, Web of Science, the Chinese Biological Medicine Database, China National Knowledge Infrastructure, Wanfang Database, and VIP information database from inception to February 14, 2022. The search was conducted to identify eligible studies without any restriction of language using the following terms in a combination: restlessness leg syndrome, RLS, Willis–Ekbom disease, periodic leg movement, quiescogenic focal akathisia, Shaoyao Gancao Tang, SG-Tang, Shakuyakukanzo, SKT, Paonia lactiflora and Glycyrrhiza uralensis decoction, and Chinese peony and licorice combination, as randomized control, randomization, randomized clinical trials, RCT, and trials. Additionally, the references of retrieved studies were manually searched. Any inconsistency was solved by a
third reviewer (Zhining Tian). The specific search strategy for PubMed is shown in the supplementary material. This has been modified correspondingly to accommodate the requirements of different databases.

Eligibility criteria

The retrieved studies were deemed eligible if they fulfilled the following pre-specified inclusion criteria: (1) type of study: RCT; (2) population: patients with RLS, regardless of age, gender, source of cases, duration of disease, ethnicity, or nationality; (3) intervention: SG-Tang treatment (no restriction on the mode and dosage of administration and course of treatment) clearly stated in the trial group either solely or in combination with other treatments versus conventional treatment, placebo, or no treatment; and (4) outcome variables: the total effective rate, the International Restless Legs Syndrome Study Group Rating Scale for Severity of Restless Legs Syndrome (IRLS), the Pittsburgh Sleep Quality Index (PSQI), and the incidence of adverse events. Non-RCTs, reviews, animal-based research, conference proceedings, literature review, studies with unclear diagnostic criteria and absence of outcome measurements, reports unable to obtain original data or complete information of the trial, and duplicated publications were excluded.

Outcome measurements

Primary outcomes were the total effective rate, and the secondary outcomes included IRLS, PSQI, and the incidence of adverse events. The “total effective rate” was predefined as the sum of cured, markedly effective, and effective rates of certain therapeutic interventions in which, “cure” was the disappearance of RLS symptoms; “markedly effective” was the significant remission of RLS symptoms; “effective” was relieving of RLS symptoms; and “ineffective rate” meant no remission of symptoms.

Total effective rate = Cured + Markedly Effective + Effective) ÷ Total Number of Cases × 100%.

Study selection

Two reviewers (Zhining Tian and Ying Xiong) independently screened the titles and abstracts of eligible studies and then reviewed the full text following the pre-specified eligibility criteria. Disagreements were solved by the third reviewer (Yunhui Chen).

Data extraction

Two reviewers (Ying Xiong and Zhining Tian) independently extracted the following information: reference ID, name of the first author, year of publication, name of the journal, design of the trial, characteristics of the patient, details of the trial intervention, details of control intervention, outcome measurements, and adverse events. Disagreements were solved by the third reviewer (Yunhui Chen). All data were cross checked and imported into the RevMan software (version 5.3).

Risk of bias assessment

Two reviewers (Ying Xiong and Jingwen Wei) independently applied the Cochrane Handbook for Systematic Reviews of Interventions to assess the methodological quality of the included studies in terms of the following seven domains: random 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 was evaluated and ranked as “low-risk,” “unclear,” and “high-risk” (Higgins et al., 2019). Any discrepancy was referred to the third reviewer (Jun Xia).

Statistical analysis

The RevMan (version 5.3) software was utilized for meta-analysis. A risk ratio (RR) with 95% confidence interval (95% CI) was used for dichotomous variables, while a mean difference (MD) with 95% CI was applied for continuous data. Statistical heterogeneity was investigated using the Chi-square and heterogeneity (I²) statistics. The random-effects model was applied when heterogeneity (I² ≥ 50%) existed in the pooled studies; otherwise, the fixed-effects model was employed. The difference was deemed as statistically significant at P < 0.05. Sensitivity analysis was performed to evaluate the robustness of the pooled effects of studies. Publication bias was evaluated with a funnel plot.

Results

Eligible studies

Following the search strategy, 61 relevant studies were retrieved from the mentioned electronic databases. After excluding 12 duplicate publications, the abstract and title of 49 studies were reviewed to exclude 21 articles. Then, 22 studies were excluded upon full-text screening for the following reasons: 18 studies of expert opinion, case report, or without comparison; three reviews; and one trial without accessibility to the full text. Eventually, six eligible studies were included in this meta-analysis (Huang and Rao, 2018; Li et al., 2020; Liu and Wang, 2015; Xue et al., 2014; Zhang, 2017; Zhao et al., 2019).
The PRISMA flowchart of the study selection and identification process is presented in Figure 1.

