INPLASY PROTOCOL

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None declared.

Comparative efficacy of different types of acupuncture for cancer-related fatigue: a protocol for systematic review and network meta-analysis

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Review question / Objective: **To evaluate the efficacy and safety of all current acupuncture therapies for the treatment of CRF through network meta-analysis.**
Condition being studied: **Cancer-related fatigue (CRF) has been defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning, as one of the most common symptoms in cancer and related therapies, presents a huge challenge to the quality of life for cancer patients. Unlike general fatigue that can be relieved with rest, CRF is more debilitating, more persistent, and manifests itself in various ways, both physically and mentally. The estimated prevalence of CRF varies widely by various fatigue evaluation indicators, types of cancer, and cancer treatments, ranging from 14.03% to 100%, however, the latest systematic review show that it can have a pooled prevalence of up to 52%, this deserves our attention. But there has been no gold standard treatment for CRF.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 July 2022 and was last updated on 03 July 2022 (registration number INPLASY202270012).

INTRODUCTION

Review question / Objective: **To evaluate the efficacy and safety of all current acupuncture therapies for the treatment of CRF through network meta-analysis.**

Rationale: **Up to now, there has been no gold standard treatment for cancer-related fatigue (CRF). A meta-analysis of 113 studies showed that exercise and psychological interventions are effective for CRF, the current interventions are mainly non-pharmacological treatment,**

including physical activity (it is considered to be the most efficient based on the current level of evidence), psychosocial interventions (such as psychosocial counselling or psychotherapy) and mind-body interventions (such as yoga). Apart from those mentioned above, the American Society of Integrative Oncology has recommended acupuncture for patients with CRF. As a representative of traditional Chinese medicine (TCM), acupuncture has been used clinically in China for thousands of years. It is currently widely distributed worldwide, including in Western countries. Although the underlying biological mechanisms of CRF remain unclear, existing research suggests it is closely linked to the disruptions of the inflammation, the immune system, the thalamic-pituitary-adrenal (HPA) axis, reduced energy metabolism and so on, among these, inflammation becomes a crucial biological pathway for CRF. There is a growing body of research showing the effects of acupuncture in reducing the inflammatory response (e.g., by activating the vagal-adrenal pathway), and it is widely used in inflammatory diseases, as well as acupuncture, moxibustion therapy with warm stimulation of acupuncture points has an anti-inflammatory effect. Acupuncture-related therapies have been used extensively in the treatment of CRF. A systematic review has been conducted to show the therapeutic potential of acupuncture in the management of CRF in cancer survivors. Additionally, other therapies related to acupuncture (e.g., acupressure, transcutaneous acupoint electrical stimulation) are also used in the treatment of CRF, but published studies vary in sample size, methodological level, and observational metrics, what type of acupuncture should be recommended is still inconclusive. Network meta-analysis (NMA) can be used to generate optimal solutions by direct and indirect comparisons. This study used the NMA method to assess the different types of acupuncture for CRF comprehensively and to provide an evidence-based approach to acupuncture therapy.

Condition being studied: Cancer-related fatigue (CRF) has been defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning, as one of the most common symptoms in cancer and related therapies, presents a huge challenge to the quality of life for cancer patients. Unlike general fatigue that can be relieved with rest, CRF is more debilitating, more persistent, and manifests itself in various ways, both physically and mentally. The estimated prevalence of CRF varies widely by various fatigue evaluation indicators, types of cancer, and cancer treatments, ranging from 14.03% to 100%, however, the latest systematic review show that it can have a pooled prevalence of up to 52%, this deserves our attention. But there has been no gold standard treatment for CRF.

METHODS

Search strategy: The retrieval method is based on the PICOS principle, with a combination of subject terms and free words. Take PubMed for example (Table 1).
Number Search Items
#1 "neoplasms" [Mesh Terms]
#2 "tumor*" OR "neoplasia*" OR"cancer*" OR "malignant neoplasm*" OR "malignancy*" OR "neoplasms, malignant" [Title/Abstract]
#3 #1 OR #2
#4 "fatigue" OR "asthenia" OR "frailty" [Mesh Terms]
#5 "cancer related-fatigue" OR "CRF" OR "cancer fatigue" OR "lassitude" [Title/Abstract]
#6 #4 OR #5
#7 #3 AND #6
#8 "acupuncture" OR "acupuncture therapy" OR "acupuncture, ear" OR "acupuncture point*" [Mesh Terms]
#9 "electroacupuncture" OR "meridian*" OR "acupressure" OR "needle" OR "acupoint" OR "moxibustion" OR "transcutaneous acupoint electrical stimulation" OR "TAES" OR "auricular

acupuncture" OR "ear acupuncture" [Title/Abstract]
#10 #8 OR #9
#11 "Randomized Controlled Trial" OR "Clinical Trial" [Publication type]
#12 "randomized" OR "randomly" OR "RCT" OR "trial" [All Fields]
#13 #11 OR #12
#14 #7 AND #10 AND #13.

