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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) is a group of symptoms of opiate addicts, it still exists months or even years after their acute withdrawal, and is the main reason for relapse. Research shows that acupuncture can be used as a treatment for POAS. We design this protocol aims to evaluate the effectiveness and safety of acupuncture in POAS.

Methods and Analysis

A comprehensive search for studies will be carried out in the following databases from inception to December 15, 2022: Web of Science, Embase, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical

Trial Registry Platform (WHO ICTRP), Clinical Trials, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang (WF), Chinese Scientific Journal Database (VIP), Chinese Clinical Trial Registry (Chi CRT). The research type only includes randomized controlled trials, but the reported articles will not be limited by language. The primary outcome is the severity of withdrawal symptoms. Two reviewers will screen the inclusion criteria, extract data, and assess the risk of bias, respectively. Revman V5.4.1 will be used for data synthesis. The evidence quality will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Ethics and Dissemination

This study will not involve patients' personal privacy, so ethical review is not required, and the results will be disseminated in a peer-reviewed journal.

Strengths and limitations of this study

This study will be the first systematic review and meta-analysis to evaluate the efficacy and safety of acupuncture for POAS.

POAS is the main reason for relapse. The results of the systematic review could help make decisions about reducing the reabsorption rate.

This study will evaluate the efficacy and safety of acupuncture in the treatment of POAS with standard opioid withdrawal assessment scale.

The reliability of this study is largely affected by the potential methodological quality, publication bias, and sample size included in the study.

Systematic review registration

PROSPERO: CRD42022382978

Keywords: acupuncture, opioid, abstinence syndrome

Introduction

Opioid withdrawal state refers to the painful subjective symptoms and objective physical signs after stopping or reducing opioids or using antagonists. The main clinical manifestations include: anxiety, irritability, restlessness, sweating, tears, runny nose, insomnia, yawning, pupil dilation, muscle soreness. In severe cases, the symptoms are tachypnea, tachycardia, hypertension, nausea, vomiting, diarrhea, erection and fever.[1-3] The withdrawal symptoms of opioids is the main obstacle of opioid withdrawal.[4-5] It is generally believed that opioid withdrawal symptoms will not endanger life safety, but severe clinical symptoms can lead to severe body fluid loss and electrolyte disorder .[6] According to the time of symptoms after drug withdrawal, it can be divided into acute abstinence symptoms and protracted abstinence symptoms.

At present, the pathophysiological mechanism of protracted opioid abstinence syndrome (POAS) has not been fully elucidated. It is generally believed that it is related to the increase of dopamine release threshold caused by long-term exposure to high-dose opioids,[7]Opioid induced changes including ventral tegmental area (VTA), nucleus accumbens and amygdala. [8-9] The recommended alternative therapy intervention for acute withdrawal symptoms is long-term opioid agonist therapy, such as methadone or buprenorphine, and opioid antagonist therapy, such as naltrexone.[2,10]There is evidence that the use of methadone or buprenorphine can reduce the desire for opioids and improve the overall survival rate.[11-12]However, the

retention rate of relapse prevention treatment with methadone or buprenorphine is not high .[13]On the other hand, due to the side effects of the drug and the legal requirements of the prescription, some patients are not interested in this treatment.[6,13-14]For the use of opioid receptor antagonists, how to effectively excessive the withdrawal period before the use of naltrexone is a challenge.[15] Although drug treatment can benefit patients, many patients relapse after drug withdrawal.[16-17]For POAS, supportive drugs are generally recommended for symptomatic treatment,[18]Such as antidepressants, sedatives and hypnotics. However, the effect on POAS is not satisfactory. A long-term follow-up study showed that,[19] During the observation period of 10-30 years, less than 30% of the patients stably abstained from using opioids. Compared with the acute stage, POAS is one of the main reasons for relapse. Therefore, it is necessary to seek a new treatment plan.

As a part of traditional Chinese medicine, acupuncture was used to treat drug addiction as early as 1972, neurosurgeon Wen Hongli unexpected discovered that acupuncture can partially eliminate the withdrawal symptoms caused by heroin withdrawal.[20] In 1985, the auricular acupuncture treatment scheme proposed by the National Acquirement Detoxification Association had been adopted by many countries.[21] Acupuncture can relieve opioid related depression and anxiety as an auxiliary treatment.[22] A META analysis shows that acupuncture combined with opioid receptor agonists can effectively control withdrawal symptoms.[23] Preclinical studies also confirmed that acupuncture may inhibit morphine withdrawal syndrome by mediating GABA receptor.[24-26] Some studies have shown that patients can also benefit from the acupuncture in POAS.[27-28]

However, there no systematic review to evaluate the clinical evidence. This study will evaluate the efficacy and safety of acupuncture as an intervention for POAS based on the

method of evidence-based medicine. This systematic analysis will provide reference for clinical decision-making.

Methods

The protocol follows the *Cochrane Handbook for Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol statement guidelines*.[29-30]

Eligibility criteria

Types of studies

We will include all randomized controlled trials of acupuncture for POAS, and the intervention methods include various types of acupuncture therapy.

Types of participants

We will include patients who meet the diagnostic criteria of opioid drug dependence. Age is more than 18 years old. And the patients are in the protracted withdrawal period, without race and gender restrictions.

The diagnosis of opioid drug dependence refers to internationally recognized diagnostic standards, such as:

1. *Diagnostic and Statistical Manual of Mental Disorders*: diagnostic criteria for opioid withdrawal;
2. *Classification and Diagnostic Criteria for Mental Disorders in China*: diagnostic criteria for opioid withdrawal;
3. *Diagnostic criteria of the International Classification of Diseases*: about mental and behavioral disorders caused by the use of psychoactive substances.

The definition of protracted abstinence period refers to *the Guiding Principles for the Diagnosis and Treatment of Disorders Related to the Use of Opioids*. The acute abstinence period of short acting opioids such as heroin lasts for about 7-10 days, and enters into the protracted abstinence period after the symptoms in the acute period subside. Therefore, this study defines the protracted abstinence period as stopping the use of opioids>10 days.

Types of interventions and comparisons

We define conventional acupuncture therapy as the experimental intervention. It includes manual acupuncture (MA), electroacupuncture (EA), auricular acupuncture (AA), or acupuncture therapy in combination with other treatments, such as drugs, psychotherapy, kinesitherapy, etc. It does not limit the theoretical background of treatment, such as traditional Chinese medicine (TCM), Chinese medicine in Japan, Korean medical science, and modern medicine. There is no limit to the frequency, duration, course, acupoint selection and needling method of treatment.

The control intervention measures include other treatments except acupuncture, such as psychotherapy, exercise therapy, traditional Chinese medicine, other traditional medicine therapies, western medicine. It also includes wait list control and sham acupuncture control. If it is a combination of acupuncture and medicine intervention, the control group can use sham acupuncture or placebo as the control.

Types of outcomes

Primary outcomes

The main primary outcome is the severity of withdrawal symptoms, and the drug craving will be evaluated with the standard opioid withdrawal assessment scale. Such as Clinical Opioid Withdrawal Scale, Short Opiate Withdrawal Scale, Himmelsbach Scoring Table for

Withdrawal symptoms, etc.

Secondary outcomes

Emotional disorders: The standard scale will be used to score the degree of anxiety and depression, such as Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Hamilton Anxiety Scale (HAM-A), Hamilton Depression Scale (HAM-D), etc.

Sleep disorders: Score the severity of sleep disorders with standard scales, such as Pittsburgh Sleep Quality Index (PSQI).

Other delayed withdrawal symptoms: Such as body pain, fatigue, gastrointestinal symptoms, etc.

