Acupuncture for protracted opioid abstinence syndrome: study protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Protracted opioid abstinence syndrome (POAS) refers to a series of physical discomforts and neuropsychiatric symptoms after discontinuation of opioid-type substances for a certain amount of time and is one of the main causes of relapse. Studies have shown that acupuncture is effective in the treatment of POAS. We plan to conduct this systematic review and meta-analysis to assess the efficacy and safety of acupuncture for POAS.

Methods and analysis A comprehensive search of studies will be carried out in the following databases from inception to 31 January 2023: Web of Science, Embase, PubMed, Chinese Biology Medicine, China National Knowledge Infrastructure, Wan Fang Database and Chinese Scientific Journal Database (VIP). WHO International Clinical Trials Registry Platform, ClinicalTrials.gov and Chinese Clinical Trial Registry will also be searched for ongoing relevant trials, and ‘grey literature’ will be identified from GreyNet International, OpenGrey and Google Scholar. Randomised controlled trials regarding acupuncture therapy for treatment of POAS will be included. The primary outcome is the severity of protracted withdrawal symptoms. Two reviewers will screen studies using the inclusion criteria, extract data and assess the risk of bias, respectively. The quality of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation. Data synthesis will be performed using RevMan V.5.4.1.

Ethics and dissemination This study will not invade patients’ personal privacy, and so ethical review is not required. The results will be disseminated in a peer-reviewed journal.

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INTRODUCTION

Opioid-type substance (OTS) abuse presents a great threat to global public health. Long-term use of these substances interferes with the central nervous system, especially the reward system, causing drug dependence1,2 and discontinuation or reduction of OTS could induce a series of physical and mental symptoms, called opioid abstinence syndrome.3 4 Opioid abstinence syndrome can be classified into acute abstinence syndrome and protracted opioid abstinence syndrome (POAS) according to the length of time from OTS discontinuation.5 7

Acute abstinence syndrome typically lasts for less than 10 days and patients experience multiple symptoms such as anxiety, irritability, restlessness, sweating, tears, runny nose, insomnia, yawning, pupil dilation and muscle soreness. Tachypnea, tachycardia, hypertension, nausea, vomiting, diarrhoea, erection and fever are also reported in severe cases.8 10 Then comes the protracted stage, which lasts for months to even years and patients suffer from persistent physical discomforts, anxiety, depression and insomnia.8 10 Most of the patients relapse to abuse OTS due to these unbearable symptoms.11 12 It is generally believed that opioid withdrawal symptoms will not endanger life; however, severe clinical symptoms can lead to severe loss of body fluid and electrolyte disorder.13

The specific mechanism of POAS has not been fully elucidated. It is generally believed that POAS is associated with the dopamine over-release caused by long-term exposure to high-dose opioids14; opioid induces changes including in the ventral tegmental area, the nucleus accumbens and the amygdala.15 16 The currently recommended treatment for POAS is alternative maintenance therapy, such as methadone or buprenorphine, and opioid antagonist therapy, such as naltrexone,9 17 which might be beneficial to several patients,18 although they often result in poor treatment compliance due to adverse reactions.19 On the other hand, due

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will include patients who are at the protracted stage of opioid abstinence syndrome.
⇒ To comprehensively search the literature, this study will search seven electronic databases, four trial registration platforms and the grey literature.
⇒ This study will evaluate the efficacy and safety of acupuncture in the treatment of protracted opioid abstinence syndrome using standard opioid withdrawal assessment scale.
⇒ The robustness and reliability of this study depend largely on the number, potential methodological quality, publication bias and sample size of the included studies.
to the side effects of the drug and the legal requirements for prescription, some patients are not interested in this treatment.13 19 20

There are also other alternative therapies that might be effective in the treatment of POAS, including psychotherapy and kinesitherapy. These therapies, however, still need to be further investigated, and their high entry barriers would limit their popularisation and application. A long-term follow-up study showed that,21 during the observation period of 10–30 years, less than 30% of patients stably abstained from using opioids. These situations highlight an urgent need for a treatment approach that would be effective and safe in alleviating the symptoms of POAS and help patients recover from opioid dependence and get back to their normal life.

