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

Su Zhang,1 Jun Luo,2 YiWei Zeng,1 Huan Ren,1 Zhihan Chen1,1 Yulan Ren2

ABSTRACT
Introduction Amphetamine-type stimulants (ATSs) are presenting a great challenge to global public health along with its worldwide abuse in recent years. Protracted amphetamine abstinence syndrome (PAAS) is one of the primary causes of relapse for ATS abusers during withdrawal. However, different conclusions are reached by previous trials. This study is designed to evaluate the efficacy and safety of acupuncture in treating PAAS.

Methods and analysis Cochrane Central Register of Controlled Trials, PubMed, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, ProQuest Dissertation and Theses, Allied and Complementary Medicine Database (AMED), ClinicalTrials.gov and who.int/clinicalsearch will be searched from the inception to February 2023 and language will be restricted to English and Chinese. Eligible randomised controlled trials will be included. The primary outcome is the intensity of withdrawal syndrome. The secondary outcomes include: (1) intensity of pain, anxiety, depression and other associated symptoms; (2) number of participants with relapse; (3) retention of treatment and (4) nature and rate of adverse effects. Data synthesis will be performed by using RevMan (5.4). The quality of evidence will be evaluated by the Grading of Recommendations, Assessment, Development and Evaluation approach. This study will strictly adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.

Ethics and dissemination Ethical approval is not required as this is a systematic review and meta-analysis based on previously published studies that do not involve patients’ privacy. The results of this study will be disseminated in a peer-reviewed journal. PROSPERO registration number CRD42022297761.

INTRODUCTION
Amphetamine-type stimulants (ATSs) refer to a wide range of synthetic psychostimulants with high potential of addiction, including amphetamine, methamphetamine (Ice), 3,4-methylenedioxymethamphetamine (ecstasy) and related substances.1 ATS abuse presents a serious problem to global public health. In 2019, 27 million people aged 15–64 years, accounting for 0.5% of the global population of the same age group, were reported to have used amphetamines.2 Between 2010 and 2015, approximately 85%–90% of the drug poisoning deaths that were reported under psychostimulants mentioned methamphetamine in the death certificate.3 ATS may lead to central nervous system damage, primarily involving dopaminergic, serotonergic and glutamatergic systems, and being associated with multiple physical and mental complications.4 The acute effects of ATS administration mainly include euphoria, hallucination, sexual disinhibition and agitation.5–7 There are also some reports of severe complications due to using ATS at high doses, such as hypertension, cardiovascular emergencies and renal failure.8 9 Chronic abuse of ATS could cause multiple neuropsychiatric disorders (eg, cognitive impairments, schizophrenia and psychosis).10 11 It is reported that the users who use more drugs are more likely to have suicidal thoughts and more violent behaviours.12 In addition, some ATS abusers may suffer long-lasting physical and mental

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ To the best of our knowledge, this study is the first systematic review and meta-analysis to evaluate the efficacy and safety of acupuncture for amphetamine-type stimulants use disorder, and this study will strictly follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
⇒ This study will systematically review quantitative data from multiple databases.
⇒ Subgroup analysis will be performed, given the potential high heterogeneity caused by different acupuncture interventions, medications and treatment duration.
⇒ The reliability of the results will largely depend on the methodological quality of included trials.
symptoms such as depression, anxiety and increasing drug craving even after a long time of withdrawal, which is defined as the ‘protracted amphetamine abstinence syndrome (PAAS)’. Clinical management of PAAS is crucial due to its persistence, which can exert adverse impacts on patients following ATS withdrawal, hindering their recovery and potentially increasing the risk of relapse.