**Characteristics of included studies**

Six RCTs enrolling 331 participants (170 in trial groups and 161 in control groups) were included in this meta-analysis (Huang and Rao, 2018; Li et al., 2020; Liu and Wang, 2015; Xue et al., 2014; Zhang, 2017; Zhao et al., 2019). All these studies were conducted in China and published in Chinese. The diagnosis of RLS was clearly identified in all studies. In the included RCTs, patients in the intervention group received STG decoction exclusively in two studies (Huang and Rao, 2018; Zhang, 2017) and together with conventional drugs in three studies (Liu and Wang, 2015; Xue et al., 2014; Zhao et al., 2019) and acupuncture in one study (Li et al., 2020). All patients in the control group were treated with conventional drugs, including Madopar in two trials (Xue et al., 2014; Zhang, 2017), pramipexole in three trials (Huang and Rao, 2018; Liu and Wang, 2015; Zhao et al., 2019), and carbamazepine in one trial (Li et al., 2020). The duration of the treatment varied from 4 to 12 weeks. For outcome variables, five trials presented the total effective rate (Huang and Rao, 2018; Li et al., 2020; Liu and Wang, 2015; Zhang, 2017; Zhao et al., 2019), four trials reported the IRLS (Huang and Rao, 2018; Li et al., 2020; Wijemanne and Ondo W, 2017; Xue et al., 2014; Zhao et al., 2019), four trials evaluated the PSQI (Huang and Rao, 2018; Li et al., 2020; Xue et al., 2014; Zhao et al., 2019), and two trials stated adverse events (Huang and Rao, 2018; Xue et al., 2014). The characteristics of the included studies are summarized in Table 1.

**Assessment of methodological quality**

Generally, the quality of the included RCTs in this review was methodologically poor. Four of the six studies were rated as unclear risk because they just mentioned “random” and did not explicitly describe the generation methods (Huang and Rao, 2018; Liu and Wang, 2015; Zhao et al., 2019), and two trials stated adverse events (Huang and Rao, 2018; Xue et al., 2014). The results of risk of bias evaluation are presented in Figure 2.
Assessment of efficacy and safety

Total effective rate

Five of the six trials reported the total effective rate (Huang and Rao, 2018; Li et al., 2020; Liu and Wang, 2015; Zhang, 2017; Zhao et al., 2019). A fixed effects model was applied due to no significant heterogeneity ($I^2 = 3\%$, $P = 0.39$). The pooled effect of meta-analysis demonstrated that the total effective rate in the patients treated with SG-Tang was significantly higher than conventional therapy (RR = 1.22, 95% CI (1.09, 1.36), $P = 0.004$) (Figure 3A).

IRLS

Four trials reported changes in the IRLS (Huang and Rao, 2018; Li et al., 2020; Xue et al., 2014; Zhao et al., 2019). A random-effects model was utilized due to significant heterogeneity ($F = 78\%$, $P = 0.004$). The pooled effect of meta-analysis demonstrated that compared to the control group, the SG-Tang trial group exhibited statistically significant decrease in the PSQI (MD = −2.54, 95% CI (−4.34, −0.74), $P = 0.006$) (Figure 3C).

Adverse events

Two trials reported adverse events (Huang and Rao, 2018; Xue et al., 2014), including dizziness, weary, nausea, and vomiting. A fixed-effects model applied as the heterogeneity was not significant ($I^2 = 0\%$, $P = 0.87$). The pooled effect of the meta-analysis showed that the incidence of adverse events in the SG-Tang treatment group was significantly less than that of the conventional group (RR = 0.21, 95% CI (0.09, 0.31), $P = 0.0005$) (Figure 3D).

Sensitivity analysis

Sensitivity analysis demonstrated that eliminating any individual trial for the total effective rate did not alter the pooled effect, suggesting that the results of the meta-analysis were relatively robust (Figure 4).