Acupuncture is an essential part of traditional Chinese medicine (TCM). Since its therapeutic effects on psychostimulant dependence were discovered in 1972,22 a large amount of studies have been conducted to investigate its efficacy and safety.23 24 In 1985, the auricular acupuncture treatment scheme was proposed by the National Acquirement Detoxification Association and has since been adopted by many countries.25 Acupuncture can alleviate negative affect (depression and anxiety), insomnia and physical abstinence symptoms in patients with POAS.26 27 Animal experiments have also confirmed that acupuncture mediates the central dopaminergic system and increases the expression of endogenous opioid peptides to alleviate protracted abstinence.28–31 Therefore, acupuncture could be a promising therapy for POAS.

However, there remains a lack of systematic review and meta-analysis that synthesises the data of currently published relevant studies. We plan to conduct this study to review the current clinical trials on acupuncture as treatment for POAS and to systematically assess its efficacy and safety in order to provide reference for clinical decision-making.

**METHODS**

This study will be conducted in strict accordance with the Cochrane Handbook for Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement guidelines.32 33

**Eligibility criteria**

**Types of studies**

Randomised controlled trials (RCTs) assessing the efficacy and safety of acupuncture for treatment of POAS will be included, and intervention methods include various types of acupuncture therapy.

**Types of participants**

Participants will include patients meeting the well-accepted diagnostic criteria for OTS dependence, age of more than 18 years old and are in the protracted withdrawal period, without race and gender restrictions.

Diagnosis of OTS dependence is according to internationally recognised diagnostic standards, such as the following:

- Diagnostic and Statistical Manual of Mental Disorders: diagnostic criteria for opioid withdrawal.
- Classification and Diagnostic Criteria for Mental Disorders in China: diagnostic criteria for opioid withdrawal.
- Diagnostic criteria of the International Classification of Diseases: about mental and behavioural disorders caused by use of psychoactive substances.

Diagnosis of protracted abstinence will follow the Guiding Principles for the Diagnosis and Treatment of Disorders Related to the Use of Opioids, which could be defined as the following:

- Discontinuation of OTS for at least 10 days.
- Reporting evident protracted abstinence symptoms: anxiety, depression, insomnia and physical discomforts.
- Persistently ‘negative’ urine morphine test.

**Types of interventions and comparisons**

The intervention should be acupuncture therapy, which refers to use of acupuncture needle and insertion into the subcutaneous tissues of the acupoints. It includes manual acupuncture, electroacupuncture and auricular acupuncture. No restrictions were set to acupuncture modalities. Other acupuncture stimulation therapies will be excluded, such as acupuncture, acupoint application and transcutaneous acupoint electrical stimulation. There is no limit to the frequency, duration, course, acupoint selection and needling method of treatment.

The control includes psychotherapy, kinesitherapy, TCM decoction, other traditional medicine therapies, positive pharmacological agents, wait-list control and sham acupuncture.

**Types of outcomes**

**Primary outcome**

The main primary outcome is the severity of protracted withdrawal symptoms assessed by validated and reliable scales such as the Clinical Opioid Withdrawal Scale, Short Opiate Withdrawal Scale, Himmelsbach Scoring Table for Withdrawal Symptoms, etc.

**Secondary outcomes**

- Severity of negative affect: anxiety and depression scored using validated scales such as the Self-Rating Anxiety Scale, Self-Rating Depression Scale, Hamilton Anxiety Scale and Hamilton Depression Scale.
- Insomnia: scored by validated scales such as the Pittsburgh Sleep Quality Index.
- Incidence of adverse events.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Information sources**

**Electronic databases**

Databases include Web of Science, Embase, PubMed, Chinese Biology Medicine, China National Knowledge
Infrastructure, Wan Fang Database and Chinese Scientific Journal Database (VIP), from inception to 31 January 2023. There will be no limitations to the language of the articles. We will also search the reference list of retrieved articles for articles that may potentially qualify in this study.

Other resources
Ongoing or unpublished trials will be retrieved through the WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, Chinese Clinical Trial Registry and Cochrane Central Register of Controlled Trials, and ‘grey literatures’ such as GreyNet International, OpenGrey and Google Scholar.

Search strategy
Search strategy will be designed according to the ‘Patient, Intervention, Comparison and Outcome (PICOS)’ principle of evidence-based medicine, and the items will be selected using Medical Subject Headings free words. The strategy is shown in table 1, taking PubMed as an example.

Selection of studies
The titles and abstracts will be browsed during the initial screening and irrelevant studies will be removed. The full text of the remaining articles will be downloaded and read. Studies meeting the inclusion criteria will be included. These processes will be conducted by two researchers independently (TL and YZ) and disagreements will be resolved through discussion or by a third researcher (YR). The selection process is shown in figure 1.