Incidence rate of adverse events.

Information sources

Electronic databases

Databases include Web of Science, Embase, PubMed, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang Database (WF), Chinese Scientific Journal Database (VIP). From the inception to December 15, 2022, the language of articles will not be limited. And we will search for potential qualification articles from the references list of retrieved articles.

Other resources

The ongoing or unpublished trials will be retrieved through the World Health Organization International Clinical Trial Registry Platform (WHO ICTRP), ClinicalTrials.gov and the Chinese Clinical Trial Registry (Chi CTR), Cochrane Central Register of Controlled Trials

(CENTRAL).

Search strategy

The retrieval strategy follows the PICOS principle of evidence-based medicine, and the search keywords are constructed by combining free words and MeSH words. The retrieval strategy in PubMed is shown in table 1.

Table1 Retrieval strategy in PubMed

Sequence	Items
#1	Opioid-Related Disorders (MeSH)
#2	Opioid-Related Disorders
#3	Addiction
#4	Opioid dependence
#5	Opioid withdrawal
#6	Opioid abstinence
#7	Opioid
#8	Drug abuse
#9	Substances abuse
#10	Protracted withdrawal
#11	Protracted abstinence
#12	Heroin
#13	Cocaine
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 OR #10 OR #11 OR #12 OR #13
#15	Acupuncture (MeSH)
#16	Acupuncture
#17	Electroacupuncture
#18	Auricular acupuncture
#19	Acupoint
#20	Needling
#21	Meridian
#22	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	Clinical trials (MeSH)
#24	Randomized Clinical trials
#25	Randomized
#26	Random
#27	Placebo
#28	Trial
#29	Groups

#30	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
#31	#14 AND #22AND #30

Selection of studies

According to the retrieval strategy, the articles will be initially screened through reading the title and abstract, exclude studies that obviously do not meet the inclusion criteria, then the full text will be checked through further evaluation. Two researchers independently completed the above two procedures. Any differences will be resolved by a third researcher through discussion or evaluation. The selection process is shown in figure 1.

Data extraction and management

For eligible articles, two independent researchers extract data and code it into the data extraction table. The data extraction table contains the following main information: first author's name, nationality, year of publication, research design, sample size, general characteristics of subjects, diagnostic criteria, intervention methods, acupoint prescriptions, treatment cycle, control methods, efficacy indicators, follow-up, and data analysis methods (full analysis set, per protocol set). Any differences will be resolved by a third researcher through discussion or evaluation. If the data is incomplete, we will try to contact the author to obtain.

Assessment of risk of bias in included studies

Two reviewers will independently use the Cochrane Collaboration's risk of bias tool to assess the bias risk in the included randomized controlled trials. The evaluation contents include: randomization 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 risks and high-risk. Differences will be

resolved by a third reviewer.

Data synthesis

Data synthesis

RevMan V5.4.1 will be used for data analysis and quantitative data synthesis. Risk ratio (RR) is used as the consolidated statistic for measurement data. Different studies may use different scales to evaluate the same observation index, and we will use the standardized mean difference (SMD) and its 95% confidence interval (CI) to combine the enumeration data. If RR and SMD are not available, we will use the available data for recalculation, such as median or p values and CIS. It is considered statistically significant when $p<0.05$.

Assessment of heterogeneity

We will use χ^2 test and I^2 statistics to assess the heterogeneity of the included studies. If I^2 is less than 50%, and P is more than 0.1(I^2 < 50%, or P > 0.1), it is considered that the included articles is homogeneous, and the fixed-effect model will be used to calculate the consolidation statistics. If not (I^2 > 50%, or $P \leq 0.1$), it is considered that there is heterogeneity in the included studies, and subgroup analysis will be used to discuss the causes of heterogeneity. When subgroup analysis cannot explain heterogeneity, random effect model is used for statistical analysis. For the three-arm test, all groups are classified according to the intervention group and the control group, and the groups of the same category are combined according to the method of combining multiple doses in the Cochrane System Evaluation Manual

Subgroup analysis

When there is heterogeneity in the included studies and the sample size is large enough, analyze the reasons for the heterogeneity through acupuncture intervention methods, such as

electroacupuncture, hand acupuncture, ear acupuncture, etc. If meta-analysis is not available, we will make a narrative description.

Sensitivity analysis

Through sensitivity analysis, we will further identify other heterogeneity caused by research methodology design or clinical differences, and evaluate the robustness of the results.

Assessment of publication bias

If the eligible articles are more than 10, we will use funnel chart to evaluate publication bias.

Quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) will be used to assess the quality of evidence. The assessment will be conducted independently by the two reviewers. Differences will be resolved through discussion by a third reviewer.

Ethics and dissemination

This study will not involve patients' personal privacy, so ethical review is not required, and the results will be disseminated in a peer-reviewed journal.

Ethics statements

Patient consent for publication

Not applicable.

References

1 WB Cammarano, JF Pittet, S Weitz, RM Schlobohm, JD Marks. Acute withdrawal syndrome related to the administration of

analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med* 1998;26(4):676-84.
2 M Gupta, SB Gokarakonda, FN Attia. Withdrawal Syndromes. 2022.
3 DR Wesson, W Ling. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs* 2003;35(2):253-59.
4 JJ Pergolizzi, RB Raffa, MH Rosenblatt. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: Current understanding and approaches to management. *J Clin Pharm Ther* 2020;45(5):892-903.
5 RD Weiss, JS Potter, ML Griffin, et al. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *J Subst Abuse Treat* 2014;47(2):140-45.
6 AB Srivastava, JJ Mariani, FR Levin. New directions in the treatment of opioid withdrawal. *Lancet* 2020;395(10241):1938-48.
7 TR Kosten, TP George. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect* 2002;1(1):13-20.
8 G Aston-Jones, GC Harris. Brain substrates for increased drug seeking during protracted withdrawal. *Neuropharmacology* 2004;47 Suppl 1:167-79.
9 GC Harris, G Aston-Jones. Activation in extended amygdala corresponds to altered hedonic processing during protracted morphine withdrawal. *Behav Brain Res* 2007;176(2):251-58.
10 D Ayanga, D Shorter, TR Kosten. Update on pharmacotherapy for treatment of opioid use disorder. *Expert Opin Pharmacother* 2016;17(17):2307-18.
11 JL Koehl, DE Zimmerman, PJ Bridgeman. Medications for management of opioid use disorder. *Am J Health Syst Pharm* 2019;76(15):1097-103.
12 L Gowing, R Ali, JM White, D Mbewe. Buprenorphine for managing opioid withdrawal. *Cochrane Database Syst Rev* 2017;2(2):D2025.
13 K McElrath. Medication-Assisted Treatment for Opioid Addiction in the United States: Critique and Commentary. *Subst Use Misuse* 2018;53(2):334-43.
14 CM Jones, GT Baldwin, T Manocchio, JO White, KA Mack. Trends in Methadone Distribution for Pain Treatment, Methadone Diversion, and Overdose Deaths - United States, 2002-2014. *MMWR Morb Mortal Wkly Rep* 2016;65(26):667-71.
15 A Bisaga, P Mannelli, M Yu, et al. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: A phase 3 randomized trial. *Drug Alcohol Depend* 2018;187:171-78.
16 G Bart. Maintenance medication for opiate addiction: the foundation of recovery. *J Addict Dis* 2012;31(3):207-25.
17 BS Bentzley, KS Barth, SE Back, SW Book. Discontinuation of buprenorphine maintenance therapy: perspectives and outcomes. *J Subst Abuse Treat* 2015;52:48-57.
18 TR Kosten, LE Baxter. Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. *Am J Addict* 2019;28(2):55-62.
19 YI Hser, E Evans, C Grella, W Ling, D Anglin. Long-term course of opioid addiction. *Harv Rev Psychiatry* 2015;23(2):76-89.
20 CL Cui, LZ Wu, YJ Li. Acupuncture for the treatment of drug addiction. *Int Rev Neurobiol* 2013;111:235-56.
21 A Margolin. Acupuncture for substance abuse. *Curr Psychiatry Rep* 2003;5(5):333-39.
22 SL Wu, AW Leung, DT Yew. Acupuncture for Detoxification in Treatment of Opioid Addiction. *East Asian Arch Psychiatry* 2016;26(2):70-76.
23 TT Liu, J Shi, DH Epstein, YP Bao, L Lu. A meta-analysis of acupuncture combined with opioid receptor agonists for treatment of opiate-withdrawal symptoms. *Cell Mol Neurobiol* 2009;29(4):449-54.
24 JH Lee, HY Kim, EY Jang, et al. Effect of acupuncture on naloxone-precipitated withdrawal syndrome in morphine-experienced rats: the mediation of GABA receptors. *Neurosci Lett* 2011;504(3):301-05.
25 BH Lee, JY Ku, RJ Zhao, et al. Acupuncture at HT7 suppresses morphine self-administration at high dose through GABA system. *Neurosci Lett* 2014;576:34-39.
26 SS Yoon, H Kim, KH Choi, et al. Acupuncture suppresses morphine self-administration through the GABA receptors. *Brain Res Bull* 2010;81(6):625-30.
27 Wang Rui. A Clinical Study on Acupuncture Treatment of Female Protracted Opioid Abstinence Syndrome. *Chengdu University of TCM*, 2020.

