

# BMJ Open Acupuncture for benign prostatic hyperplasia: a systematic review protocol

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**To cite:** Zhang W, Yu J, Liu Z, *et al.* Acupuncture for benign prostatic hyperplasia: a systematic review protocol. *BMJ Open* 2015;5:e007009. doi:10.1136/bmjopen-2014-007009

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2014-007009>).

Received 24 October 2014  
Revised 1 March 2015  
Accepted 3 March 2015

## ABSTRACT

**Introduction:** Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate commonly encountered in older men. BPH has been treated with acupuncture inside and outside China, but its effects are uncertain. This review aims to assess the efficacy and safety of acupuncture therapy for BPH.

**Methods and analysis:** Seven databases will be searched from their inception: the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Chinese Biomedical Database, the China National Knowledge Infrastructure, the VIP Database and Wanfang Database. Randomised controlled clinical trials using acupuncture to treat BPH will be included. Outcome measures included urological symptom scores, urodynamic measures and quality-of-life scales. Adverse events will be assessed and reported for safety evaluation. Study selection and data extraction will be performed by two independent reviewers. Quality assessment (assessment of risk of bias) and data synthesis will be implemented using Review Manager (RevMan) software (V.5.2.3).

**Ethics and dissemination:** Ethical approval is not necessary because this systematic review will not include specific patient data. Updates will be conducted if there is enough new evidence that may cause any change in review conclusions.

**Trial registration number:** PROSPERO CRD42014013645.

## INTRODUCTION

### Description of the condition

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate commonly encountered among older men. One histological investigation from 1984 showed that more than 40% of men in their 50s and nearly 90% of men in their 80s experience BPH.<sup>1</sup> However, different absolute prevalence rates were reported later in multinational population-based studies.<sup>2–3</sup> Lower urinary tract symptoms (LUTS) associated with BPH include obstructive symptoms (weak urinary stream, hesitancy, intermittency, incomplete bladder emptying, terminal urine dribbling and abdominal straining) and irritative symptoms (urinary frequency, urgency and

## Strengths and limitations of this study

- Databases will be searched and trials will be screened without restriction to languages. Trials published in languages other than Chinese and English will be translated by qualified translators if they can be potentially included after reading their English titles and abstracts.
- The trial screening, data extraction and risk of bias assessment of this review will be conducted by two reviewers independently.
- Highly individualised treatment has always been characteristic of acupuncture therapy, including variation of treatment frequency, stimulation methods and courses of treatment. This may make it difficult to perform data synthesis because of clinical heterogeneity.

nocturia).<sup>4–5</sup> In the USA, treatment for BPH accounted for approximately 4.5 million physician-office visits in 2000<sup>6</sup> and resulted in more than 300 000 prostatectomies in 1994.<sup>7</sup> In China, prostate specimens from 321 deceased patients were collected from 1989 to 1992. The frequency of BPH was 13.2% among those aged 41–50 years and increased until it reached 83.3% among those aged 81–90 years. This histological frequency of BPH in China was similar to that in western countries.<sup>8</sup> Treatment for BPH includes minimally invasive therapy, surgery and medical therapy. The pharmacological use of plants and herbs (phytotherapy) is another option for the treatment of BPH and its use has been growing steadily in some countries.<sup>9–10</sup>

### Description of the intervention

Acupuncture is a very important part of traditional Chinese medicine (TCM) with a literary history of more than 2000 years.<sup>11</sup> Acupuncture is a therapy that inserts needles into certain points of the body called “Xue Wei”. Centuries ago, acupuncture was developed into a discipline with its own theory and practice. TCM theorises that acupuncture can strengthen the human body’s vital essence, called “Qi”, and remove the blockages in channels.<sup>12</sup> Both a WHO report



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and a National Institutes of Health consensus conference have provided lists of conditions that could be potentially treated with acupuncture.<sup>13 14</sup>

### How the intervention might work

Acupuncture is also helpful for a wide range of other diseases.<sup>15</sup> In China, BPH has been treated with acupuncture and the procedure's efficacy has been tested by some studies. In one animal model, it was reported that acupuncture can neutralise pathological changes in low levels of nitric oxide synthase and impaired kidney function, which manifested as high blood urea nitrogen and serum creatinine.<sup>16</sup>

### Why it is important to do this review

There have been some researches which provide evidence for the clinical application of acupuncture for BPH. A clinical study published recently has shown that acupuncture could improve the International Prostate Symptom Score (IPSS), maximum flow rate and residual urine volume with a treatment course of 3 months.<sup>17</sup> A systematic review of acupuncture and moxibustion versus western medicine for BPH was published in 2010.<sup>18</sup> However, its conclusion was uncertain because of the low quality and limited quantity of literature. Also, this systematic review only compared acupuncture and western medicine, which was merely a part of existing interventions for BPH. So evidence needs to be collected and analysed for evaluation of effect and safety of acupuncture for BPH.

