BMJ Open | Acupuncture for erectile dysfunction: a systematic review protocol

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ABSTRACT

Introduction: This systematic review protocol aims to provide a protocol for assessing the safety and effectiveness of acupuncture for the treatment of erectile dysfunction(ED). Previous systematic reviews did not draw convincing conclusions owing to high heterogeneity and few included randomised controlled trials, so it is necessary to reassess the efficacy and safety of acupuncture for ED.

Methods and analysis: Eight electronic databases will be searched: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PubMed, EMBASE, PsycInfo, the Chinese Biomedical Literature Database (CBM), the Chinese Medical Current Content (CMCC) and the China National Knowledge Infrastructure (CNKI). Related Chinese literature will be searched in other Chinese databases. All relevant randomised controlled trials in English or Chinese without any restrictions of publication type will be included. The main outcome measure will be improvements in sexual activity assessed by validated questionnaires. Assessment of risk of bias, data synthesis and subgroup analysis will be carried out using Review Manager 5.3.

Ethics and dissemination: The results of the systematic review will be disseminated via publication in a peer-reviewed journal and presented at a relevant conference. The data we will use do not include individual patient data, so ethical approval is not required.

Trial registration number: PROSPERO CRD42014013575.

Strengths and limitations of this study

- Study selection, data extraction and quality assessment will be performed independently by two researchers, which will ensure that all relevant studies are included without personal biases.
- Medical databases in other languages (eg, Korean and Japanese) will not be searched because of language barriers, so language bias may exist.
- There may be high heterogeneity from the various evaluation standards in different acupuncture therapies.

The pathophysiology of ED may include arterial, neurogenic, hormonal, cavernous, iatrogenic and psychogenic causes.[7] ED can also result from a generalised vascular disorder caused by endothelial dysfunction.[8] A comprehensive evaluation for ED consists of a complete medical and sexual history, a physical examination, a psychological assessment and appropriate laboratory tests.[9]

The current therapies for ED include oral pharmacotherapy, intracavernous injections and implantation of a penile prosthesis.[10] Phosphodiesterase type 5 inhibitors such as sildenafil are currently used as the first-line treatments for ED.[11] However, there is still a significant population of patients who remain refractory to this therapy.[12] For patients treated with intracavernous injections, 29–41% have mild penile pain.[10 13] Moreover, implantation of a penile prosthesis is expensive, and may cause penile deformity.[10 13] Therefore, an ideal treatment for ED has not as yet been developed.

INTRODUCTION
Description of the condition

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain an erection sufficient to permit satisfactory sexual performance.[1 2] Epidemiological study found that the prevalence of ED is high; for example, it affects approximately 22% of US men.[3] About 150 million individuals are estimated to suffer from ED worldwide.[4 5] As the life expectancy of the general population increases, the healthcare burden and quality-of-life issues associated with ED are expected to be considerable.[6]

Description of the intervention

Traditional medicine (TM) is increasingly accepted by people in the developing and developed world as an alternative to conventional treatments.[14] One-third of American residents seek service from TM practitioners every year for illnesses that do not respond to conventional treatment.[15] Acupuncture, which involves the insertion of fine needles into the skin at specific points, has a long

history of use in China and is one of the important treatments used in TM.

How the intervention might work

Traditional Chinese medicine (TCM), which is an important part of TM, is based on the theoretical concepts of Yin-Yang and the five elements, and theorises that health is maintained by a balance of energy within the body. Acupuncture helps to correct imbalances to relieve symptoms by stimulating various meridian points. The equilibrium of the autonomic nervous system is the modern equivalent to Yin-Yang balance.[16] Acupuncture may positively affect the pathophysiology of ED based on its homeostatic influence on the autonomic nervous system.[17] Many in vivo studies demonstrate that neuropeptides, which are vital to the central control of male sexual behaviour, are involved in the mechanisms of pain relief after acupuncture.[18–20] Moreover, acupuncture might modulate nitric oxide, which is related to the treatment of ED.[2] Some studies indicate a high success rate in patients with ED after TCM treatment, including acupuncture.[21–24]

OBJECTIVES

This article describes the protocol for a systematic review that will assess the evidence for the effectiveness and safety of acupuncture for ED.