Table 1. Characteristics of included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Sample size (T/C)</th>
<th>Average age (T/C)</th>
<th>Course of disease (T/C)</th>
<th>Diagnostic criteria</th>
<th>Intervention</th>
<th>Treatment duration</th>
<th>Outcome variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xue et al.</td>
<td>2014</td>
<td>26/20</td>
<td>75.15/74.50</td>
<td>–</td>
<td>CMA criteria 2009</td>
<td>SG-Tang and Madopar</td>
<td>30 days</td>
<td>②+③+④</td>
</tr>
<tr>
<td>Liu and Wang</td>
<td>2015</td>
<td>25/25</td>
<td>–</td>
<td>41.2 ± 8.1 months</td>
<td>IRLSSG criteria 2003</td>
<td>SG-Tang, Banxia Xie Xin decoction, and pramipexole</td>
<td>8 weeks</td>
<td>①</td>
</tr>
<tr>
<td>Zhang</td>
<td>2017</td>
<td>28/25</td>
<td>57.4/59.5</td>
<td>9 to 16 months/8 to 77 months</td>
<td>IRLSSG criteria 2003</td>
<td>SG-Tang</td>
<td>Madopar</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Huang and Rao</td>
<td>2018</td>
<td>32/32</td>
<td>47.3/44.5</td>
<td>44.5 ± 6.4 months/6.2 ± 8.3 months</td>
<td>IRLSSG criteria 2003</td>
<td>SG-Tang</td>
<td>Pramipexole</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Zhao et al.</td>
<td>2019</td>
<td>21/21</td>
<td>68/–</td>
<td>–</td>
<td>IRLSSG criteria 2014</td>
<td>SG-Tang and pramipexole</td>
<td>4 weeks</td>
<td>①+②+③</td>
</tr>
<tr>
<td>Li et al.</td>
<td>2020</td>
<td>38/38</td>
<td>59.94/58.62</td>
<td>3.1 ± 2.6 years/4.1 ± 2.2 years</td>
<td>IRLSSG criteria 2014</td>
<td>SG-Tang and acupuncture</td>
<td>Carbamazepine</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

T: treatment group; C: control group; –: not reported; CMA: Chinese Medical Association; IRLSSG: International Restless Legs Syndrome Study Group; SG-Tang: Shaoyao Gancao decoction; ①Total effective rate; ②IRLS: International Restless Legs Syndrome Study Group Rating Scale for Severity of Restless Legs Syndrome; ③PSQI: Pittsburgh Sleep Quality Index; ④Adverse events.

A random-effects model was utilized due to significant heterogeneity ($F = 78\%$, $P = 0.004$). The pooled effect of meta-analysis demonstrated that compared to the control group, the SG-Tang trial group exhibited statistically significant decrease in the PSQI (MD = −2.54, 95% CI (−4.34, −0.74), $P = 0.006$) (Figure 3C).
Publication bias

Publication bias was evaluated using the inverted funnel plot analysis in terms of the effective rate. The funnel plot displayed a slight asymmetry, suggesting minor possibility of publication bias (Figure 5).

Discussion

Research in RLS has increased dramatically over the past decades. Although a cure for RLS is not available yet, appropriate treatment can keep the disease under control, minimize its symptoms, and improve patients’ quality of life. IRLS has been extensively applied as the gold-standard outcome measure in almost all clinical trial settings of RLS. It was specifically developed for RLS severity scaling with desirable clinimetric properties to investigate responsiveness to changes (Walters et al., 2003). The results of this meta-analysis have displayed overall (pooled) improvements in the total effective rate and IRLS, indicating that SG-Tang might yield an effective complementary and alternative approach in the treatment of RLS. Moreover, as impaired sleep...
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quantity and quality are the most frequent complaints in RLS, besides efficacy parameters, the PSQI has been utilized as well in the clinical trial settings of RLS as the most common measure of sleep quality with high validity and reliability (Didato et al., 2020; Pilz et al., 2018). The PSQI-rated results in this study showed that the quality of sleep was improved significantly for patients receiving SG-Tang, suggesting an associated relationship between alleviated RLS symptoms and improved sleep. In sum, these findings indicate that SG-Tang, either solely or in combination with other interventions, can significantly improve the total effective rate, IRLS, and PSQI with fewer adverse effects for RLS patients.

Pathologically, RLS is considered a complex disease attributable to the overall dysfunction of the body. Therefore, physicians should be concerned about the local pathology and, most importantly, must identify...
and analyze the underlying multifactorial dysfunction to provide appropriate treatment. In recent years, various effective compounds, such as flavonoids, triterpene glycosides, monoterpenoid glycosides, phenolic acids, tannins, alkaloids, and saccharides, have been identified from this formula (Wu et al., 2021). Furthermore, a compelling body of research has demonstrated that its pharmacological effects of spasmylosis, analgesic, sedative, hypnotic, and neuroprotection could be associated with its ingredients of paeoniflorin, benzoyl paeoniflorin, albiflorin, paeoniflorin oxide, glycyrrhizic acid, liquiritin, isoliquiritigenin, and ammonium glycyrrhetate, which may act synergistically to treat RLS with improved symptoms and better sleep quantity and quality (Gu et al., 2016; Huang et al., 2019; Ji, 2003; Yin et al., 2016; Zhu et al., 2015).

