Efficacy and safety of acupuncture for post-COVID-19 depression: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Post-COVID-19 depression (PCD) is a possible sequela of COVID-19. Some doctors have used acupuncture to treat PCD, but no systematic review or meta-analysis has yet evaluated its efficacy and safety for the treatment of PCD. The aim of this systematic review is to assess the efficacy and safety of acupuncture therapy for PCD.

Methods and analysis Two reviewers will independently search the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (PubMed), Excerpt Medica Database (EMBASE), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP) and Wan-Fang Database from inception to 24 January 2023. Study selection, data extraction and assessment of study quality will be independently performed by two reviewers. If a meta-analysis is appropriate, Review Manager V.5.3 will be used for data synthesis; otherwise, a descriptive analysis will be conducted. Data will be synthesised using a fixed-effects or random-effects model, according to the results of a heterogeneity test. The results will be presented as risk ratios with 95% CIs for dichotomous data, and weighted mean differences or standardised mean differences with 95% CIs for continuous data.

Ethics and dissemination The entire process used for this systematic review does not use private information, so ethical approval is not required. The results of this meta-analysis will be disseminated through publication in a peer-reviewed journal and/or conference presentations.

INTRODUCTION

The SARS-CoV-2 virus is responsible for the worldwide COVID-19 pandemic during the past 3 years. Hundreds of millions of people around the world have been infected with this virus, and approximately 80% of patients who were hospitalised for COVID-19 have experienced post-COVID-19 sequelae. The main postacute sequelae are fatigue and cognitive impairment, and the other long-lasting neuropsychiatric disorders include depression and certain physical manifestations, such as dyspnoea. These symptoms can persist for at least 4 weeks following infection, and are colloquially referred to as ‘long COVID’.

Some studies showed that the incidence of depression in patients undergoing COVID-19 rehabilitation was about 30%, and that depression after 1 year of recovery and even longer periods are common. This depression may also cause sleep disorders and post-traumatic stress disorder, and these two disorders are positively correlated. Therefore, post-COVID-19 depression (PCD) is now considered a disease that is classified as a serious sequela of COVID-19.

Depression is one of the main causes of disability globally, and PCD has a significant negative impact on affected individuals. According to Mazza et al., female sex, a previous psychiatric diagnosis and psychopathology at a 1-month follow-up were the most consistent predictors of PCD. In recent months, the Omicron variant has become the dominant form of SARS-CoV-2, and this variant is responsible for new rounds of infections worldwide. This variant is more transmissible and is associated with a higher rate of infection, but is also less virulent and more likely to escape immune protection. As the
COVID-19 epidemic continues, the number of people suffering from PCD continues to increase.

For treatment of PCD, clinicians commonly administer a variety of different antidepressants, such as citalopram, escitalopram, nortriptyline, milnacipran, mirtazapine, piracetam and fluoxetine. However, many antidepressants can cause adverse effects such as blurred vision, urinary retention, low blood pressure, sexual dysfunction, tremors and severe insomnia. Another issue is that up to 60% of patients do not respond adequately to antidepressant treatment. Therefore, it is necessary to identify alternative methods that are effective and safe for the treatment of PCD.

Acupuncture is a traditional Chinese therapy that has been used to treat mental disorders since ancient times. Current research provides some evidence for the use of acupuncture for depression. Some of the studies that reported these beneficial effects suggested that the mechanisms might include the direct or indirect modulation of activity and connectivity of key brain regions that function in depression and mood regulation. For example, acupuncture can reduce the hyperactivity of hypothalamic–pituitary–adrenal axis and increase the serum level of 5-hydroxytryptamine and inhibit the expression of inflammatory cytokines in different brain regions.

Several studies have provided some low-quality to moderate-quality evidence supporting acupuncture for depression, other clinical studies reported mixed results. In addition, there is very little known about the effect of acupuncture on PCD, a specific type of depression. We performed a comprehensive literature review and found no systematic reviews that specifically investigated the efficacy of acupuncture for PCD. Therefore, we plan to conduct a systematic review and meta-analysis of the efficacy and safety of acupuncture for the treatment of PCD, and analyse the effects of using different acupoints on PCD. Our general purpose is to provide reliable evidence regarding the clinical use of acupuncture as a treatment for PCD.

METHODS AND ANALYSIS
Study registration
This systematic review protocol was registered in the international prospective register of systematic reviews (PROSPERO, trial registration number: CRD42022379312). All procedures will adhere to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.

Patient and public involvement
No patients or other individuals are involved in the design, conduct, reporting or dissemination of this research.

