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The efficacy and safety of moxibustion for chronic fatigue syndrome
A protocol for systematic review and meta-analysis

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Abstract

Background: The pathogenesis of chronic fatigue syndrome (CFS) is not clear. The main purpose of treatment is to improve autoimmune function and relieve fatigue symptoms. Moxibustion is often used to treat diseases caused by low autoimmunity, especially in relieving fatigue symptoms. It is a superior therapy for CFS in traditional Chinese medicine. At present, there is a lack of the high level clinical evidence to support the moxibustion in the treatment of CFS, so this study will systematically review and analyze the currently available randomized controlled trials to evaluate the efficacy and safety of moxibustion in the treatment of CFS.

Methods: We will systematically search PubMed, EMBASE, Cochrane library, Sinomed, CNKI, VIP, and Wanfang Database, ClinicalTrials.gov and Chinese Clinical Trial Registry will also be searched. The time range for the search will be from database activation to March 31, 2021. The randomized controlled trials (RCTs) associated with moxibustion for CFS will be included, regardless of language.

We will use the standard proposed in Cochrane Handbook 5.1.0 to assess the bias risk of a single RCT. The main outcome index of the study is Fatigue Assessment Instrument (FAI), secondary outcome indexes will include Fatigue Scale -14 (FS-14), Fatigue Severity Scale (FSS), Pittsburgh sleep quality index (PSQI), natural killer (NK) cells, interleukin- 2 (IL-2), T lymphocyte subsets (CD_4^+ , CD_8^+), cure rate, total efficiency and adverse reactions. The random effect model meta was used to analyze the effect data of a single RCT. Heterogeneity will be measured by Cochran Q test and I-squared statistics. We will use 2 subgroup analyses to explore the source of heterogeneity. RCTs with high bias risk was excluded and adjustment effect model was used for sensitivity analysis to test the robustness of the meta-analysis results. The publication bias included in RCTs will be assessed by funnel plot and Egger test.

Results: This study will objectively and comprehensively evaluate the efficacy and safety of randomized controlled trials of moxibustion in the treatment of chronic fatigue syndrome, and the results will be submitted to peer-reviewed journals for publication.

Conclusion: This systematic review will provide clinicians with the latest high-quality evidence for the use of moxibustion in the treatment of chronic fatigue syndrome.

INPLASY registration number: INPLASY202140063.

Abbreviations: CFS = chronic fatigue symdrome, RCT = randomized controlled trial.

Keywords: chronic fatigue syndrome, meta-analysis, moxibustion, protocol, systematic review

1. Introduction

1.1. Description of the condition

Chronic fatigue syndrome is a worldwide disease of unknown cause, which is characterized by long-term extreme fatigue for more than 6 months, accompanied by inattention, memory loss, sleep disorders, and many other nonspecific symptoms.[1] Chronic fatigue significantly reduces the quality of patients' life and even may induce dysfunction, which has become one of the most severe public health problems in the world.[2] A recent systematic review showed that the prevalence of CFS ranges from 0.01% to 7.62%, and the prevalence of women is 1.5 to 2 times higher than that of men.[3] A previous study found that only 13% of CFS patients were able to stick to their jobs, more than 25% of CFS patients were forced to be isolated at home, and severe cases were bedridden.[4] At present, the etiology and pathogenesis of CFS are not yet clear, and the neuro-endocrine-immune network may be the key link in the pathogenesis of CFS.[5] Modern medicine mainly supports the treatment of CFS such as anti-

anxiety, immune regulation, and nutritional supplementation, but the effectiveness is still controversial.[6–8]

1.2. Description of the intervention

The origin of moxibustion can be traced back to primitive society.[9] It is an external treatment method that burns moxa, produces moxa smoke, and applies heat to acupoints or lesions on the body surface to prevent and cure diseases.[10] Moxa is the most commonly used moxibustion material. Burning of moxa has the effect of warming yang and dispelling cold, activating meridians, and strengthening the body, especially suitable for chronic weakness diseases such as CFS. Moxibustion can be divided into direct moxibustion that burns moxa directly above the skin,[11] and indirect moxibustion that separates media between moxa and the skin (such as ginger, garlic, salt, medicinal cake, etc).[12] Indirect moxibustion combines the effects of moxa and the medium, and the synergistic effect can be achieved by transdermal administration of moxa heat. Studies have shown that moxibustion can effectively relieve fatigue,[13,14] and improve sleep quality,[15] pain and paresthesia,[16] gastrointestinal dysfunction,[17] and other CFS-related symptoms.