Although a few therapeutic options are applied to ATS use disorder, including pharmacological treatment and psychotherapy, the evidence is insufficient to support the clinical application of these agents. Therefore, no medication is available for treating ATS use disorder, not to mention the PAAS, which makes it more urgent to explore new effective treatments. Acupuncture is an important component of Traditional Chinese medicine. It is a non-pharmacological therapy with considerable safety and availability and has been used to treat various diseases in China for thousands of years. Recently, increasing studies have demonstrated that acupuncture could alleviate symptoms associated with many kinds of substance use disorders (eg, alcohol, opioids, ATS). These studies indicate that acupuncture could be a potential therapeutic approach to the clinical management of PAAS. Ge et al have conducted a systematic review and meta-analysis of acupuncture for illicit drug withdrawal syndrome. However, this review maybe focus more on the opioid-type stimulants not ATS use disorder or PAAS. Significant differences are between opioid use disorder and PAAS. The sign of opioid withdrawal mostly includes anxiety, insomnia, myalgias/arthritis/abdominal pain, diarrhoea and nausea/vomiting. While PAAS includes depression, motor retardation, agitation poor concentration, irritability, tension and other associated symptoms. Therefore, this study will include a systematic review and synthesise the eligible controlled trials to critically evaluate the efficacy and safety of acupuncture for PAAS, and thus provide evidence-based references for the clinical management of the patients with PAAS.

**METHODS AND ANALYSIS**

**Search strategy**

Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, ProQuest Dissertation and Theses, Allied and Complementary Medicine Database (AMED), OpenGrey, ClinicalTrials.gov and who.int/trial-search will be searched from the inception to February 2023. The search terms will include subject headings and free terms for three major topics of amphetamine use, amphetamine-related disorders and acupuncture. Different sets of results will be produced by multiple variations of search themes. Language will be restricted to English and Chinese. Keywords or medical subject heading terms will be defined appropriately for the literature search, and necessary adaption will be made to all the search terms in order to cater the specific syntax rules of each database (the detailed electronic search strategy in table 1 and more in online supplemental file).

<table>
<thead>
<tr>
<th>No</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>(((((amphetamine[MeSH Terms]) OR (abuse, amphetamine[MeSH Terms])) OR (addiction, amphetamine[MeSH Terms]))) OR (amphetamine addiction[MeSH Terms])) OR (amphetamine abuse[MeSH Terms])) OR (methamphetamine[MeSH Terms])) OR (mdma[MeSH Terms])</td>
</tr>
<tr>
<td>#2</td>
<td>(((((((methylene) OR (ecstasy)) OR (dioxyme)) OR (methamphetamine)) OR (benzedrine)) OR (amphetamine)) OR (3,4-methylenedioxyamphetamine)) OR (4,5-methylenedioxyamphetamine)</td>
</tr>
<tr>
<td>#3</td>
<td>#1 OR #2</td>
</tr>
<tr>
<td>#4</td>
<td>((((((acupuncture[MeSH Terms]) OR (acupressure[MeSH Terms])) OR (acupoint[MeSH Terms])) OR (acupoints[MeSH Terms])) OR (acupuncture point[MeSH Terms])) OR (acupuncture points[MeSH Terms])) OR (electroacupuncture[MeSH Terms])) OR (acupuncture, auricular[MeSH Terms])) OR (((acupuncture) OR (acupressure))) OR (acupoint*)) OR (auricular)) OR (manual acupuncture) OR (electroacupuncture))</td>
</tr>
<tr>
<td>#5</td>
<td>#3 AND #4</td>
</tr>
</tbody>
</table>

**Inclusion criteria**

**Types of studies**

Randomised controlled trials (RCTs) and quasi-RCTs, including adult participants regardless of biological sex who have received acupuncture treatment in treating their PAAS, are included in this study, as well as ongoing RCTs. Exclusion criteria were as follows: (1) non-human and molecular studies; (2) cross-over trials and cluster RCTs; (3) non-original research (reviews, case reports, observational studies, editorials, non-research letters and protocols) and (4) non-RCTs.

**Types of participants**

PAAS patients with a confirmed negative urine drug screen. The diagnosis should be made based on validated and well-accepted criteria, such as the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition. Regardless of whether ATSs are used medically or illegally, individuals with PAAS will be included. Participants with any other substance use disorders (eg, opioid, cocaine, alcohol and cannabis) will be excluded. There will be no restrictions on participants’ sex and race.