28 Gao Xiaoyue, Liang Yan, Huo Lili, et al. Effect of Warm Needling on Protracted Withdrawal Symptoms in Heroin Addicts of Kidney Yang Deficiency Pattern. *Shanghai Journal of Acupuncture and Moxibustion* 2021;40(10):1217-22.

29 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2016;354:i4086.

30 D Moher, L Shamseer, M Clarke, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

Supplementary materials

Figure 1.

Author Contributions

TL and YZ contributed equally. TL and YZ designed this study. YR is the guarantor for the article. The manuscript of this protocol was drafted by TL and revised by YR and YZ. The research strategy was developed 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 be served as the third author for settlement of disagreement. YR and YZ will be the adviser for methodology. All authors have approved the publication of the protocol.

Funding

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Competing interest

None declared.

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.

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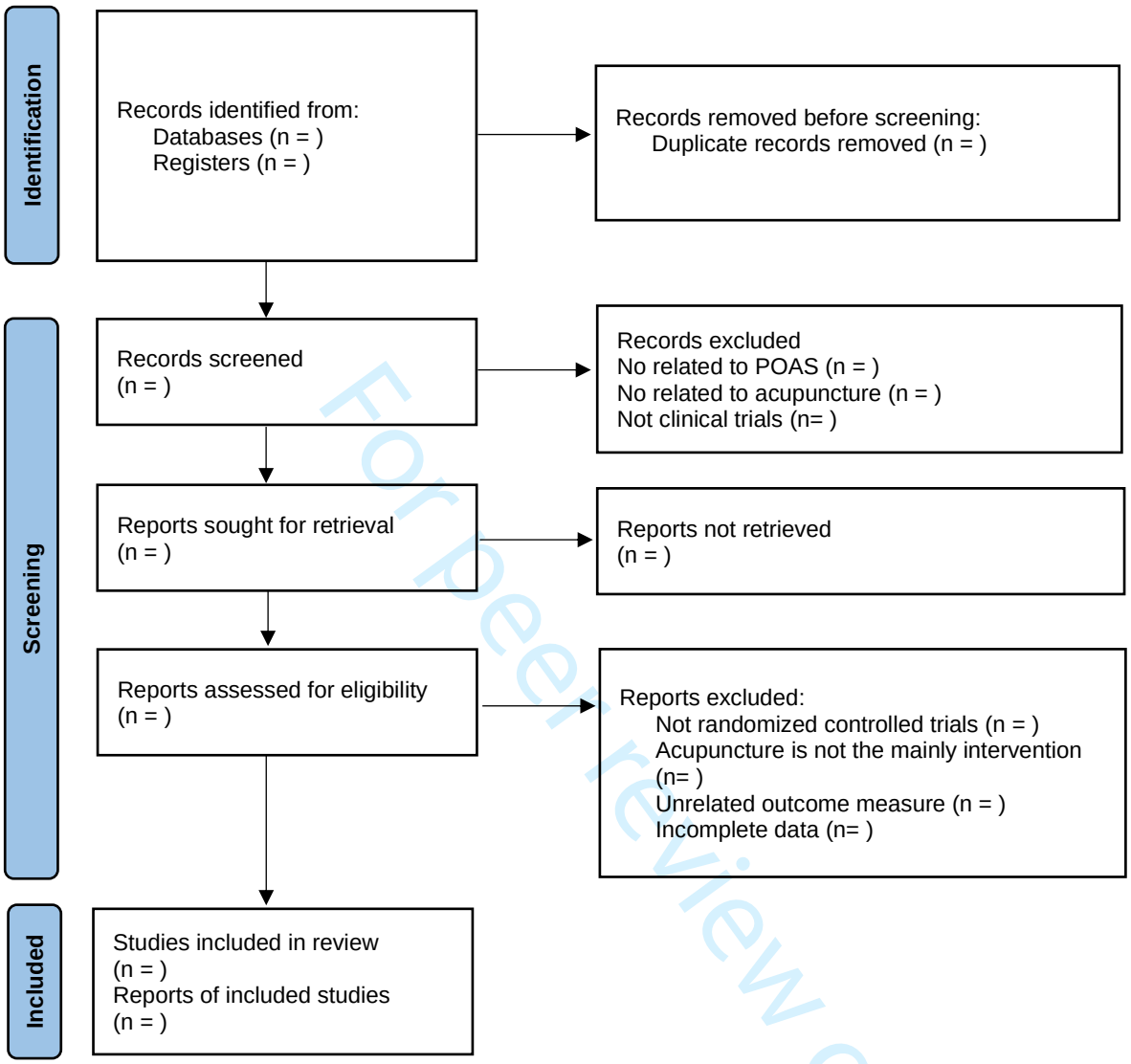

Figure 1 Flow diagram of the study selection process. POAS, protracted opioid abstinence syndrome.

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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-types substances (OTS) for a certain amount of time, which is one of the main causes of relapse. Studies have shown that acupuncture would be effective for treating 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 for studies will be carried out in the following databases from inception to January 31, 2023: Web of Science, Embase, PubMed, China Biology Medicine

(CBM), China National Knowledge Infrastructure (CNKI), Wan Fang (WF), and Chinese Scientific Journal Database (VIP). World Health Organization International Clinical Trial Registry Platform (WHO ICTRP), ClinicalTrials.gov, and Chinese Clinical Trial Registry (Chi CRT) will also be searched for ongoing relevant trials, and "grey literatures" will be identified from GreyNet International, Open Grey and Google Scholar. Randomized controlled trials (RCTs) regarding acupuncture therapy for the treatment of POAS will be included. The primary outcome is the severity of protracted withdrawal symptoms. Two reviewers will screen the inclusion criteria, extract data, and assess the risk of bias, respectively. The evidence quality will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE), and data synthesis will be performed using Revman V5.4.1.

Ethics and dissemination

This study will not involve patients' personal privacy, so ethical review is not required, and the results will be disseminated in a peer-reviewed journal.