Ethics and communication
This study is a systematic review. Private information of individual patients is not collected, and ethical approval is therefore not required.

Inclusion and exclusion criteria
Types of studies
All randomised controlled trials (RCTs) will be included, without restrictions regarding publication status, but the language will be limited to English and Chinese. Other types of studies, including reviews, animal experiments, theoretical discussions, case reports, conference articles, letters to editor and non-RCTs, will be excluded.

Types of participants
This study will include participants with PCD, regardless of gender, age, occupation or education. It will include patients who had confirmed COVID-19 or asymptomatic SARS-CoV-2 infections based on the results from nucleic acid testing, antigen testing and clinical criteria. Depression will be diagnosed according to the International Classification of Diseases (10th edition), the Diagnostic and Statistical Manual of Mental Disorders (5th edition), the Chinese Classification of Mental Disorders and the Hamilton Depression Rating Scale (HDRS). The diagnosis of depression cannot be explained by causes other than COVID-19. Patients with primary depression or a serious underlying disease who are unsuitable for acupuncture treatment will be excluded.

Types of interventions
The interventions will consist of acupuncture or acupuncture combined with other therapies, without limitations regarding acupoint or course of treatment. The acupoint selection and acupuncture methods are derived from traditional Chinese medicine. Studies that examined the treatment of non-traditional acupoints (e.g., ear acupuncture, scalp acupuncture and other methods) will be excluded.

Types of comparisons
There are no restrictions regarding the type of control treatment. Thus, the control treatment may include no treatment, placebo, other types of acupuncture treatment or any other control treatment considered for suitable for comparison.

Types of outcome measures
Primary outcome
HDRS. No depression (0–7), mild depression (8–16), moderate depression (17–23) and severe depression (≥24).

Secondary outcomes
Self-rating Depression Scale, total efficacy rate (determined after removal of invalid subjects), cure rate (determined for all subjects), acupoints selection rules and adverse reactions.

Data sources and search strategies
The following databases will be searched by two independent reviewers (XL and JP) for eligible publications from inception to 24 January 2021, without restrictions regarding publication status: the Cochrane Central
Register of Controlled Trials (CENTRAL), Medline (via PubMed), Excerpt Medica Database (EMBASE), China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP database) and Wan-Fang Database. The search strategy for Medline (via PubMed) database was established according to the Cochrane handbook guidelines (table 1). The same search strategy will be used for the other databases with appropriate adjustments of syntax. Before this review is completed, the same two reviewers will conduct the search again to ensure the most recent studies are included.

Selection of studies

This systematic review will be conducted from 24 January 2023 to 10 June 2023 (figure 1). All reviewers have received training to ensure a basic understanding of the background and purpose of the review. After electronic searching, the records will be uploaded to a database set up by EndNote X7 software. Records selected from other sources will also be added to the database. Two reviewers (BL and HL) will independently screen the titles, abstracts and keywords of all retrieved studies and identify trials that meet the inclusion criteria. The full text of all possibly relevant studies will be collected for further assessment, and excluded studies will be recorded with explanations. Any disagreements will be resolved by discussion between the same two reviewers, and a third author (CL) will participate in arbitrations when necessary. The reviewers of previous trials will be contacted for clarifications when necessary.

Data extraction and management

A unified data extraction form will be designed by all of the reviewers, and two reviewers (BL and XL) will then independently extract data in the following domains: general information, characteristics of participants, methods, interventions, outcomes, adverse events and other information. Any disagreements will be discussed between these two reviewers, and disagreements will be arbitrated by a third author (JP).

Accounting for missing data

For studies with missing data, attempts will be made to contact the first author or the corresponding author by telephone or email to obtain these missing or insufficient trial data. If missing data are unavailable, an assumption using the terms ‘missing at random’ or ‘not missing at random’ will be used to represent the different scenarios, as recommended in the Cochrane Handbook. For data ‘missing at random’, only available data will be analysed; for data ‘not missing at random’, the missing data will be replaced with values and a sensitivity analysis will be used to determine whether the results are inconsistent.