1.3. How the intervention might work

The mechanism of moxibustion in the treatment of chronic fatigue syndrome may be related to neuroendocrine, immune inflammation, energy metabolism and so on. Yi et al found that moxibustion can increase the expression of procorticotropin mRNA and protein in the hippocampus, and relieve the fatigue symptoms of CFS rats by inhibiting the excessive activity of the hypothalamus-pituitary-adrenal axis.[18] Studies have shown that the proinflammatory cytokine IL-6 may be an essential factor in inducing fatigue.[19] Several teams have proposed that moxibustion can regulate the levels of peripheral and central proinflammatory cytokine IL-6 and anti-inflammatory cytokine IL−10 to help rats recover from fatigue.[20–22] Moxibustion can regulate the energy metabolism of rats with exercise-induced fatigue. Lu et al found that moxibustion can increase the liver glycogen content of exhausted fatigue rats.[23] Gao et al also confirmed that moxibustion can significantly up-regulate the glycogen content of the gastrocnemius muscle of fatigued rats, reduced the level of lactic acid, and delayed the occurrence of exercise-induced fatigue.[24]

1.4. Why it is important to perform this review

Moxibustion does not invade the body, nor does it need to bear the toxic and side effects of drug metabolism. It is one of the most popular treatment methods for patients. However, due to insufficient evidence of clinical efficacy, as another important part of acupuncture therapy in addition to "needle," "moxibustion" is not as popular as "needle therapy" in both Eastern and Western countries, people often mistakenly believe that acupuncture is just a treatment method about needling. Some systematic reviews and meta-analyses combine moxibustion and needle therapy as a whole, but there is few systematic review and meta-analysis for moxibustion alone. With the publication of more and more randomized controlled trials of moxibustion in the treatment of CFS, it is necessary to use comprehensive and accurate retrieval methods to evaluate the effectiveness and safety of moxibustion in the treatment of CFS, which will help clinical doctors, researchers and patients to understand the safety and efficacy of moxibustion in the treatment of CFS, providing evidence support for clinical decision-making.

1.5. Objective

The efficacy and safety of moxibustion in the treatment of CFS will be evaluated by systematically reviewing and analyzing the currently available randomized controlled trials.

2. Methods

2.1. Study registration

The program was registered on the INPLASY platform (Registration Number:INPLASY202140063, https://inplasy.com/inplasy-2021-4-0063). We reported the program according to the preferred reporting program of the systematic review and meta-analysis program (PRISMA-P).[25]

2.2. Inclusion and exclusion criteria

2.2.1. Type of study.
We will include the randomized controlled trials of moxibustion in the treatment of CFS, whether published or not. However, case reports and comments, clinical studies comparing different types of moxibustion, randomized crossover trials, animal trials, and the literature only published in the form of abstracts will be excluded. For republished research, the RCT with the latest results and the longest follow-up period will be selected.

2.2.2. Participants.
We will include patients according to the criteria of the US CDC definition (1988[26] or 1994[1]) for CFS, without restrictions on gender, age, course of disease, severity, and source of cases.

2.2.3. Interventions and controls.
Moxibustion that ignites moxa and produces moxa smoke and temperature is the intervention measure concerned in this study. We do not restrict the production forms of moxa (moxa cone, moxaroll), nor the types of moxibustion (direct moxibustion, indirect moxibustion), but electronic moxibustion will be excluded. We will include the following 2 types of randomized controlled trials:

1. The experimental group uses moxibustion alone to treat CFS, and the control group uses other methods except moxibustion to treat CFS;
2. The experimental group uses moxibustion combined with other methods to treat CFS, and the control group uses the same combined method alone as the experimental group to treat CFS.

2.2.4. Outcomes

2.2.4.1. Primary outcomes.
The main outcome is Fatigue Assessment Instrument (FAI).[27]

2.2.4.2. Secondary outcomes.
Secondary outcome: Fatigue Scale-14 (FS-14), Fatigue Severity Scale (FSS), Pittsburgh Sleep Quality Index (PSQI), natural killer (NK) Cells, interleukin 2 (IL-2), T lymphocyte subsets (CD_4^+, CD_8^+), cure rate, total efficiency, and adverse reactions.

2.3. Data sources and search strategy

We will systematically search 7 major databases [PubMed, EMBASE, Cochrane library, Sinomed, CNKI (China National

Table 1

Search strategy in PubMed.

No.	Search terms
1	chronic fatigue syndrome[mh]
2	chronic fatigue syndrome[tw]
3	chronic fatigue [tw]
4	fatigue syndrome[tw]
5	fatigue disorder[tw]
6	fatigue fibromyalgia syndrome[tw]
7	myalgic encephalomyelitis[tw]
8	#1 OR #2 OR #3 OR #4OR #5OR #6OR #7
9	moxibustion[tw]
10	moxibustion therapy [tw]
11	#9 OR #10
12	animals[mh]
13	humans[mh]
14	#8 AND #11
15	#12 NOT #13
16	#14 NOT #15

Knowledge Infrastructure), VIP (Chinese Scientific Journals Database) and Database Wanfang] and collect the RCTs of moxibustion treatment of CFS. The time range of the search will be from the database to March 31, 2021. We will use a combination of medical subject words and free words to search for terms such as "Chronic Fatigue syndrome," "chronic Fatigue ," "and Moxibustion," a search strategy in PubMed was listed in Table 1. For including more studies, we will also search the 2 trial registration platforms ClinicalTrials.gov and Chinese Clinic Trials.gov, as well as references from related reviews.