**Types of interventions**

RCTs that applied acupuncture treatment such as manual acupuncture (MA), electroacupuncture (EA) and auricular acupuncture (AA) with or without conventional

---

**Table 1** Electronic search strategy in PubMed

<table>
<thead>
<tr>
<th>No</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>(((((amphetamine[MeSH Terms]) OR (abuse, amphetamine[MeSH Terms])) OR (addiction, amphetamine[MeSH Terms]))) OR (amphetamine addiction[MeSH Terms])) OR (amphetamine abuse[MeSH Terms])) OR (methamphetamine[MeSH Terms])) OR (mdma[MeSH Terms])</td>
</tr>
<tr>
<td>#2</td>
<td>(((((((methylene) OR (ecstasy)) OR (dioxyme)) OR (methamphetamine)) OR (benzedrine)) OR (amphetamine)) OR (3,4-methylenedioxyamphetamine)) OR (4,5-methylenedioxyamphetamine)</td>
</tr>
<tr>
<td>#3</td>
<td>#1 OR #2</td>
</tr>
<tr>
<td>#4</td>
<td>((((((acupuncture[MeSH Terms]) OR (acupressure[MeSH Terms])) OR (acupoint[MeSH Terms])) OR (acupoints[MeSH Terms])) OR (acupuncture point[MeSH Terms])) OR (acupuncture points[MeSH Terms])) OR (electroacupuncture[MeSH Terms])) OR (acupuncture, auricular[MeSH Terms])) OR (((acupuncture) OR (acupressure))) OR (acupoint*)) OR (auricular)) OR (manual acupuncture) OR (electroacupuncture))</td>
</tr>
<tr>
<td>#5</td>
<td>#3 AND #4</td>
</tr>
</tbody>
</table>
medications will be included in this study. Bee-venom acupuncture, acupoint injection and other noninvasive acupoints-stimulation therapies with other noninvasive acupoints stimulation will be excluded. No limitations will be placed on the duration of treatment.

Types of control
Waiting-list control, placebo, sham acupuncture, medications and other methods of acupoints-stimulation therapies (eg, acupressure and moxibustion).

Outcome assessments
Primary outcomes
Intensity of withdrawal syndrome measured by validated tools such as Amphetamine Cessation Symptom Assessment and Amphetamine Withdrawal Questionnaire.24 25

Secondary outcomes
1. Intensity of pain, anxiety, depression, motor retardation, agitation, craving, poor concentration, irritability, tension and other associated symptoms.
2. Number of participants with relapse.

Patient and public involvement
This systematic review will be carried out based on published studies, so patients and members of the public will not be involved directly. Only data from published literature and/or the aforementioned sources will be used.

Data collection and analysis
Selection of studies
EndNote V.X9 (Clarivate Analytics, Pennsylvania, USA) will be used to manage the search results from abovementioned databases. Two reviewers (SZ and JL) will independently perform article-screening through title and abstract. RCTs and quasi-RCTs assessing the efficacy of acupuncture for patients with PAAS will be included. Full text of eligible studies will be retrieved and screened according to inclusion criteria. The two reviewers will cross-check the selection results. Any disagreements will be settled by the third reviewer (YR) to make the final decision. Unique study IDs will be allocated to the corresponding eligible studies, which will comprise the last name of the first author and the year of publication (eg, Zhang, 2021). The Preferred Reporting Items for Systematic Reviews and Meta- Analyses flow diagram of selection process is shown in figure 1.

Data extraction
The two reviewers (SZ and JL) will independently extract the data using the self-designed data extraction forms, which will include basic information (article title, authors, publication data, country), study design (study type, sample size, characteristics of participants, time of drug abuse, daily ATS use, intervention details, duration, outcome measures) and conclusions. The completed data extraction forms will be cross-checked by the two reviewers. Any disparities will be resolved by the third reviewer (YR).

Assessment of risk of bias
The two reviewers (SZ and JL) will independently assess the risk of bias for each included study according to the Cochrane risk of bias assessment tool, which includes six domains: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias.26 The risk of bias will be graded as low risk, high risk or unclear risk. The assessment results will be cross-checked by the two reviewers and the disagreements will be handled by the third reviewer (YR).