## OBJECTIVES

We aim to conduct a systematic review and, if possible, a quantitative meta-analysis, with evidence available from randomised controlled trials (RCTs) into the comparative effectiveness and harms of acupuncture for men with symptomatic BPH compared with various types of control interventions. Outcomes including validated urological symptom scores, quality-of-life score, urodynamic measures and prostate size measurements will be included.

## METHODS

The protocol of this systematic review has been registered on PROSPERO 2014 (registration number: CRD42014013645). This systematic review protocol has been developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.<sup>19</sup>

### Criteria for considering studies for this review

#### Types of studies

Parallel-group RCTs of acupuncture for BPH without any language or publication status restrictions will be included in this systematic review. Non-RCTs and uncontrolled clinical trials such as case studies will be excluded.

### Types of participants

We will include studies investigating men with symptomatic BPH determined by elevated urinary symptom scores including the Boyarsky Score,<sup>20</sup> the American Urologic Association Symptom Index and the IPSS.<sup>21</sup> There will be no restrictions on other diagnostic methods such as urinary flow rates or ultrasound. Patients with diagnoses of other diseases that may cause urinary tract symptoms such as prostatic cancer and neurogenic bladder will be excluded.

### Types of interventions

For the treatment group, acupuncture therapy with needle insertion will be considered, including body acupuncture, auricular acupuncture, scalp acupuncture and electroacupuncture. We will also include acupuncture combined with other treatments or medications, such as herbs. Excluded interventions will be any stimulation other than that of a needle, such as acupressure, seed stimulation or surface electrodes.

Control interventions will include: no intervention, placebo acupuncture, sham acupuncture, pharmacological treatments (herbal medicine or conventional medicine, such as 5- $\alpha$  reductase inhibitors and  $\alpha$ -blockers), surgery or any other interventions. Placebo acupuncture includes treatments that attach a needle to the skin surface (not penetrating the skin but at the same acupoints).<sup>22</sup> Sham acupuncture includes: a needle placed in an area close to but not in an acupuncture point,<sup>23</sup> and subliminal skin electrostimulation via electrodes attached to the skin.<sup>24</sup>

### Types of outcome measures

Primary outcome measures will be changes in urological symptoms as measured by validated urological symptom scores, including the Boyarsky Score,<sup>20</sup> the American Urologic Association Symptom Score and IPSS.<sup>21</sup> Secondary outcome measures will include: quality-of-life score; urodynamic measures, which are defined as changes in peak urine flow (measured in mL/s); mean urine flow (measured in mL/s) and residual urine volume (measured in mL); nocturia (measured in times per evening); and changes in prostate size (measured in cc).

Adverse events will be recorded including intolerable pain during acupuncture, bleeding during or after the session, breaking or winding of the needles, injury to organs (eg, pneumothorax) and fainting. The number and severity of adverse events will be recorded.

### Search methods for identification of studies

#### Electronic searches

We will search the following electronic databases irrespective of language and publication status: the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, the Chinese Biomedical Database, the China National Knowledge Infrastructure, the VIP Database and the Wanfang Database.

**Table 1** Ovid MEDLINE search strategy

Search items	
1	randomised controlled trial
2	controlled clinical trial
3	randomised
4	randomized
5	randomly
6	trial
7	or/1-6
8	benign prostatic hyperplasia or bph/
9	lower urinary tract symptoms or luts/
10	or/8-9
11	acupuncture/
12	acupuncture points/
13	(electroacupuncture or electro- acupuncture).tw.
14	electroacupuncture.tw.
15	acupuncture\$.tw.
16	acupoints.tw.
17	meridians/
18	or/11-17
19	7 and 10 and 18

### Other sources

A non-electronic search will be implemented for further information including the references of all included studies of this systematic review, bibliographic references

in urological textbooks, previous reviews of acupuncture for BPH and relevant conference proceedings.