METHODS AND ANALYSIS
Criteria for considering studies for this review
Types of studies

All relevant randomised controlled trials (RCTs) in English and Chinese without any restrictions on publication type will be included and quasi-RCTs will be excluded.

Types of participants

Studies evaluating men aged more than 18 years of any ethnic background and nationality will be included. ED must be diagnosed by clinical and/or instrumental methods. The diagnosis will be based on the Diagnostic and Statistical Manual of Mental Disorders Third Edition (DSM)-III, DSM-III-R, DSM-IV, International Statistical Classification of Diseases and Related Health Problems (ICD)-10 criteria or any other described criteria. Patients with drug-induced ED, external genital malformation or organic damage to the genitourinary system such as pudendal nerve injury from trauma or surgery will be excluded.

Types of interventions

Acupuncture type can include: body acupuncture, electroacupuncture, scalp acupuncture, ear acupuncture, fire needling, elongated needle, intradermal needling or dry needling. Laser acupuncture and point injection will be excluded. The control intervention can include: no treatment, placebo/sham acupuncture or other interventions (eg, drugs, physical therapy). Trials that evaluate acupuncture plus another therapy compared with the other therapy alone will also be included. Trials that only compare different types of acupuncture or different points will be excluded.

Types of outcome measures
Primary outcomes

The primary outcome will be improvement in sexual activity. This will be assessed through validated questionnaires such as the International Index of Erectile Function (IIEF).[25] Trials with non-validated questionnaires or no clear descriptions of evaluation methods will be excluded.

Secondary outcomes

1. Quality of life
2. Satisfaction with the treatment
3. Improvement in depression or anxiety indices
4. Safety assessment as measured by incidence and severity of adverse effects (eg, pain or dizziness)

Search methods for identification of studies
Electronic searches

An electronic search strategy will be designed to search relevant references in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PubMed, EMBASE, PsycInfo, the Chinese Biomedical Literature Database (CBM), the Chinese Medical Current Content (CMCC) and the China National Knowledge Infrastructure (CNKI). The search will be performed in English and Chinese. The following terms will be used: acupuncture, acupuncture therapy, electroacupuncture, fire needling, elongated needle, intradermal needling, dry needling, erectile dysfunction, impotence, erection failure, male sexual dysfunction, randomised controlled trials, double-blind method and single-blind method (table 1 details of the search strategy for EMBASE). The search terms will be translated into Chinese when reviewers search the Chinese databases. The following literature sources in Chinese will also be searched: dissertations in CNKI, and conference papers in the China Conference Paper Database. Relevant references cited in selected studies will also be searched.

Searching other resources

Reference texts including andrology textbooks, integrative/alternative and complementary medicine textbooks and clinical guidelines for relevant trials will also be searched manually.

Data collection and analysis
Selection of studies

The abstracts of all publications will be independently screened by the review authors (XC and JZ). The full text of articles potentially suitable for the review will be obtained to assess relevance based on the inclusion/

Table 1	EMBASE search strategy
No	**Searching item**
1	Clinical article
2	Clinical study
3	Clinical trial
4	Controlled study
5	Randomized controlled trials
6	Major clinical study
7	Double blind method
8	Multicenter study
9	Single blind method
10	Crossover procedure
11	Placebo
12	Or/1–11
13	Erectile dysfunction
14	Impotence
15	Erection failure
16	Male sexual dysfunction
17	Penis erection
18	Or/13–17
19	Exp ACUPUNCTURE
20	acupuncture.tw
21	electroacupuncture.tw.
22	Exp Acupuncture Therapy
23	Fire needling
24	Elongated needle
25	Intradermal needling
26	Scalp acupuncture
27	Ear acupuncture
28	Dry needling
29	Or/19–28
30	12 and 18 and 29

exclusion criteria. We will discuss with ZL if there are any discrepancies. The studies that do not fulfil the inclusion criteria will be excluded and listed with reasons for their exclusion.

Data extraction and management

Data for the trials will be extracted independently by two review authors (XC and JZ) using a standard form. The following information will be included.

1. Study methods and characteristics (design, method of randomisation, inclusion/exclusion criteria and withdrawals/dropouts).
2. Participants (number of participants, age range, diagnostic criteria, disease course).
3. Intervention (type of acupuncture therapy, duration of session).
4. Control (no treatment, placebo therapy or other active treatment).
5. Outcomes (types of outcome measures, reported outcomes, adverse events, follow-up time and results).

