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

Tao Li,1 Yi Wei Zeng,1 Feng Zhang,2 Xin Zhou,3 Yulan Ren3

ABSTRACT

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 discomfort, anxiety, depression and insomnia.8-12 Most of the patients relapse to abuse OTS due to these unbearable symptoms.9-11 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 release caused by long-term exposure to high-dose opioids14; opioid induces changes 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.


BMJ Open: first published as 10.1136/bmjopen-2023-071864 on 19 June 2023. Downloaded from http://bmjopen.bmj.com/ on September 16, 2023 by guest. Protected by copyright.
to the side effects of the drug and the legal requirements for prescription, some patients are not interested in this treatment.\textsuperscript{15,19,20}

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,\textsuperscript{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 psycho-stimulant dependence were discovered in 1972,\textsuperscript{22} a large amount of studies have been conducted to investigate its efficacy and safety.\textsuperscript{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.\textsuperscript{25} Acupuncture can alleviate negative affect (depression and anxiety), insomnia and physical abstinence symptoms in patients with POAS.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 acupressure, 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≤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>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
<td>Items</td>
</tr>
<tr>
<td>#1</td>
<td>Opioid-Related Disorders (MeSH)</td>
</tr>
<tr>
<td>#2</td>
<td>Opioid-Related Disorders</td>
</tr>
<tr>
<td>#3</td>
<td>Addiction</td>
</tr>
<tr>
<td>#4</td>
<td>Opioid dependence</td>
</tr>
<tr>
<td>#5</td>
<td>Opioid withdrawal</td>
</tr>
<tr>
<td>#6</td>
<td>Opioid abstinence</td>
</tr>
<tr>
<td>#7</td>
<td>Opioid</td>
</tr>
<tr>
<td>#8</td>
<td>Drug abuse</td>
</tr>
<tr>
<td>#9</td>
<td>Substances abuse</td>
</tr>
<tr>
<td>#10</td>
<td>Protracted withdrawal</td>
</tr>
<tr>
<td>#11</td>
<td>Protracted abstinence</td>
</tr>
<tr>
<td>#12</td>
<td>Heroin</td>
</tr>
<tr>
<td>#13</td>
<td>Cocaine</td>
</tr>
<tr>
<td>#14</td>
<td>#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13</td>
</tr>
<tr>
<td>#15</td>
<td>Acupuncture (MeSH)</td>
</tr>
<tr>
<td>#16</td>
<td>Acupuncture</td>
</tr>
<tr>
<td>#17</td>
<td>Electroacupuncture</td>
</tr>
<tr>
<td>#18</td>
<td>Auricular acupuncture</td>
</tr>
<tr>
<td>#19</td>
<td>Acupoint</td>
</tr>
<tr>
<td>#20</td>
<td>Needling</td>
</tr>
<tr>
<td>#21</td>
<td>Meridian</td>
</tr>
<tr>
<td>#22</td>
<td>#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21</td>
</tr>
<tr>
<td>#23</td>
<td>Clinical trials (MeSH)</td>
</tr>
<tr>
<td>#24</td>
<td>Randomized Clinical trials</td>
</tr>
<tr>
<td>#25</td>
<td>Randomized</td>
</tr>
<tr>
<td>#26</td>
<td>Random</td>
</tr>
<tr>
<td>#27</td>
<td>Placebo</td>
</tr>
<tr>
<td>#28</td>
<td>Trial</td>
</tr>
<tr>
<td>#29</td>
<td>Groups</td>
</tr>
<tr>
<td>#30</td>
<td>#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29</td>
</tr>
<tr>
<td>#31</td>
<td>#14 AND #22 AND #30</td>
</tr>
</tbody>
</table>
The results will be disseminated in a peer-reviewed journal.

**References**