Data extraction
Data of the included studies will be extracted using a predesigned form which contains the following information: name of the first author, nationality, publication date, study design, sample size, diagnostic criteria, intervention, control, acupoint prescriptions, treatment duration, outcome measures, follow-up, analytic set and characteristics of the participants (mean age, gender distribution, history of substance abuse, comorbidities, etc). Missing data will be obtained by contacting the authors.

Risk of bias assessment
Two reviewers will independently use the Cochrane Collaboration’s risk of bias tool to assess the risk of bias of the included RCTs. Evaluation content includes randomisation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data, selective reporting and other bias. Each problem is divided into low risk, unclear risk and high risk. Differences will be resolved by a third reviewer.

Data synthesis
RevMan V.5.4.1 will be used for data analysis and quantitative data synthesis. Risk ratio will be used as pooled statistics for dichotomous data, and standardised mean difference will be used for continuous data. The 95% CI of each effect will be provided. A p value less than 0.05 will indicate statistical significance.

Assessment of heterogeneity
The \( \chi^2 \) test and \( I^2 \) statistics will be employed to assess the heterogeneity of the included studies. If \( I^2 \) is <50% with \( p>0.1 \), no significant heterogeneity will be considered among the studies and fixed-effect model will be used to calculate for meta-analysis. Otherwise, if \( I^2 \) is >50% or \( p \leq 0.1 \), significant heterogeneity will be considered and subgroup analysis will be performed to identify the source of heterogeneity. If the heterogeneity could not be processed by subgroup analysis, a random-effect model will be used. For the three-arm test, all the groups

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Search strategy for PubMed</th>
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<tbody>
<tr>
<td>Sequence</td>
<td>Items</td>
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<tr>
<td>#1</td>
<td>Opioid-Related Disorders (MeSH)</td>
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<tr>
<td>#2</td>
<td>Opioid-Related Disorders</td>
</tr>
<tr>
<td>#3</td>
<td>Addiction</td>
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<tr>
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<td>Opioid dependence</td>
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<tr>
<td>#5</td>
<td>Opioid withdrawal</td>
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<tr>
<td>#6</td>
<td>Opioid abstinence</td>
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<td>#7</td>
<td>Opioid</td>
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<tr>
<td>#8</td>
<td>Drug abuse</td>
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<tr>
<td>#9</td>
<td>Substances abuse</td>
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<tr>
<td>#11</td>
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<td>#16</td>
<td>Acupuncture</td>
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<td>#17</td>
<td>Electroacupuncture</td>
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<tr>
<td>#18</td>
<td>Auricular acupuncture</td>
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<td>#19</td>
<td>Acupoint</td>
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<tr>
<td>#31</td>
<td>#14 AND #22 AND #30</td>
</tr>
</tbody>
</table>
This study will not involve patients’ personal privacy and so ethical review is not required. The results will be disseminated in a peer-reviewed journal.

**Figure 1** Flow diagram of the study selection process. POAS, protracted opioid abstinence syndrome.

Subgroup analysis
Subgroup analysis will be performed to process the heterogeneity among the studies. The subgroups will be set according to the Standards for Reporting Interventions in Clinical Trials of Acupuncture regulations, such as acupuncture modalities, needle retention time, number of treatment sessions, etc.34

Sensitivity analysis
Sensitivity analysis will be conducted by removing the included studies one by one to test the robustness of the results.

**Assessment of publication bias**
Funnel plot will be applied to evaluate publication bias if more than 20 studies are included.

Summary of evidence
The Grading of Recommendations, Assessment, Development and Evaluation will be used to assess the quality of evidence. This process will be completed by two researchers independently (TL and YZ), and disagreements will be resolved through discussion or by a third researcher (YR).

**Ethics and dissemination**
This study will not involve patients’ personal privacy and so ethical review is not required. The results will be disseminated in a peer-reviewed journal.

**REFERENCES**

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**Contributors** TL and YZ contributed equally to the drafting and revision of the manuscript. TL and YZ designed this study. YR serves as the supervisor of this study. The search strategy for each database will be designed by all review authors. XZ and FZ will independently carry out the search, selection and identification of studies and the data extraction. TL will perform the data synthesis and analysis. YR will serve as the third author for settlement of disagreement. YR and YZ will be the adviser on the methodology. All authors have approved the publication of this study protocol.

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**Competing interests** None declared.

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