Quality assessment of evidence
The two reviewers (SZ and JL) will conduct the quality assessment of evidence for outcomes according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, which refers to the following domains: study design and implementation, directness of evidence, unexplained heterogeneity, imprecision of results and publication bias. Each included RCT will be graded as high, moderate, low or very low quality. The results of assessment will be cross-checked by the two reviewers and be generated by GRADE profiler (GRADE pro) V.3.6.1 (Evidence Prime, Ontario, Canada). Any controversy will be handled by the third reviewer (YR).
Data synthesis and analysis
Valid data from included studies will be analysed by using RevMan V.5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). For dichotomous outcomes, risk ratio with 95% CI will be applied as pooled statistics. Standardised mean difference with 95% CI will be used as pooled statistics for continuous data since the intensity of primary outcome and most of the secondary outcomes are assessed by different scoring tools.

If there are missing data, we will attempt to contact authors of included studies for relevant information. If data are ‘missing at random’, available data will be analysed; if data are ‘not missing at random’, we will attempt to contact authors or investigators by the contacts recorded in the clinical trials registry platform to obtain the data. If we could not get the relevant information we need still, relevant studies would be excluded. Furthermore, sensitivity analysis will be conducted to assess how sensitive the results are to reasonable changes in the already-made assumptions, if possible. If a meta-analysis is not feasible, we will provide a narrative summary of the results from individual studies.

Assessment of heterogeneity
Heterogeneity will be assessed by using $\chi^2$ test and $I^2$ statistics. If $I^2$ ranges from 0% to 40%, the heterogeneity might not be important; if $I^2$ ranges from 30% to 60%, the heterogeneity may be moderate; if $I^2$ ranges from 50% to 90%, the heterogeneity may be substantial; if $I^2$ ranges from 75% to 100%, the heterogeneity may be considerable. Thus, if $I^2>50\%$ and $p<0.1$, data will be analysed by using random-effects model; if $I^2<50\%$ and $p>0.1$, data will be analysed by using fixed-effect model. In addition, subgroup analyses or meta-regression will be used to explore heterogeneity and we will try to explain heterogeneity from clinical and methodological differences.

Subgroup analysis and sensitivity analysis
On the basis of the primary and secondary outcomes, subgroup analysis will be performed to detect possible causes of heterogeneity. The following subgroups will be investigated respectively: different types of acupuncture intervention (eg, AA, MA and EA), different types of control, treatment duration and the severity of symptoms at baseline. In addition, severity of symptoms measured by the same scale will be assigned into one subgroup. Sensitivity analysis was performed by removing the included studies one by one to assess the robustness of the results. Due to the varieties of acupuncture styles, medication, duration of drug use and their influence on clinical therapeutic efficacy, subgroup analyses on these factors will be conducted if data is sufficient.

Assessment of reporting bias
Reporting bias include publication bias, time lag bias, duplicate publication bias, outcome reporting bias and the others in the Cochrane Handbook. To avoid reporting bias as much as possible, we will search the most important databases, including international general healthcare databases, subject-specific electronic bibliographic databases, citation index database, dissertations and theses database, grey literature database and clinical trials registry platform. Moreover, a funnel plot will be used to assess reporting bias if the number of included studies exceeds 10.

ETHICS AND DISSEMINATION
The results of this systematic review and meta-analysis will be disseminated in a peer-reviewed journal. No ethical approval is required since this study will not contain participants’ privacy.

Contributors
YR is the guarantor for the study. SZ and JL contributed equally to the drafting of the manuscript of this protocol, which was revised by YR, SZ, JL, ZC, YZ and HR designed this study. All reviewers developed the search strategies. SZ and JL will independently carry out the search, selection and identification of studies and the data extraction. SZ and JL will perform the data synthesis and analysis. YR will serve as the third reviewer for settling disagreement. YR and ZC will be the adviser for the methodology. All authors have approved the publication of this protocol.

Funding
This study was supported by a major R&D project of the Sichuan Provincial Department of Science and Technology of China (approval number: 2018SZ0071).

Competing interests
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.

Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Su Zhang http://orcid.org/0000-0001-5473-6361
YiWei Zeng http://orcid.org/0000-0002-7042-2503
Zhihan Chen http://orcid.org/0000-0002-0237-7501

REFERENCES


CENTEAL

#1 MeSH descriptor: [Amphetamines] explode all trees
#2 MeSH descriptor: [Methamphetamine] explode all trees
#3 MeSH descriptor: [Amphetamine-Related Disorders] explode all trees
#4 methylene
#5 ecstasy
#6 mada
#7 methamphetamine
#8 amphetamine
#9 benzedrine
#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

Embase

#1 exp amphetamine/
#2 MDMA
#3 ecstasy
#4 methylene
#5 benzedrine
#6 3,4-methylenedioxymethamphetamine
#7 4,5-methylenedioxymethamphetamine
#8 or/1-7
#9 exp acupuncture/
#10 electroacupuncture
#11 acupunctur$ 
#12 acup$
#13 auricular
#14 acupressure
#15 acupoint?
#16 or/9-15
#17 8 and 16

Web of science
1: ((((((TS=(amphetamine)) OR TS=(methamphetamine)) OR TS=(ecstasy)) OR TS=(mdma)) OR TS=(methylene)) OR TS=(methylene)) OR TS=(benzedrine)) OR TS=(3,4-methylenedioxymethamphetamine)) OR TS=(4,5-methylenedioxymethamphetamine)
2: (((TS=(acupunctur*)) OR TS=(acupressure)) OR TS=(acupoint?)) OR TS=(auricular)) OR TS=(electro-acupuncture)
3: #1 AND #2

CINAHL and PsycINFO (via EBSCO)
( (amphetamine) OR (methamphetamine) OR (MDMA) OR (ecstasy) OR (methylene) OR (benzedrine) OR (3,4-methylenedioxymethamphetamine) OR (4,5-methylenedioxymethamphetamine) ) AND ( (acupunctur*) OR (acupressure) OR (acupoint?) OR (auricular) OR (electro-acupuncture) )

ProQuest Dissertation and Theses
S1 all(amphetamine) OR all(methamphetamine) OR all(MDMA) OR (ecstasy) OR (methylene) OR (benzedrine) OR (3,4-methylenedioxymethamphetamine) OR (4,5-
methyleneoxymethamphetamine)
S2 all(acupunctur*) OR all(electro-acupunctur*) OR all(acupressure*) OR all(acupressure) OR all(acupoint*) OR all(auricular)
S3 S1 AND S2

AMED (via OVID) search strategy
1 exp Acupuncture/
2 exp acupuncture therapy/ or exp acupoints/ or exp acupressure/ or exp ear acupuncture/ or exp electroacupuncture/
3 "acupuncture*".ti,hw,ab.
4 "electroacupuncture*".ti,hw,ab.
5 "acupressure*".ti,hw,ab.
6 "acupoint*".ti,hw,ab.
7 1 or 2 or 3 or 4 or 5 or 6
7 exp amphetamine/
8 "methamphetamine*".ti,hw,ab.
9 "MDMA*".ti,hw,ab.
10 "ecstasy*".ti,hw,ab.
11 "methylene*".ti,hw,ab.
12 "benzedrine*".ti,hw,ab.
13 "3,4-methylenedioxymethamphetamine*".ti,hw,ab.
14 "4,5-methylenedioxymethamphetamine*".ti,hw,ab.
15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 7 and 15

Clinicaltrials.gov search strategy
1 acupuncture and amphetamine
2 acupuncture and methamphetamine
3 acupuncture and ecstasy
4 acupuncture and MDMA
5 acupuncture and methylene
6 acupuncture and Benzedrine
7 electroacupuncture and amphetamine
8 electroacupuncture and methamphetamine
9 electroacupuncture and ecstasy
10 electroacupuncture and MDMA
11 electroacupuncture and methylene
12 electroacupuncture and benzedrine
13 electroacupuncture and amphetamine
14 electroacupuncture and methamphetamine
15 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

who. int / trialsearch search strategy
1 acupuncture and amphetamine
2 acupuncture and methamphetamine
3 acupuncture and ecstasy
4 acupuncture and MDMA
5 acupuncture and methylene
6 acupuncture and Benzedrine
7 electroacupuncture and amphetamine
8 electroacupuncture and methamphetamine
9 electroacupuncture and ecstasy
10 electroacupuncture and MDMA
11 electroacupuncture and methylene
12 electroacupuncture and benzedrine
13 electroacupuncture and amphetamine
14 electroacupuncture and methamphetamine
15 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
OpenGrey

(amphetamine OR methamphetamine OR ecstasy OR methylene OR Benzedrine OR MDMA) AND ((acupunct* OR auricular OR electro-acupuncture OR acupressure OR acupoint))