2.4. Data collection and analysis

2.4.1. Study selection. The retrieved research literature will be imported into Endnote X9 (clarivate analytics US LLC) to exclude repetitive literature. Two reviewers will screen the literature independently and repeatedly. Firstly, irrelevant literature will be excluded by reading the title and abstract, and then the full text will be further checked to determine whether to include it. The reviewers will cross-check the results, they will return to the screen together when there is difference, and consult the third reviewer to resolve them if necessary. The flow chart of APRISMA-style literature screening is shown in Figure 1.

2.4.2. Data extraction. We will use the standardized tables to extract data from included RCTs. It consists of 3 parts group to:

1. Publishing features: title, first author, establishments, journals, and publication date;
2. patients and treatment: sex, age, source of the patients, sample size, with or without blinding, moxibustion site, moxibustion strength, duration of treatment, adverse reactions, adverse events, follow-up time, loss rate, and reasons;
3. outcome data: baseline and follow-up measurement of each index.

2.4.3. Risk of bias assessment. The risk of bias included in the RCTs will be obtained using the risk of bias assessment tool in the Cochrane Handbook 5.1.0.[28] It includes 7 projects:

1. random sequence generation method,
2. allocation concealment method,
3. blinding method of clinicians and patients,
4. blinding method of result evaluators,
5. completeness of data,
6. selective reporting, and
7. other sources of bias.

Items 1 and 2 indicates selection bias, while items 3, 4, 5, and 6 which reflects performance bias, detection bias, loss of follow-up bias, and reporting bias, respectively. According to the description of the method in each study, each will be rated as a low, high, or uncertain risk. Two examiners will independently and repeatedly assess the bias and cross-checks. Any difference will be resolved through discussions with the third examiner.

2.4.4. Managing missing data. We will try to obtain exact information of any missing data in the full text of the RCT by sending an email to the corresponding author. If the author can not provide the missing standard deviation, the median of the standard deviation in other randomized controlled trials will be used to estimate the missing standard deviation.

2.4.5. Data synthesis. We will extract data from individual randomized controlled trials through RevMan version 5.3 meta-analysis of random effects model (Copenhagen: Nordic Cochrane Center, Cochrane Collaborative Organization, 2014). According to its normality, the weighted mean deviations (WMDs) or standardized mean deviations (SMD) will be used to measure the impact on continuous results, and the inverse variance method will be used as a meta-analysis method. Using the mantel Haenszel method, risk ratio (ORS) will be used to measure the result of binary classification. 95% confidence interval (CIS) will be calculated to express the estimation accuracy.

2.4.6. Assessment of heterogeneity. In the meta-analysis, we will use the Cochran Q test to determine whether there is statistically significant heterogeneity among randomized controlled trials, and use the I-squared statistic to quantitatively detect the level of heterogeneity. When a P value lower than .10 or an I^2 higher than 50%, there is heterogeneity among the studies, and the source of the heterogeneity should be analyzed first. If the source of heterogeneity is obvious, such as obvious abnormalities in the original data, large differences in the quality of the original research and treatment time, etc. Sensitivity analysis or subgroup analysis according to the sources of differences should be performed.

2.4.7. Subgroup analysis. Based on the experience of moxibustion therapy in clinical application, when there is obvious heterogeneity in the analysis results, we will analyze the source of the heterogeneity from the following subgroups:

1. Subgroup analysis by moxibustion type: the randomized controlled trial of indirect moxibustion was compared with that of direct moxibustion. It is expected that the former has a better curative effect.
2. Subgroup analysis by treatment course: we will compare randomized controlled trials with a course of treatment >2 weeks and ≤2 weeks. The former is expected to have a better effect.