Strengths and limitations of this study

This study will be the first systematic review and meta-analysis to evaluate the efficacy and safety of acupuncture for POAS.

POAS usually induces persistent abuse of OTS and relapse after rehabilitation. This study will be able to provide evidence-based support for the clinical application of acupuncture in POAS treatment so as to alleviate the patients' symptoms and prevent them from continuous OTS abuse.

This study will evaluate the efficacy and safety of acupuncture in the treatment of POAS with 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.

Systematic review registration

The study protocol has been registered on PROSPERO (Registration No. CRD42022382978).

Keywords: acupuncture, protracted opioid abstinence syndrome, substances abuse, opioid dependence.

Introduction

Opioid-type substances (OTS) abuse presents a great threat to global public health. Long-term use of these substances interferes the central neural system, especially the reward system causing drug dependence,[1-2] and discontinuation or reduction of OTS could induce a series of physical and mental symptoms, called opioid abstinence syndrome, [3-4] which can be classified into acute abstinence opioid syndrome (AAOS) and protracted opioid abstinence syndrome (POAS) according to the time-length of OTS discontinuation.[5-7] The acute abstinence syndrome typically last for less than 10 days, and the patients experience multiple symptoms like anxiety, irritability, restlessness, sweating, tears, runny nose, insomnia, yawning, pupil dilation, muscle soreness. Tachypnea, tachycardia, hypertension, nausea, vomiting, diarrhea, erection and fever are also reported in severe cases.[8-10] Then came the protracted stage, which will last for months even years, and the patients would suffer persistent physical discomforts, anxiety, depression, and insomnia.[5-7] 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 safety, but severe clinical symptoms can lead to severe body fluid loss 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 opioids,[14]opioid induced changes including ventral tegmental area (VTA), nucleus accumbens and amygdala.[15-16] 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 for several patients,[18] while it often results in poor treatment compliance due to its adverse reactions.[19]On the other hand, due to the side effects of the drug and the legal requirements of the prescription, some patients are not interested in this treatment.[13,19-20]There are also other alternative therapies that have might be effective for POAS, such as psychotherapy and kinesitherapy. These therapies still need to be further investigated, and their high entry barriers would limit the popularization and application. A long-term follow-up study showed that,[21] during the observation period of 10-30 years, less than 30% of the patients stably abstained from using opioids. The above situations highlight an urgent need for a treatment approach that would be effective and safe in alleviating the symptoms of POAS patients so as to help them rehabilitate from opioid dependence and back to their normal life.

Acupuncture is an essential part of traditional Chinese medicine (TCM), since its therapeutic effects on psychostimulant-dependence have been 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 proposed by the National Acquirement Detoxification

Association had been adopted by many countries.[25] Acupuncture can alleviate the negative affect (depression and anxiety) , insomnia, and physical abstinence symptoms in POAS patients.[26-27]Animal experiments also confirmed that acupuncture mediate central dopaminergic system and increase the expression of endogenous opioid peptides (EOP) to alleviate the protracted abstinence. [28-31]Therefore, acupuncture could be a promising therapy for POAS.

However, there remains a lack of systematic review and meta-analysis to synthesize the data of currently published relevant studies. We plan to conduct this study to review the current clinical trials regarding acupuncture for POAS treatment and systematically assess the efficacy and safety, so as 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 Reviews and Meta-Analyses Protocol statement guidelines.*[32-33]

Eligibility criteria

Types of studies

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

Types of participants

Patients meeting the well-accepted diagnostic criteria of OTS dependence. Age is more than

18 years old. And the patients are in the protracted withdrawal period, without race and gender restrictions.

The diagnosis of OTS dependence refers to internationally recognized diagnostic standards, such as:

1. *Diagnostic and Statistical Manual of Mental Disorders (DSM)*: diagnostic criteria for opioid withdrawal;
2. *Classification and Diagnostic Criteria for Mental Disorders in China*: diagnostic criteria for opioid withdrawal;
3. *Diagnostic criteria of the International Classification of Diseases*: about mental and behavioral disorders caused by the use of psychoactive substances.

The 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:

1. Discontinuation of OTS for at least 10 days.

2. Reporting evident protracted abstinence symptoms: anxiety, depression, insomnia, and physical discomforts.

3. Persistent "negative" in urine morphine test.

Types of interventions and comparisons

The intervention should be the acupuncture therapy, which refers to using acupuncture needle and inserting into the subcutaneous tissues of the acupoints. It includes manual acupuncture (MA), electroacupuncture (EA), auricular acupuncture (AA). No restrictions were set to acupuncture modalities. Other acupoint stimulation therapies will be excluded, such as acupressure, acupoint application, and transcutaneous acupoint electrical stimulation (TAES).

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 outcomes

The main primary outcome is the severity of protracted withdrawal symptoms that are assessed by validated and reliable scales like Clinical Opioid Withdrawal Scale (COWs), Short Opiate Withdrawal Scale (SOWs), Himmelsbach Scoring Table for Withdrawal symptoms, etc..

Secondary outcomes

1. Severity of negative affect

Anxiety and depression scored using validated scales such as Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Hamilton Anxiety Scale (HAM-A), Hamilton Depression Scale (HAM-D).

2. Insomnia

Insomnia scored by validated scales such as Pittsburgh Sleep Quality Index (PSQI).

3.Incidence of adverse events (AEs).

Information sources

Electronic databases

Databases include Web of Science, Embase, PubMed, China Biology Medicine (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang Database (WF), Chinese Scientific Journal Database (VIP). From the inception to January 31, 2023, the language of articles will

not be limited. And we will search for potential qualification articles from the references list of retrieved articles.

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#6	Opioid abstinence
#7	Opioid
#8	Drug abuse
#9	Substances abuse
#10	Protracted withdrawal
#11	Protracted abstinence
#12	Heroin
#13	Cocaine
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 OR #10 OR #11 OR #12 OR #13
#15	Acupuncture (MeSH)
#16	Acupuncture
#17	Electroacupuncture

#18	Auricular acupuncture
#19	Acupoint
#20	Needling
#21	Meridian
#22	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	Clinical trials (MeSH)
#24	Randomized Clinical trials
#25	Randomized
#26	Random
#27	Placebo
#28	Trial
#29	Groups
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#31	#14 AND #22AND #30

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RevMan V5.4.1 will be used for data analysis and quantitative data synthesis. Risk ratio (RR) will be used as pooled statistic for dichotomous data, and standardized mean difference (SMD) will be used for continuous data. The 95% confidence interval (95%CI) of each effect will be provided. A *p* value less than 0.05 will indicate statistical significance.

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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 research 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 be served as the third author for settlement of disagreement. YR and YZ will be the adviser for methodology. All authors have approved the publication of this study protocol.

Competing interest

None declared.