Extracted data will be compared by two review authors for completeness and accuracy and double-checked by another review author if necessary. Disagreements will be solved through discussion with ZL. New data will be transferred into Review Manager 5.3.[26]

Assessment of risk of bias in included studies

The risk of bias in the included studies will be assessed independently by two authors (XC and JZ) and presented in a risk of bias table. Decisions will be made based on the domains and criteria of the Cochrane Collaboration's tool[27] for assessing risk of bias. The following domains will be assessed:

1. Selection bias: random sequence generation and allocation concealment.
2. Performance bias: blinding of investigators, participants and care providers.
3. Detection bias: blinding of outcome assessment.
4. Attrition bias: incomplete data/differential dropout.
5. Reporting bias: selective reporting.
6. Other bias: for example, conflicts of interest, follow-up, non-intention-to-treat or per-protocol analysis.

For each domain, the following description will be used to assess proper management of the risk of bias: 'low risk,' 'high risk,' or 'unclear.' We will grade the quality of included studies and risk of bias using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[28] with GRADEprofiler (GRADEpro) V.3.6 software. Any disagreements will be resolved by discussion with ZL.

Measures of treatment effect

For continuous data, the mean difference (MD) will be used to measure treatment effect with 95% CIs. In case outcome variables have different scales, the standardised mean difference will be used with 95% CIs.

For dichotomous data, treatment effects are presented as a risk ratio (RR) with 95% CIs. Other binary data will be changed into the RR form.

Unit of analysis issues

The unit of analysis will be each patient recruited into the trials.

Dealing with missing data

For each included study, the number of dropouts, exclusions from the analysis and missing data will be gathered by contacting the study author. If we fail to obtain sufficient data, we will assume dichotomous outcomes for patients not experiencing any change in their clinical outcome variables. We will then perform sensitivity analyses to assess how sensitive the results are to changes in the assumptions made.

If necessary, the potential impact of missing data on the findings of the review will be described in the 'Discussion' section.

Assessment of heterogeneity

Cochran's Q test[29] will be performed for the detection of heterogeneity. The I^2 statistic will be used to measure heterogeneity among the trials in each analysis. An I^2 value of 50% or more indicates a substantial level of inconsistency. If we identify substantial heterogeneity, we

will report it and explore possible causes using subgroup analyses.

Assessment of reporting biases

If we are able to pool data from more than 10 trials for the primary outcome, a funnel plot will be created and examined to explore possible small study biases. We will interpret results carefully based on several explanations for funnel plot asymmetry.

Data synthesis

If two or more eligible RCTs are identified, meta-analyses will be performed with Review Manager 5.3. Whether a fixed effects model or a random effects model will be used depends on the results of the χ^2 test and I^2 test for heterogeneity. If substantial statistical heterogeneity is found, we will adopt a random effects model. If no substantial statistical heterogeneity is detected ($I^2 < 50\%$), we will use a fixed effects model. If clinical and methodological heterogeneity is present, we will perform subgroup analyses. If not, we will not pool

the data but conduct a systematic narrative synthesis providing information to summarise and explain the characteristics and findings of the included studies.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses, if possible.
1. Comparison between acupuncture and sham, placebo or no treatment.
2. Comparison between acupuncture and routine Western medicine treatment.
3. Comparison between manual acupuncture and electroacupuncture.
4. Comparison between psychosocial ED and physiological ED.

We will use the formal test for subgroup interactions in Review Manager 5.3.