2.4.8. Sensitivity analysis. In order to verify the robustness of the meta-analysis results, we will conduct the following 2 sets of sensitivity analyses:

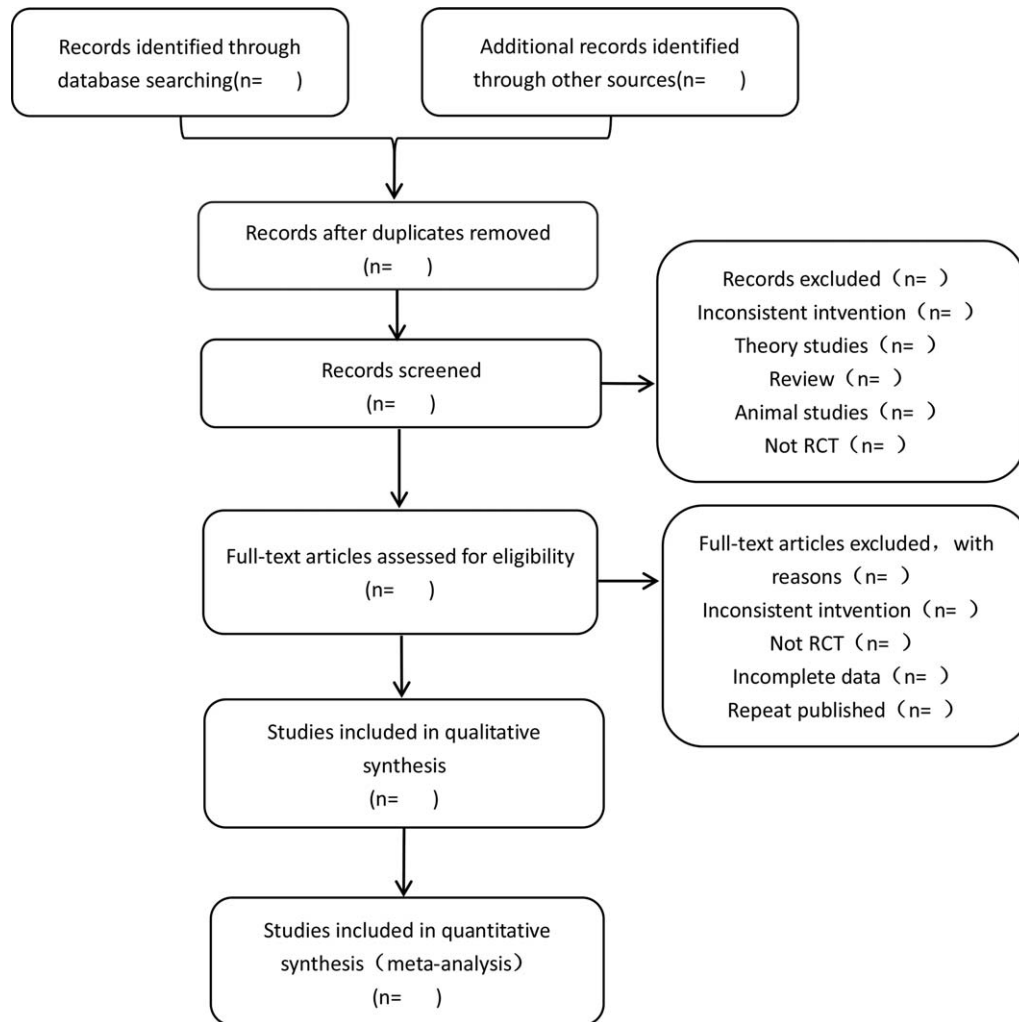1. excluding studies with high risk of bias;

Figure 1. PRISMA-style flow chart of literature screening.

2. using a fixed-effects model to collect the data from the meta-analysis.

2.4.9. Assessment of publication bias. We will draw a funnel chart and perform an Egger test to determine whether there is a potential publication bias in the case of a sufficient number of studies. The funnel chart is relatively symmetrical, when there is no bias in the analysis results. If the distribution pattern is asymmetric, it can be considered that there is publication bias, and further screening is needed.

2.4.10. Assessment of the quality of evidence. We will assess the quality of evidence for each research result based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. We rate the quality of evidence in 5 areas (risk of bias, indirection, inconsistency, imprecision, and publication bias). Finally, the quality of evidence will be determined as high (no obvious restrictions in all aspects), medium (downgrade 1), low quality (downgrade 2), and very low quality (downgrade 3 or more).

2.5. Ethics and dissemination

This study does not involve personal and human test data, so ethical approval is not required. Our goal is to publish the results of this systematic review in a peer-reviewed journal.

3. Discussion

Most of the existing systematic reviews are based on the combination of needle therapy and moxibustion, but there is few systematic review with high-quality of moxibustion in the treatment of chronic fatigue syndrome alone. A previous Chinese systematic review evaluated the effectiveness and safety of moxibustion in the treatment of chronic fatigue syndrome,[29] but its methodological quality was low, and the evaluation results were not convincing. The emergence of more convincing randomized controlled trials has promoted the formulation of this systematic review program.

In this systematic review, we will make effort to improve the reliability of the results, including systematic literature search, strict risk of bias, reasonable data analysis, objective evidence

evaluation quality, and conduct research in strict accordance with the agreement. We believe that the results of this systematic review will help to improve the evidence of clinical moxibustion in the treatment of CFS for clinical decision-making.

Author contributions

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