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References

1 EL Gardner. Addiction and brain reward and antireward pathways. *Adv Psychosom Med* 2011;30:22-60.

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7 Zhang Ruimin, Zhang Ruiling, Zhao Min, et al. Guidelines for the Diagnosis and Treatment of Opioid Related Disorders. *Chinese Journal of Drug Abuse Prevention and Treatment* 2017;23(01):1-03.
8 WB Cammarano, JF Pittet, S Weitz, RM Schlobohm, JD Marks. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med* 1998;26(4):676-84.
9 M Gupta, SB Gokarakonda, FN Attia. Withdrawal Syndromes. 2022.
10 DR Wesson, W Ling. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs* 2003;35(2):253-59.
11 JJ Pergolizzi, RB Raffa, MH Rosenblatt. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: Current understanding and approaches to management. *J Clin Pharm Ther* 2020;45(5):892-903.
12 RD Weiss, JS Potter, ML Griffin, et al. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *J Subst Abuse Treat* 2014;47(2):140-45.
13 AB Srivastava, JJ Mariani, FR Levin. New directions in the treatment of opioid withdrawal. *Lancet* 2020;395(10241):1938-48.
14 TR Kosten, TP George. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect* 2002;1(1):13-20.
15 G Aston-Jones, GC Harris. Brain substrates for increased drug seeking during protracted withdrawal. *Neuropharmacology* 2004;47 Suppl 1:167-79.
16 GC Harris, G Aston-Jones. Activation in extended amygdala corresponds to altered hedonic processing during protracted morphine withdrawal. *Behav Brain Res* 2007;176(2):251-58.
17 D Ayanga, D Shorter, TR Kosten. Update on pharmacotherapy for treatment of opioid use disorder. *Expert Opin Pharmacother* 2016;17(17):2307-18.
18 JL Koehl, DE Zimmerman, PJ Bridgeman. Medications for management of opioid use disorder. *Am J Health Syst Pharm* 2019;76(15):1097-103.
19 K McElrath. Medication-Assisted Treatment for Opioid Addiction in the United States: Critique and Commentary. *Subst Use Misuse* 2018;53(2):334-43.
20 CM Jones, GT Baldwin, T Manocchio, JO White, KA Mack. Trends in Methadone Distribution for Pain Treatment, Methadone Diversion, and Overdose Deaths - United States, 2002-2014. *MMWR Morb Mortal Wkly Rep* 2016;65(26):667-71.
21 YI Hser, E Evans, C Grella, W Ling, D Anglin. Long-term course of opioid addiction. *Harv Rev Psychiatry* 2015;23(2):76-89.
22 CL Cui, LZ Wu, YJ Li. Acupuncture for the treatment of drug addiction. *Int Rev Neurobiol* 2013;111:235-56.
23 Wang Rui. A Clinical Study on Acupuncture Treatment of Female Protracted Opioid Abstinence Syndrome. *Chengdu University of TCM*, 2020.
24 Gao Xiaoyue, Liang Yan, Huo Lili, et al. Effect of Warm Needling on Protracted Withdrawal Symptoms in Heroin Addicts of Kidney Yang Deficiency Pattern. *Shanghai Journal of Acupuncture and Moxibustion* 2021;40(10):1217-22.
25 A Margolin. Acupuncture for substance abuse. *Curr Psychiatry Rep* 2003;5(5):333-39.
26 SL Wu, AW Leung, DT Yew. Acupuncture for Detoxification in Treatment of Opioid Addiction. *East Asian Arch Psychiatry* 2016;26(2):70-76.
27 TT Liu, J Shi, DH Epstein, YP Bao, L Lu. A meta-analysis of acupuncture combined with opioid receptor agonists for treatment of opiate-withdrawal symptoms. *Cell Mol Neurobiol* 2009;29(4):449-54.
28 B Wang, F Luo, YQ Xia, JS Han. Peripheral electric stimulation inhibits morphine-induced place preference in rats. *Neuroreport* 2000;11(5):1017-20.
29 J Liang, XJ Ping, YJ Li, et al. Morphine-induced conditioned place preference in rats is inhibited by electroacupuncture at 2 Hz: role of enkephalin in the nucleus accumbens. *Neuropharmacology* 2010;58(1):233-40.
30 LZ Wu, CL Cui, JB Tian, D Ji, JS Han. Suppression of morphine withdrawal by electroacupuncture in rats: dynorphin and kappa-opioid receptor implicated. *Brain Res* 1999;851(1-2):290-96.
31 JS Han, RL Zhang. Suppression of morphine abstinence syndrome by body electroacupuncture of different frequencies in rats.

Drug Alcohol Depend 1993;31(2):169-75.

32 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2016;354:i4086.

33 D Moher, L Shamseer, M Clarke, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

34 H MacPherson, DG Altman, R Hammerschlag, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *J Altern Complement Med* 2010;16(10):T1-14.

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

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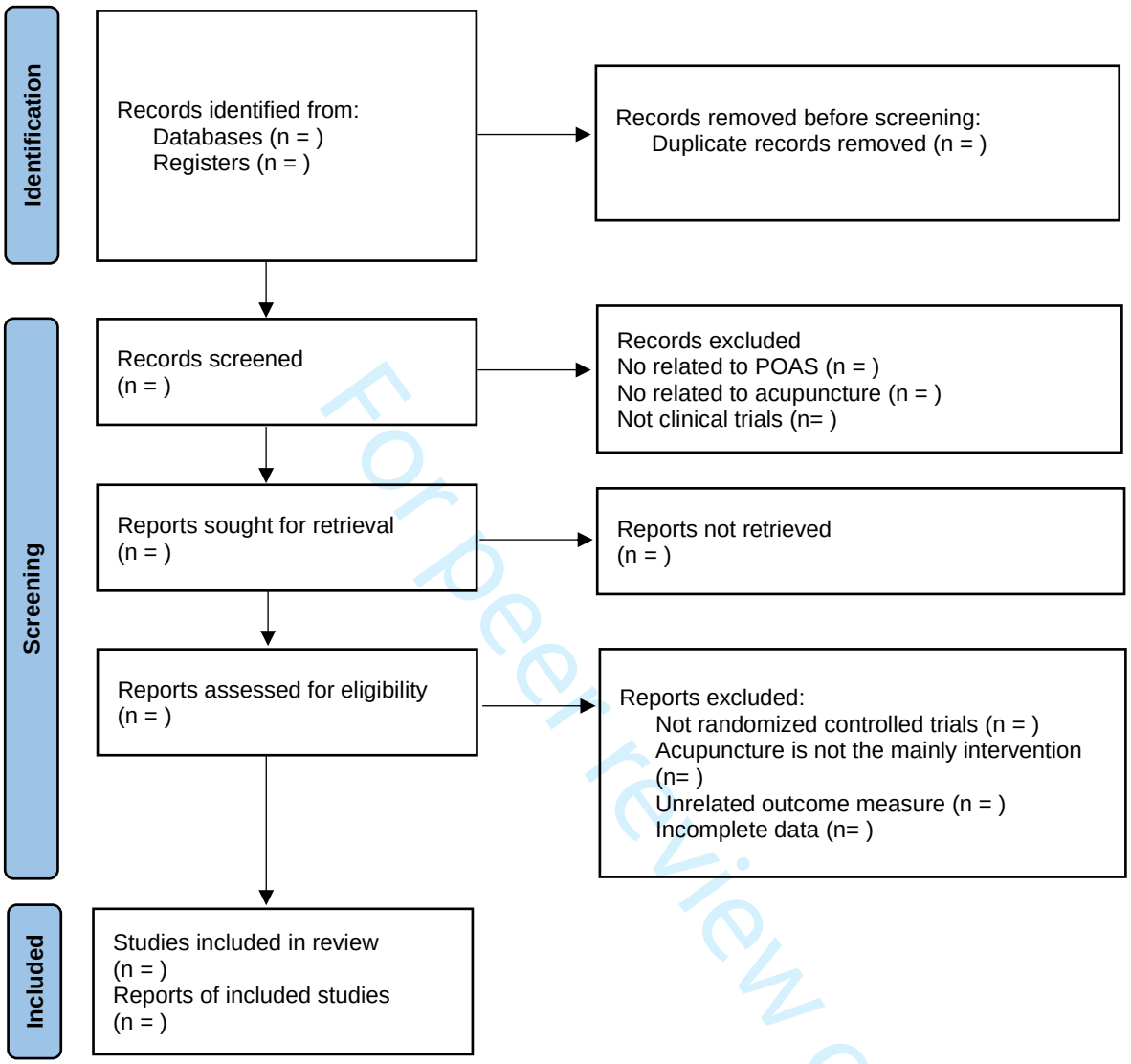