Sensitivity analysis

Sensitivity analysis will be conducted to explore the effects of trial risk of bias on important outcomes. In the
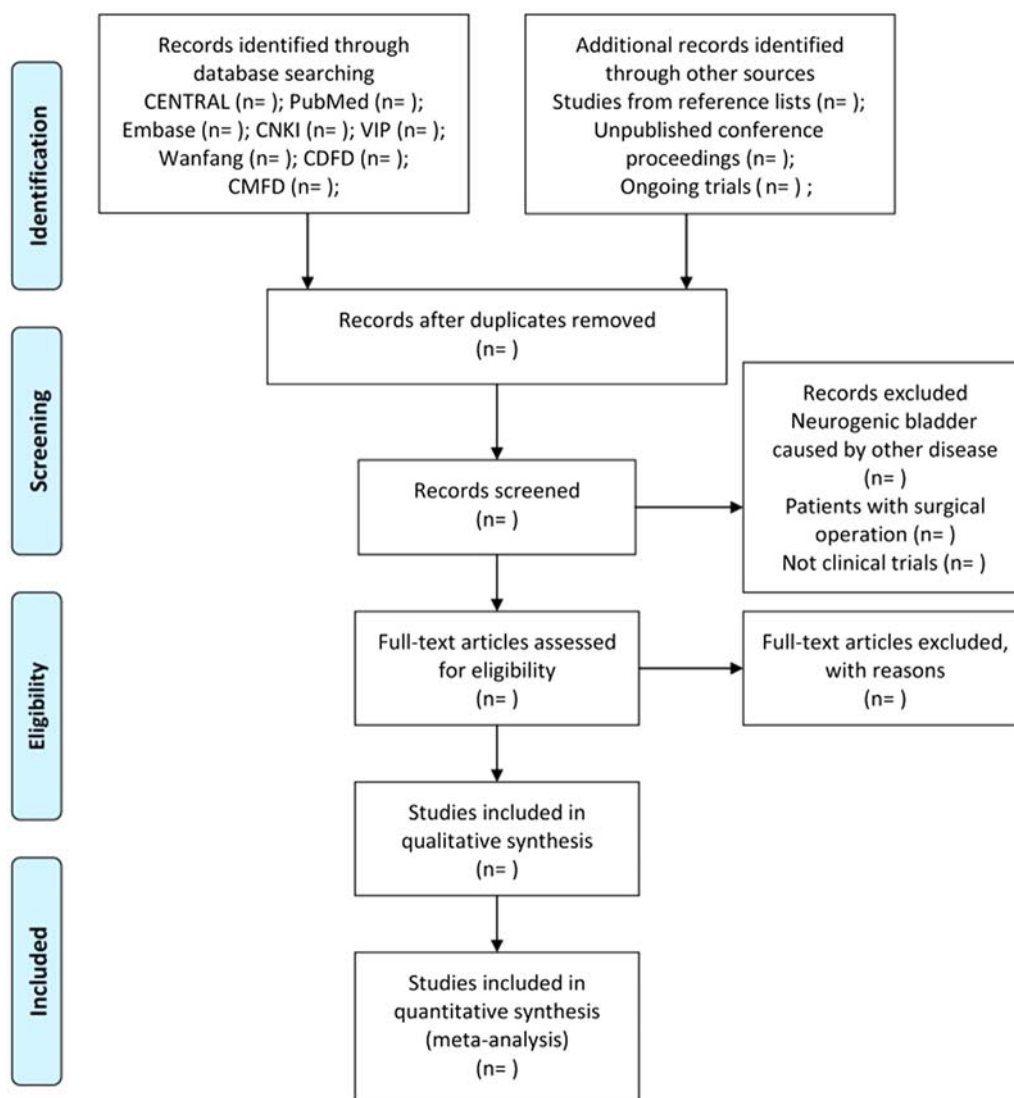
Figure 1 Process of the systematic review.

analysis, we will exclude lower quality trials and compare the results with those using the worst-case strategy to combine studies. Then we will have a discussion to decide whether the lower quality trials should be excluded, depending on their sample size, strength of evidence and influence on pooled effect size.

DISCUSSION

The previous review which was published 6 years ago failed to determine if there are beneficial effects of acupuncture therapy in ED treatment.[30] Nearly 30–40 RCTs have been published within the past 6 years on acupuncture and ED, so it is necessary to reassess the efficacy and safety of acupuncture for ED.

The flow chart of this systematic review is shown in figure 1. This review will be helpful to clinicians treating ED and may provide evidence for researchers. Patients with ED may also benefit from potential alternative interventions.

However, this systematic review will have some limitations. The medical databases in other languages (eg, Korean and Japanese) will not be covered because of language barriers, so a language bias may exist. High heterogeneity may also arise from the various evaluation standards from different acupuncture therapies. Nevertheless, this systematic view should help further expand our understanding of acupuncture treatments for ED

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