Table 1 The search strategy for PubMed

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<tr>
<th>Order</th>
<th>Strategy</th>
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<tbody>
<tr>
<td>#1</td>
<td>Search: “COVID-19”(Mesh)</td>
</tr>
<tr>
<td>#3</td>
<td>#1 OR #2</td>
</tr>
<tr>
<td>#4</td>
<td>Search: “Depressive Disorder”(Mesh)</td>
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<tr>
<td>#5</td>
<td>Search: “Depressive Disorders”(Tiab) OR “Neurosis, Depressive”(Tiab) OR “Depression, Endogenous”(Tiab) OR “Depressive Syndrome”(Tiab) OR “Neurotic Depression”(Tiab) OR “Melancholia”(Tiab) OR “Unipolar Depression”(Tiab)</td>
</tr>
<tr>
<td>#6</td>
<td>#4 OR #5</td>
</tr>
<tr>
<td>#8</td>
<td>Search: “randomised controlled trial”(Publication Type) OR “RCT randomised controlled”(Publication Type) OR “random allocation”(Tiab) OR “allocation, random”(Tiab) OR “randomised, controlled”(Tiab) OR “clinical trial”(Tiab)</td>
</tr>
<tr>
<td>#9</td>
<td>Search: “humans”(MeSH Terms) NOT “animals”(MeSH Terms)</td>
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<tr>
<td>#10</td>
<td>#8 AND #9</td>
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<tr>
<td>#11</td>
<td>#3 AND #6 AND #7 AND #10</td>
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Assessment of risk of bias
The risk of bias will be assessed by two reviewers (HT and CH) using the appropriate tool from the Cochrane Collaborations. The risk of bias in the included studies will be evaluated according to: sequence generation; allocation sequence concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources. The assessments will be classified as ‘low risk’, ‘high risk’ or ‘unclear risk’.

Data analysis and synthesis
Review Manager V.5.3 software will be used for data analysis and quantitative data synthesis. For continuous data, the standardised mean differences with 95% CIs will be used to assess treatment effect. For dichotomous data, risk ratios with 95% CIs will be used. Based on data heterogeneity, a random effects model (I²<50%) or a finite effects model (I²≥50%) will be employed for analysis. In addition, if the heterogeneity is considered significant, then a subgroup or sensitivity analysis will be performed to identify its source. When data are insufficient for quantitative analysis, a descriptive analysis will be performed.

Subgroup analysis
If the results show high heterogeneity, a subgroup analysis will be performed based on the type of acupuncture intervention, severity of depression, treatment duration and other relevant parameters.

Sensitivity analysis
Sensitivity analysis will be performed by reevaluating methodological quality, study type, sample size, missing data and other possible factors to validate the robustness of the primary results. If a difference is significant, the reason for the difference will be thoroughly investigated.

Assessment of reporting biases
If more than 10 studies reported the same outcome measure, a funnel plot and Egger regression test will be used to evaluate reporting bias.

Grading the quality of evidence
The methodology of the Grading of Recommendations Assessment, Development and Evaluation working group will be used to assess the quality of evidence for all outcomes. The following six domains will be assessed: risk of bias, consistency, directness, precision, publication bias and additional points. These assessments will be categorised as ‘high’, ‘moderate’, ‘low’ or ‘very low’.

DISCUSSION
Acupuncture is an ancient and traditional Chinese medical technology that has been in use for thousands of years. At present, many European countries, the USA, Japan, South Korea and other countries have recognised the potential therapeutic benefits of acupuncture. Doctors in many countries outside of China have also recognised acupuncture as a potential treatment for depression. For example, a Canadian clinical guideline identified acupuncture as a potential adjunctive treatment for depression. Traditional Chinese therapies have always emphasised the ‘harmony between humans and nature’, in which nature includes the natural and social environment. These therapies also emphasise the ‘unity of body and mind’, in which there is a harmony of the human body and spirit. These two features coincide with the understanding of health by modern medicine, which defines health based on physical, mental and social well-being.

PCD may be considered a type of psychological disorder, and is more insidious and often co-occurs with other symptoms, such as anxiety and insomnia. Therefore, during the early stage of PCD, a patient may not acknowledge the presence of depression, and this could lead to misdiagnosis. Patients with depression experience physical and psychological suffering, symptoms that are often difficult to treat. Although antidepressants are widely used in clinical practice, their adverse effects sometimes may overwhelm their therapeutic benefits. Therefore, many patients with depression do not accept long-term drug treatment, and decide to either endure the suffering or seek alternative medical treatments.

Many studies have examined the effects of acupuncture on postpartum depression, poststroke depression and other types of depression, and very few patients experience adverse effects when acupuncture is performed properly. However, because PCD is such a new disease, it is necessary to analyse the efficacy and safety of acupuncture as a treatment. Our study probably offers evidence that allows the evaluation of acupuncture as a treatment for PCD and will also assess the use of different acupoints. The results may provide some insight for clinicians in the treatment of PCD, and may useful as a guideline for acupuncture therapies.