Participant or population: Only adult patients (≥18 years) can be included, both men and women. There are recognized diagnostic criteria, and all patients included are diagnosed with CRF (fatigue is related to cancer or cancer treatments), with no restrictions on cancer types, stage of cancer, or cause of CRF.

Intervention: The intervention methods included in this study are acupuncture and related therapies, the following methods will be included: manual acupuncture, self-acupuncture, acupressure, electro-acupuncture, moxibustion, transcutaneous acupoint electrical stimulation, auricular acupuncture, acupoint application, and other acupuncture-related therapies. We will exclude therapies based on non-TCM interventions, such as dry acupuncture and laser acupuncture.

Comparator: The control group interventions include placebo, sham acupuncture, sham transcutaneous acupoint electrical stimulation, usual care, blank control, health promotion, or the same western medication as the treatment group; those comparing different acupuncture-related therapies will also be included. However, a trial comparing different acupuncture manipulations on the same acupoint prescriptions will be excluded.

Study designs to be included: All available randomized controlled trials will be included, regardless of whether randomized methods are reported. Retrospective studies, case reports, reviews, commentaries, mechanistic studies, guidelines, and animal studies will be excluded.

Eligibility criteria: Inclusion criteria Types of studies All available randomized controlled trials will be included, regardless of whether randomized methods are reported. Retrospective studies, case reports, reviews, commentaries, mechanistic studies, guidelines, and animal studies will be excluded.Types of participantsOnly adult patients (≥18 years) can be included, both men and women. There are recognized diagnostic criteria, and all patients included are diagnosed with CRF(fatigue is related to cancer or cancer treatments), with no restrictions on cancer types, stage of cancer, or cause of CRF.Types of interventions The intervention methods included in this study are acupuncture and related therapies, the following methods will be included: manual acupuncture, self-acupuncture, acupressure, electro-acupuncture, moxibustion, transcutaneous acupoint electrical stimulation, auricular acupuncture, acupoint application, and other acupuncture-related therapies. We will exclude therapies based on non-TCM interventions, such as dry acupuncture and laser acupuncture.Types of control groupsThe control group interventions include placebo, sham acupuncture, sham transcutaneous acupoint electrical stimulation, usual care, blank control, health promotion, or the same western medication as the treatment group; those comparing different acupuncture-related therapies will also be included. However, a trial comparing different acupuncture manipulations on the same acupoint prescriptions will be excluded.Types of outcome measuresStudies that included at least one of the following outcomes were eligible for inclusion.Primary outcomesThere are no objective indicators for evaluating CRF, which are mainly assessed by scale. Therefore, we will select outcome indicators that reflect the severity of cancer-related fatigue, such as clinical efficiency (total effective rate), fatigue scales: Brief Fatigue Inventory (BFI), Multidimensional Fatigue Inventory (MFI), Revised Piper Fatigue Scale (RPFS), Cancer Fatigue Scale (CFS), Cancer Related Fatigue Distress Scale (CRFDS) or other validated scales. Secondary

outcomes To comprehensively assess the effect of acupuncture therapy on CRF, the following results will be analyzed.1. The Quality of Life Scale: the European Organization for Research and Treatment of Cancer of Life Questionnaire (EORTC-QLQC30), the General Version of the Functional Assessment of Cancer Therapy (FACT-G), or other validated scales.2. TCM Symptom Score (cumulative symptoms associated with CRF).3. Sleep quality: Pittsburgh Sleep Quality Index or other validated scales.4. The rate of adverse reactions related to treatment.

Information sources: A total of eleven databases will be searched from inception to July 2022, including four main Chinese databases (CNKI, Wanfang, VIP, CBM), four English databases (PubMed, Embase, Cochrane Library, Web of Science), and three clinical trial registration platform (WHO International Clinical Trials Registry Platform, Chinese Clinical Trial Registry, Clinicaltrials.gov). The language is limited to Chinese and English. In addition, a careful review of previous CRF-related systematic reviews was conducted to identify additional literature.

Main outcome(s): There are no objective indicators for evaluating CRF, which are mainly assessed by scale. Therefore, we will select outcome indicators that reflect the severity of cancer-related fatigue, such as clinical efficiency (total effective rate), fatigue scales: Brief Fatigue Inventory (BFI), Multidimensional Fatigue Inventory (MFI), Revised Piper Fatigue Scale (RPFS), Cancer Fatigue Scale (CFS), Cancer Related Fatigue Distress Scale (CRFDS) or other validated scales.

Additional outcome(s): To comprehensively assess the effect of acupuncture therapy on CRF, the following results will be analyzed. 1. The Quality of Life Scale: the European Organization for Research and Treatment of Cancer of Life Questionnaire (EORTC-QLQC30), the General Version of the Functional Assessment of Cancer Therapy (FACT-G), or other validated scales. 2. TCM Symptom Score (cumulative symptoms associated with CRF). 3. Sleep quality: Pittsburgh Sleep Quality Index or other validated scales. 4. The rate of adverse reactions related to treatment.