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Secondary Subject Heading:	Addiction
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Acupuncture for protracted opioid abstinence syndrome: study protocol for a systematic review and meta-analysis

Tao Li[1], Yiwei Zeng[1], Feng Zhang[2], Xin Zhou[1], Yulan Ren[3]

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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-types substances (OTS) for a certain amount of time, which is one of the main causes of relapse. Studies have shown that acupuncture would be effective for treating 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 for studies will be carried out in the following databases from inception to January 31, 2023: Web of Science, Embase, PubMed, China Biology Medicine

(CBM), China National Knowledge Infrastructure (CNKI), Wan Fang (WF), and Chinese Scientific Journal Database (VIP). World Health Organization International Clinical Trial Registry Platform (WHO ICTRP), ClinicalTrials.gov, and Chinese Clinical Trial Registry (Chi CRT) will also be searched for ongoing relevant trials, and "grey literatures" will be identified from GreyNet International, Open Grey and Google Scholar. Randomized controlled trials (RCTs) regarding acupuncture therapy for the treatment of POAS will be included. The primary outcome is the severity of protracted withdrawal symptoms. Two reviewers will screen the inclusion criteria, extract data, and assess the risk of bias, respectively. The evidence quality will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE), and data synthesis will be performed using Revman V5.4.1.

Ethics and dissemination

This study will not involve patients' personal privacy, so ethical review is not required, and the results will be disseminated in a peer-reviewed journal.

Strengths and limitations of this study

This study will include patients who are in the protracted stage of opioid abstinence syndrome.

In order to comprehensively search for literature, this study will search seven electronic databases, four trial registration platforms, and gray literature.

This study will evaluate the efficacy and safety of acupuncture in the treatment of POAS with 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.

Systematic review registration

The study protocol has been registered on PROSPERO (Registration No. CRD42022382978).

Keywords: acupuncture, protracted opioid abstinence syndrome, substances abuse, opioid dependence.

Introduction

Opioid-type substances (OTS) abuse presents a great threat to global public health. Long-term use of these substances interferes the central neural system, especially the reward system causing drug dependence,[1-2] and discontinuation or reduction of OTS could induce a series of physical and mental symptoms, called opioid abstinence syndrome, [3-4] which can be classified into acute abstinence opioid syndrome (AAOS) and protracted opioid abstinence syndrome (POAS) according to the time-length of OTS discontinuation.[5-7] The acute abstinence syndrome typically last for less than 10 days, and the patients experience multiple symptoms like anxiety, irritability, restlessness, sweating, tears, runny nose, insomnia, yawning, pupil dilation, muscle soreness. Tachypnea, tachycardia, hypertension, nausea, vomiting, diarrhea, erection and fever are also reported in severe cases.[8-10] Then came the protracted stage, which will last for months even years, and the patients would suffer persistent physical discomforts, anxiety, depression, and insomnia.[5-7] 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 safety, but severe clinical symptoms can lead to severe body fluid loss 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 opioids,[14]opioid induced changes including ventral tegmental area (VTA), nucleus accumbens and amygdala.[15-16] 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 for several patients,[18] while it often results in poor treatment compliance due to its adverse reactions.[19]On the other hand, due to the side effects of the drug and the legal requirements of the prescription, some patients are not interested in this treatment.[13,19-20]There are also other alternative therapies that have might be effective for POAS, such as psychotherapy and kinesitherapy. These therapies still need to be further investigated, and their high entry barriers would limit the popularization and application. A long-term follow-up study showed that,[21] during the observation period of 10-30 years, less than 30% of the patients stably abstained from using opioids. The above situations highlight an urgent need for a treatment approach that would be effective and safe in alleviating the symptoms of POAS patients so as to help them rehabilitate from opioid dependence and back to their normal life.

Acupuncture is an essential part of traditional Chinese medicine (TCM), since its therapeutic effects on psychostimulant-dependence have been 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 proposed by the National Acquirement Detoxification Association had been adopted by many countries.[25] Acupuncture can alleviate the negative

affect (depression and anxiety) , insomnia, and physical abstinence symptoms in POAS patients.[26-27]Animal experiments also confirmed that acupuncture mediate central dopaminergic system and increase the expression of endogenous opioid peptides (EOP) to alleviate the protracted abstinence. [28-31]Therefore, acupuncture could be a promising therapy for POAS.

However, there remains a lack of systematic review and meta-analysis to synthesize the data of currently published relevant studies. We plan to conduct this study to review the current clinical trials regarding acupuncture for POAS treatment and systematically assess the efficacy and safety, so as 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 Reviews and Meta-Analyses Protocol statement guidelines.*[32-33]

Eligibility criteria

Types of studies

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

Types of participants

Patients meeting the well-accepted diagnostic criteria of OTS dependence. Age is more than 18 years old. And the patients are in the protracted withdrawal period, without race and gender

restrictions.

The diagnosis of OTS dependence refers to internationally recognized diagnostic standards, such as:

1. *Diagnostic and Statistical Manual of Mental Disorders (DSM)*: diagnostic criteria for opioid withdrawal;
2. *Classification and Diagnostic Criteria for Mental Disorders in China*: diagnostic criteria for opioid withdrawal;
3. *Diagnostic criteria of the International Classification of Diseases*: about mental and behavioral disorders caused by the use of psychoactive substances.

The 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:

1. Discontinuation of OTS for at least 10 days.

2. Reporting evident protracted abstinence symptoms: anxiety, depression, insomnia, and physical discomforts.

3. Persistent "negative" in urine morphine test.

Types of interventions and comparisons

The intervention should be the acupuncture therapy, which refers to using acupuncture needle and inserting into the subcutaneous tissues of the acupoints. It includes manual acupuncture (MA), electroacupuncture (EA), auricular acupuncture (AA). No restrictions were set to acupuncture modalities. Other acupoint stimulation therapies will be excluded, such as acupressure, acupoint application, and transcutaneous acupoint electrical stimulation (TAES). 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 outcomes

The main primary outcome is the severity of protracted withdrawal symptoms that are assessed by validated and reliable scales like Clinical Opioid Withdrawal Scale (COWs), Short Opiate Withdrawal Scale (SOWs), Himmelsbach Scoring Table for Withdrawal symptoms, etc..

Secondary outcomes

1. Severity of negative affect

Anxiety and depression scored using validated scales such as Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), Hamilton Anxiety Scale (HAM-A), Hamilton Depression Scale (HAM-D).