### Search strategy

Table 1 presents the search strategy for MEDLINE, a Chinese version of the same search items, which will be used for searching the Chinese databases.

### Data collection and analysis

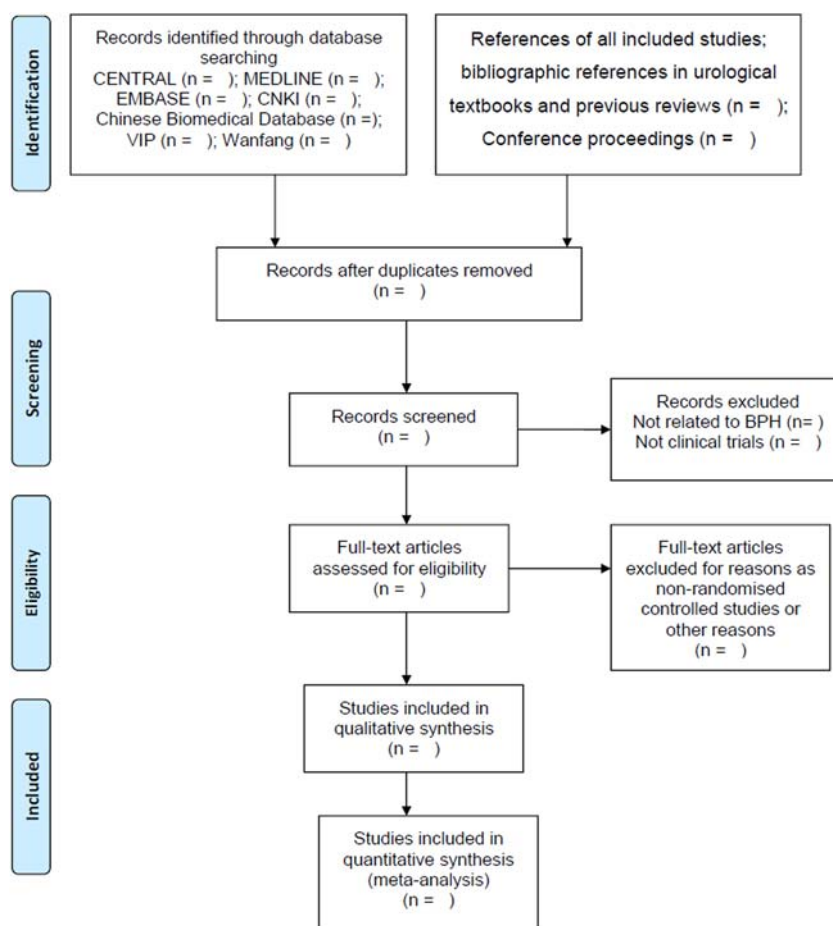
#### Selection of studies

Two reviewers, WZ and WP, will independently determine the eligibility of studies. Duplicates and non-clinical trials will be removed by screening the titles and abstracts. Reviewers will read the full text if they are not sure whether the studies meet the inclusion criteria. Studies will be excluded if they are not truly randomised (Quasi-RCTs) or involve any unqualified interventions. A third party (ZL) will resolve any disagreements. Study selection is summarised in a PRISMA flow diagram (figure 1).

#### Data extraction and management

A data extraction form will be developed and study data will be assessed and extracted independently by two reviewers, JY and WP. The following data will be extracted from each included study: patients' demographic characteristics, including maximum, minimum

**Figure 1** Flow diagram of the study selection process (BPH, benign prostatic hyperplasia).



and mean age; inclusion and exclusion criteria; type, frequency and treatment course of acupuncture therapy; and all outcomes. Type, severity, number of adverse effects, as well as number/reasons for dropouts, withdrawals, and patients lost to follow-up will also be recorded. Information not available in the trials will be sought from authors by email, telephone or post. Extracted data will be reviewed by WZ and discrepancies will be judged by the arbitrator, ZL.