Although the effectiveness and safety of SG-Tang for RLS treatment were meta-analyzed, this study has several limitations: (1) considerably high heterogeneity was notified in the outcome measurements of IRLS and PSQI, and the possible reasons could be the small sample size and different baseline conditions of each included trial. However, subgroup analysis cannot be conducted due to the limited number of studies, which could affect the accuracy and practicality of the results; (2) a limited number of studies were included, and the sample size of the studies was small, which carried a considerable risk of overrating the effectiveness and could result in downgraded confidence levels in results; (3) most RCTs were poor in methodological quality and could also result in overestimation of the therapeutic effect; (4) there was no consistent criteria for the effectiveness and therapeutic duration across studies; (5) only published RCTs were retrieved. The search strategy did not cover gray literature or preprint, which could have resulted in an overestimated pooled outcome; and (6) although the literature was searched without language restrictions, all the publications were from China and might have caused publication bias.

In addition, large-size, well-designed, and high-quality studies are required to tackle several key problems unresolved by the available studies, including: (1) allowing confidence in the evaluation of therapeutic benefits of SG-Tang, currently based on small studies with few participants and without follow-up or followed for a relatively shorter period; (2) understanding the effect of SG-Tang intervention on such variables in patients with RLS as the quality of life and sleep quantity and quality; and (3) optimal timing of SG-Tang intervention and monitoring of patients’ treatment responses based on the severity of RLS.

Conclusion

In summary, this study demonstrates that Shaoyao Gancao Tang may be effective and safe for RLS as a complementary and alternative approach to conventional therapy. However, the results are required to be interpreted with caution because of the limited data and the low methodological quality of the included studies, and further verified with more well-designed and high-quality multi-center RCTs in a larger sample size.

Author contributions

Yunhui Chen, Zhining Tian, and Dan Liu conceptualized the study. Rong Li, Ying Xiong, and Zhining Tian did data curation for this study. Formal analysis of the data was exercised by Ying Xiong, Jingwen Wei, Wenying Huai, and Yunhui Chen. Yunhui Chen acquired funding for this research. Ying Xiong, Jingwen Wei, and Yunhui Chen carried investigations. Methodology was undertaken by Ying Xiong and Yunhui Chen. Yunhui Chen acquired funding for this research. Ying Xiong, Jingwen Wei, and Yunhui Chen carried investigations. Methodology was undertaken by Ying Xiong and Yunhui Chen. Yunhui Chen did project administration and supervision. Validation of the study was done by Jingwen, Hua Jiang, and Jun Xia. Original draft of the study was written by Zhining Tian, Yunhui Chen, Ying Xiong, and Jingwen Wei. Finally, Yunhui Chen and Ying Xiong wrote, reviewed, and editing the paper.

Funding statement

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and analysis, decision to publish, or preparation of the manuscript.

**Competing interests**

The authors declared that no competing interests existed.

**Availability of data, code, and other material**

All relevant data are within the manuscript and its supporting information files.

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Walters AS, LeBrocq C, Dhar A, et al., 2003. Validation of the International Restless Legs Syndrome Study Group rating...
Tian Z et al.


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Table S1. Search strategy for the PubMed.

<table>
<thead>
<tr>
<th>No.</th>
<th>Search terms</th>
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<tbody>
<tr>
<td>1</td>
<td>Restless Legs Syndrome [Mesh]</td>
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<tr>
<td>2</td>
<td>Restless Legs</td>
</tr>
<tr>
<td>3</td>
<td>Willis–Ekbom Disease</td>
</tr>
<tr>
<td>4</td>
<td>Disease, Willis–Ekbom</td>
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<tr>
<td>5</td>
<td>Wittmaack–Ekbom Syndrome</td>
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<tr>
<td>6</td>
<td>Syndrome, Wittmaack–Ekbom</td>
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<tr>
<td>7</td>
<td>Willis–Ekbom Disease</td>
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<td>8</td>
<td>Disease, Willis–Ekbom</td>
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<td>9</td>
<td>Willis–Ekbom Syndrome</td>
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<td>RLS</td>
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<td>periodic leg movement</td>
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<td>quiescegenic focal akathisia</td>
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<td>OR 1–19</td>
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<td>Shaoyao Gancao Tang</td>
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<td>SG Tang</td>
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<td>Shakuyakukanzoto</td>
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<td>24</td>
<td>SKT</td>
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<td>25</td>
<td>Paeonia lactiflflora and Glycyrrhiza uralensis decoction</td>
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<td>Chinese Peony and Licorice Combination</td>
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<td>OR 21–26</td>
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<td>28</td>
<td>randomized controlled trial [pt]</td>
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<td>trial [tiab]</td>
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