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References

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6 Li Bo. Systematic evaluation and clinical research on the treatment of opioid withdrawal syndrome with traditional Chinese medicine. *Beijing University of TCM* 2006.
7 Zhang Ruimin, Zhang Ruiling, Zhao Min, et al. Guidelines for the Diagnosis and Treatment of Opioid Related Disorders. *Chinese Journal of Drug Abuse Prevention and Treatment* 2017;23(01):1-03.
8 WB Cammarano, JF Pittet, S Weitz, RM Schlobohm, JD Marks. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med* 1998;26(4):676-84.
9 M Gupta, SB Gokarakonda, FN Attia. Withdrawal Syndromes. 2022.
10 DR Wesson, W Ling. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs* 2003;35(2):253-59.
11 JJ Pergolizzi, RB Raffa, MH Rosenblatt. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: Current understanding and approaches to management. *J Clin Pharm Ther* 2020;45(5):892-903.
12 RD Weiss, JS Potter, ML Griffin, et al. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *J Subst Abuse Treat* 2014;47(2):140-45.
13 AB Srivastava, JJ Mariani, FR Levin. New directions in the treatment of opioid withdrawal. *Lancet* 2020;395(10241):1938-48.
14 TR Kosten, TP George. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect* 2002;1(1):13-20.
15 G Aston-Jones, GC Harris. Brain substrates for increased drug seeking during protracted withdrawal. *Neuropharmacology* 2004;47 Suppl 1:167-79.
16 GC Harris, G Aston-Jones. Activation in extended amygdala corresponds to altered hedonic processing during protracted morphine withdrawal. *Behav Brain Res* 2007;176(2):251-58.
17 D Ayanga, D Shorter, TR Kosten. Update on pharmacotherapy for treatment of opioid use disorder. *Expert Opin Pharmacother* 2016;17(17):2307-18.
18 JL Koehl, DE Zimmerman, PJ Bridgeman. Medications for management of opioid use disorder. *Am J Health Syst Pharm* 2019;76(15):1097-103.
19 K McElrath. Medication-Assisted Treatment for Opioid Addiction in the United States: Critique and Commentary. *Subst Use Misuse* 2018;53(2):334-43.
20 CM Jones, GT Baldwin, T Manocchio, JO White, KA Mack. Trends in Methadone Distribution for Pain Treatment, Methadone Diversion, and Overdose Deaths - United States, 2002-2014. *MMWR Morb Mortal Wkly Rep* 2016;65(26):667-71.
21 YI Hser, E Evans, C Grella, W Ling, D Anglin. Long-term course of opioid addiction. *Harv Rev Psychiatry* 2015;23(2):76-89.
22 CL Cui, LZ Wu, YJ Li. Acupuncture for the treatment of drug addiction. *Int Rev Neurobiol* 2013;111:235-56.
23 Wang Rui. A Clinical Study on Acupuncture Treatment of Female Protracted Opioid Abstinence Syndrome. *Chengdu University of TCM*, 2020.
24 Gao Xiaoyue, Liang Yan, Huo Lili, et al. Effect of Warm Needling on Protracted Withdrawal Symptoms in Heroin Addicts of Kidney Yang Deficiency Pattern. *Shanghai Journal of Acupuncture and Moxibustion* 2021;40(10):1217-22.
25 A Margolin. Acupuncture for substance abuse. *Curr Psychiatry Rep* 2003;5(5):333-39.
26 SL Wu, AW Leung, DT Yew. Acupuncture for Detoxification in Treatment of Opioid Addiction. *East Asian Arch Psychiatry* 2016;26(2):70-76.
27 TT Liu, J Shi, DH Epstein, YP Bao, L Lu. A meta-analysis of acupuncture combined with opioid receptor agonists for treatment of opiate-withdrawal symptoms. *Cell Mol Neurobiol* 2009;29(4):449-54.
28 B Wang, F Luo, YQ Xia, JS Han. Peripheral electric stimulation inhibits morphine-induced place preference in rats.

Neuroreport 2000;11(5):1017-20.

29 J Liang, XJ Ping, YJ Li, et al. Morphine-induced conditioned place preference in rats is inhibited by electroacupuncture at 2 Hz: role of enkephalin in the nucleus accumbens. *Neuropharmacology* 2010;58(1):233-40.

30 LZ Wu, CL Cui, JB Tian, D Ji, JS Han. Suppression of morphine withdrawal by electroacupuncture in rats: dynorphin and kappa-opioid receptor implicated. *Brain Res* 1999;851(1-2):290-96.

31 JS Han, RL Zhang. Suppression of morphine abstinence syndrome by body electroacupuncture of different frequencies in rats. *Drug Alcohol Depend* 1993;31(2):169-75.

32 Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2016;354:i4086.

33 D Moher, L Shamseer, M Clarke, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.

34 H MacPherson, DG Altman, R Hammerschlag, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *J Altern Complement Med* 2010;16(10):T1-14.

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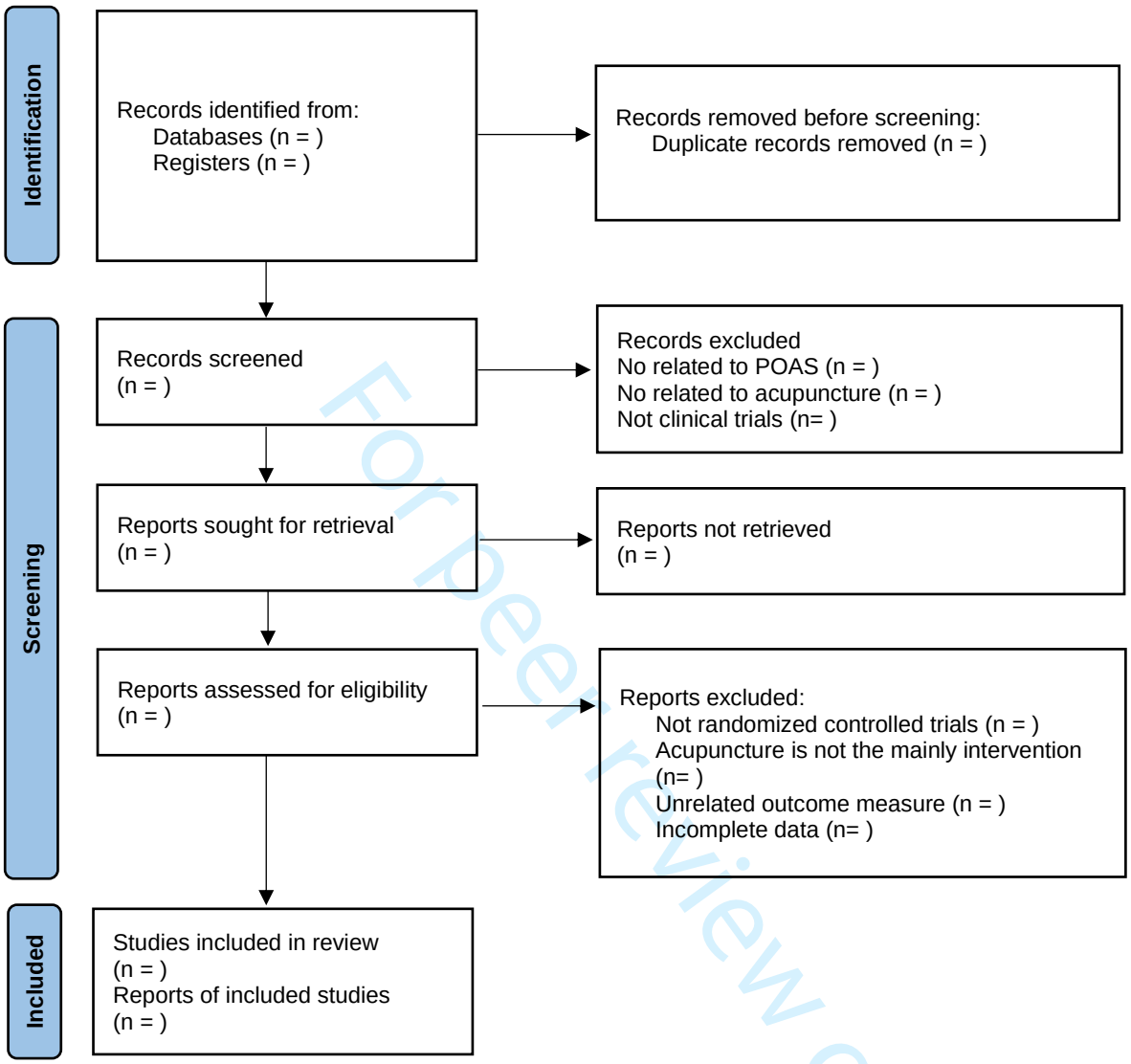

Figure 1 Flow diagram of the study selection process. POAS, protracted opioid abstinence syndrome.