#### Risk of bias assessment

A tool introduced in the Cochrane Handbook for systematic reviews of interventions (V.5.1) will be used to assess a broad category of biases. This tool, available through the collaboration's website and Review Manager (RevMan) software, includes five sources of bias in clinical trials and their relevant domains. The sources of bias are: selection bias: random sequence generation and allocation concealment; performance bias: blinding of participants and personnel; detection bias: blinding of outcome assessment; attrition bias: incomplete outcome data; and reporting bias: selective outcome reporting. Specific features of included studies will be judged by two reviewers independently in each entry of a "risk of bias" table, where the risk of bias will be addressed as low, high or unclear.<sup>25</sup>

#### Measures of treatment effect

For dichotomous data, relative risk (RR) with corresponding 95% CIs will be used while continuous data will be expressed as mean differences (MD) with 95% CIs. MD will be used for data measured on the same scales and for which the same units are used. Standardised mean differences will be used if all studies assess the same outcome but measure it in various ways.

#### Unit of analysis issues

In case unit of analysis issues arise in studies of long duration, time frames will be defined as 1, 3 and 6 months to reflect short-term, medium-term and long-term follow-up, respectively.

#### Dealing with missing data

Reviewers will try to obtain necessary information by contacting the first or corresponding authors of included trials by phone, email or post if there are missing data.

#### Assessment of heterogeneity

We will test for statistical heterogeneity between trial results using a standard  $\chi^2$  test with a significance level of  $p < 0.1$ , and  $I^2$  test will be used for quantifying inconsistency among the included studies.<sup>26</sup>

#### Assessment of reporting biases

Potential reporting biases will be investigated using the funnel plot. We will use a linear regression approach to measure funnel plot asymmetry.<sup>27</sup>

#### Data synthesis

A meta-analysis will be implemented with the Cochrane Collaboration Review Manager (RevMan V.5.2.3) software. All the primary and secondary outcome measures will be combined and analysed for evidence of homogeneity ( $p > 0.1$ ) using a fixed-effects model. Dichotomous results will be expressed as RR with 95% CIs. For continuous variables, MD, the difference between treatment and control pooled means at end points, and their 95% CIs will be calculated. A random-effects model will be used if there is substantial ( $I^2 > 75\%$ ) statistical heterogeneity.

A narrative synthesis will be provided if the meta-analysis cannot be performed for all or some of the expected data from included studies. Text and tables will be used to summarise and explain findings concerning the efficacy and safety of acupuncture both within and between studies with reference to participants, interventions, comparators and outcomes.

#### Sensitivity analysis

We will implement sensitivity analyses to explore the impacts of methodological quality and sample size on the robustness of review conclusions. Meta-analyses will be repeated after excluding studies with lower methodological quality and studies with sample sizes much bigger than those of other studies. Sensitivity analyses will be reported with a summary table and review conclusions will be interpreted with concerns for comparisons between the two meta-analyses.

#### Subgroup analyses

We will compare the effects between subgroups by: different acupuncture types, including electroacupuncture, elongated needle and fire needle; different control interventions, such as herbal medicine, western medicine and phytotherapy; and study locations.

#### Confidence in cumulative evidence

The quality of evidence for all outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology across the domains of risk of bias, consistency, directness, precision and publication bias.<sup>28</sup> Quality of evidence will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect).

## DISCUSSION

This review aims to analyse the effects and safety of acupuncture on BPH. The systematic review of acupuncture and moxibustion versus western medicine for BPH

published by Chen and colleagues included only six studies from 2003 to 2006. After that, RCTs with higher methodological qualities investigating acupuncture in BPH treatment have been published.<sup>29 30</sup> This review will provide comprehensive and current evidence on the therapeutic effects of acupuncture on BPH, which may benefit practitioners, patients and policymakers.

**Acknowledgements** This protocol was edited by Edanz Editing China, an editing company in Beijing for language polishing.

**Contributors** WZ is the guarantor. WZ and ZL contributed to the conception of this review. WZ drafted the manuscript of the protocol and ZL revised it. ZL and WZ developed the search strategies while WP and JY will implement them. WP and JY will also screen the potential studies, extract data and assess quality. In case of disagreement between the two data extractors, ZL will advise on the methodology and work as arbitrator. WZ will complete data synthesis. All authors approved the final version for the publication.

**Funding** This work was funded by the Clinical Research Fund from the China Academy of Chinese Medical Sciences, Guang'anmen Hospital, with a funding reference number 84382. This fund covers the expenses including using databases, papers printing, communication and English editing.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** The findings of the full review from this protocol will be disseminated via peer-reviewed publications and conference presentations. All of the data will be available.

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