Data management: Data extraction will be carried out independently by two reviewers (ZJ and ZG) according to a pre-designed EXCEL form, extracting information including general information (title, year, first author, country), study design (randomization, allocation concealment, blinding), participants (age, sex, sample size, the type and stage of cancer, the severity of fatigue), interventions (type of acupuncture, acupoints selection, deqi, treatment duration/frequency/session), comparator (intervention type, dosage and frequency); outcomes (data and point of outcome measures, side effects, reasons for dropping out and several people), all extracted information will be cross-checked by the previous two reviewers, in case of disagreement resolved in consultation with the corresponding author (LC), missing data obtained by contacting the author by email.

Quality assessment / Risk of bias analysis:
Risk of bias assessment
The first (ZC) and second author (ZJ) appraise the methodological quality of the included studies with reference to the Cochrane Collaboration's tool for assessing the risk of bias, respectively, including random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome evaluators (measurement bias), incomplete outcome data, selective reporting (reporting bias), and other biases. The above entries will be classified as high/unclear/low risk of bias. In the event of a disagreement, a decision is made in consultation with another reviewer (LC). RevMan V.5.3 is used to generate a literature quality evaluation map.
Confidence in cumulative evidence
The Grading of Recommendations Assessment, Development and Evaluation System (GRADE) evaluation tool will be used by two reviewers (MW and ZW) to rank the quality of evidence for main outcomes in terms of the five dimensions:

risk of bias, inconsistency, indirectness, imprecision and publication bias, and the quality of evidence will be ranked as high, moderate, low and very low. A third reviewer (LC) will mediate any disagreement until a consensus is reached.

Strategy of data synthesis: We will use STATA V.15.0 and GeMTC V.0.14.3 to perform the network meta-analysis. Dichotomous data will be examined by using the odds ratio (OR), and continuous data will be analysed using mean differences (MD), effect sizes for both types will be expressed at a 95% confidence interval (CI), and values of P<0.05 will be considered statistically significant. STATA V.15.0 is used to create the evidence network diagram to present the interrelationships between the interventions. In GeMTC V.0.14.3 software, Bayesian NMA is implemented by Markov Chain Monte Carlo (MCMC) method. The potential scale educed factor (PSRF) was used to evaluate the convergence of the results, and when 1 ≤ PSRF ≤ 1.05, the convergence of the results is good, and the confidence of the results obtained is high. To rank the efficacy of the various interventions, the STATA V.15.0 is used to calculate the surface under the cumulative ranking curve (SUCRA) and the area under the SUCRA curve, with larger values and larger areas under the curve indicating that the intervention is more likely to be the optimal intervention.

Subgroup analysis: If the number of included trials is sufficient, we will conduct a subgroups analysis according to cancer type, degree of fatigue, and treatment course, the treatment course is divided into short-term≤2 weeks,2 weeks <medium-term≤4 weeks, and long-term≥4weekss.

Sensitivity analysis: In order to verify the robustness of the review's conclusions, a sensitivity analysis is required. We will remove the low-quality studies and the high-risk of bias studies one by one to investigate whether they have an effect on heterogeneity and effect size.

Language: The language is limited to Chinese and English.

Country(ies) involved: China.

Other relevant information: Assessment of inconsistency - Since indirect comparisons originating from NMA spoil the randomness of RCT (i.e., the participants for indirect comparisons do not conform to the principle of randomness), it increases the potential for bias and errors in assessing effects. Therefore, To ensure the validity and reliability of the results of the NMA, the assessment of inconsistency is necessary. This study will use the node-split method to test for inconsistency. P > 0.05 indicates that there is no inconsistency (direct evidence is the same as indirect evidence), and the consistency model is chosen for analysis; conversely, the non-consistency model is used for analysis. Assessment of heterogeneity - Assessment of clinical and methodological heterogeneity is based on study design, interventions, characteristics of participants, treatment course, and outcomes.I2 statistic will be used to evaluate statistical heterogeneity, when I2≤50%, statistical heterogeneity between studies are considered acceptable, when I2>50%, statistical heterogeneity between studies are considered significant, a sensitivity analysis will be conducted to remove studies with high heterogeneity before Meta-analysis, In addition, descriptive analyses will be performed if heterogeneity cannot be explored.

Keywords: acupuncture; cancer-related fatigue; systematic review; network meta-analysis.

Dissemination plans: The final report of this review will be disseminated through peer-reviewed journals.

Contributions of each author:

Author 1 - Ziying Chen - The authors conceived the study and wrote the manuscript, developed the search strategy, and will run the strategy, perform the risk of bias assessment and analyse the data.
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Author 2 - Zefei Jiang - The author conceived this study and wrote the manuscript, conducts risk of bias assessments and analyse the data.
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Author 3 - Ziyun Guo - The author contributed extract and managed the data, conducts risk of bias assessments and analyse the data.
Author 4 - Mengchao Wang - The author conducts risk of bias assessments and analyse the data.
Author 5 - Zhen Wang - The author conducts risk of bias assessments and analyse the data.
Author 6 - Liwei Chen - LC provided methodological advice and revised the manuscript. All authors have reviewed this protocol and approved the final manuscript.