Web of science search strategy

1:((((((((((TS=(opioid-Related Disorders)) OR TS=(addiction)) OR TS=(opioid dependence)) OR TS=(opioid withdrawal)) OR TS=(opioid abstinence)) OR TS=(opioid)) OR TS=(drug abuse)) OR TS=(substances abuse)) OR TS=(protracted withdrawal)) OR TS=(protracted abstinence)) OR TS=(heroin)) OR TS=(cocaine)

2: (((((TS=(acupuncture)) OR TS=(electroacupuncture)) OR TS=(auricular acupuncture)) OR TS=(acupoint)) OR TS=(needling)) OR TS=(meridian)

3: #1 AND #2

Embase search strategy

#1 exp opiate addiction/

#2 opiate addict

#3 opiate alkaloid addict

#4 opiate alkaloid dependency

#5 opiate alkaloids addict

#6 opiate crisis

#7 opiate dependence

#8 opiate dependency

#9 opiate epidemic

#10 opioid addict

#11 opioid addiction

#12 opioid crisis

#13 opioid dependence

#14 opioid dependency

#15 opioid epidemic

#16 opioid-related disorders

#17 opioids addict

#18 opioids addiction

#19 opioids crisis

#20 opioids dependence

#21 opioids dependency

#22 opioids epidemic

#23 opium addict

#24 opium addiction

#25 opium alkaloid addict

#26 opium alkaloid addiction

#27 opium dependence

#28 opium dependency

#29 opium epidemic

#30 heroin

#31 cocaine

#32 or/1-31

#33 exp acupuncture/

#34 electroacupuncture

#35 acupunctur$

#36 acup$

#37 auricular

#38 acupressure

#39 acupoint?

#40 or/33-39

#17 32 and 40

CBM search strategy

#1 Opioid-Related Disorders（MeSH）

#2 Opioid dependence

#3 Opioid withdrawal

#4 Opioid abstinence

#5 Protracted withdrawal

#6 Protracted abstinence

#7 Heroin

#8 Cocaine

#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

#10 Acupuncture (MeSH)

#11 Electroacupuncture

#12 Auricular acupuncture

#13 Acupoint

#14 Meridian

#15 #10 OR #11 OR #12 OR #13 OR #14

#16 #9AND #15

CNKI search strategy

#1 Opioid-Related Disorders（subjects）OR Addiction Opioid dependence （subjects）OR Opioid withdrawal（subjects）OR Opioid abstinence（subjects） OR Opioid（subjects）OR Drug abuse（subjects）OR Substances abuse （subjects）OR Protracted withdrawal（subjects）OR Protracted abstinence （subjects）OR Heroin（subjects）OR Cocaine（subjects）

#2 Acupuncture（subjects）OR Electroacupuncture（subjects）OR Auricular acupuncture（subjects）OR Acupoint

#3 #1 AND #2

WF search strategy

subjects: (“Opioid-Related Disorders” OR “Addiction Opioid dependence” OR “Opioid withdrawal” OR “Opioid abstinence” OR “Opioid” OR “Drug abuse” OR “Substances abuse” OR “Protracted withdrawal” OR “Protracted abstinence” OR “Heroin” OR “Cocaine”) AND subjects: (“Acupuncture” OR “Electroacupuncture” OR “Auricular acupuncture” OR “Acupoint”)

VIP search strategy

K=(Opioid-Related Disorders OR Addiction Opioid dependence OR Opioid

withdrawal OR Opioid abstinence OR Opioid OR Drug abuse OR Substances abuse OR Protracted withdrawal OR Protracted abstinence OR Heroin OR Cocaine) AND K=(Acupuncture OR Electroacupuncture OR Auricular acupuncture OR Acupoint)

WHO ICTRP search strategy

(Opioid-Related Disorders OR Addiction Opioid dependence OR Opioid withdrawal OR Opioid abstinence OR Opioid OR Drug abuse OR Substances abuse OR Protracted withdrawal OR Protracted abstinence OR Heroin OR Cocaine) AND (Acupuncture OR Electroacupuncture OR Auricular acupuncture OR Acupoint)

Clinicaltrials. gov search strategy

1 acupuncture and Opioid-Related Disorders

2 acupuncture and Opioid dependence

3 acupuncture and Opioid withdrawal

4 acupuncture and Opioid abstinence

5 acupuncture and Heroin

6 acupuncture and Cocaine

7 acupuncture and Opioid

8 acupuncture and Substances abuse

9 electroacupuncture and Opioid-Related Disorders

10 electroacupuncture and Opioid dependence

11 electroacupuncture and Opioid withdrawal

12 electroacupuncture and Opioid abstinence

13 electroacupuncture and Heroin

14 electroacupuncture and Cocaine

15 electroacupuncture and Opioid

16 electroacupuncture and Substances abuse

17 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 or 14 or 15 or 16

Chi CTR search strategy

1 Registry title: Opioid AND Intervention: Acupuncture

2 Registry title: Heroin AND Intervention: Acupuncture

3 Registry title: Cocaine AND Intervention: Acupuncture

4 Registry title: Opioid AND Intervention: Electroacupuncture

5 Registry title: Heroin AND Intervention: Electroacupuncture

6 Registry title: Cocaine AND Intervention: Electroacupuncture

7 1 or 2 or 3 or 4 or 5 or 6

CENTEAL

#1 MeSH descriptor: [Opioid-Related Disorders] explode all trees

#2 MeSH descriptor: [Opioid] explode all trees

#3 MeSH descriptor: [Addiction] explode all trees

#4 Opioid dependence

#5 Opioid withdrawal

#6 Opioid abstinence

#7 Drug abuse

#8 Heroin

#9 Cocaine

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 MeSH descriptor: [Acupuncture] explode all trees

#12 MeSH descriptor: [Acupuncture Points] explode all trees

#13 MeSH descriptor: [Acupuncture, Ear] explode all trees

#14 MeSH descriptor: [Acupressure] explode all trees

#15 acupunctur*

#16 acupoint?

#17 auricular

#18 electro-acupuncture

#19 acupressure

#20 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

#21 #10 AND #20

GreyNet International

Subject :(Opioid-Related Disorders OR Addiction Opioid dependence OR Opioid withdrawal OR Opioid abstinence OR Opioid OR Drug abuse OR Substances abuse OR Protracted withdrawal OR Protracted abstinence OR Heroin OR Cocaine) AND (Acupuncture OR Electroacupuncture OR Auricular acupuncture OR Acupoint)

OpenGrey

(Opioid-Related Disorders OR Addiction Opioid dependence OR Opioid withdrawal OR Opioid abstinence OR Opioid OR Drug abuse OR Substances abuse OR Protracted withdrawal OR Protracted abstinence OR Heroin OR Cocaine) AND (Acupuncture OR Electroacupuncture OR Auricular acupuncture OR Acupoint)

Google Scholar

("Opioid-Related Disorders" OR "Addiction Opioid dependence" OR "Opioid withdrawal" OR "Opioid abstinence" OR "Opioid" OR "Drug abuse" OR "Substances abuse" OR "Protracted withdrawal" OR "Protracted abstinence" OR "Heroin" OR "Cocaine") AND ("Acupuncture" OR "Electroacupuncture" OR "Auricular acupuncture" OR "Acupoint")