

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Acupuncture therapies for postherpetic neuralgia: a protocol for a systematic review and Bayesian network meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056632
Article Type:	Protocol
Date Submitted by the Author:	20-Aug-2021
Complete List of Authors:	<p>Bian, Zhiyuan; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Yu, Jie; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province; Affiliated Hangzhou First People's Hospital Zhejiang University School of Medicine, Department of Acupuncture and Massage</p> <p>Tu, Mingqi; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Liao, Binjun; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Huang, Jingmei; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Izumoji, Genki; Zhejiang Chinese Medical University, International Education College</p> <p>Sun, Ruohan; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Xu, Yunyun; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Jiang, Yongliang; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>He, Xiaofen; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Fang, Jian-Qiao; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p>
Keywords:	COMPLEMENTARY MEDICINE, Neurological pain < NEUROLOGY, PAIN MANAGEMENT

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



# Acupuncture therapies for postherpetic neuralgia : a protocol for a systematic review and Bayesian network meta-analysis

Zhiyuan Bian,<sup>1#</sup> Jie Yu,<sup>2#</sup> Mingqi Tu,<sup>1</sup> Binjun Liao,<sup>1</sup> Jingmei Huang,<sup>1</sup> Genki Izumoji,<sup>3</sup> Ruohan Sun,<sup>1</sup> Yunyun Xu,<sup>1</sup> Yongliang Jiang,<sup>1</sup> Xiaofen He,<sup>1</sup> Jianqiao Fang<sup>1\*</sup>

<sup>1</sup> Department of Neurobiology and Acupuncture Research, The Third Clinical Medical College, Zhejiang Chinese Medical University, Key Laboratory of Acupuncture and Neurology of Zhejiang Province, Hangzhou, China

<sup>2</sup> Department of Acupuncture and Massage, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine. Hangzhou, China

<sup>3</sup> International Education College, Zhejiang Chinese Medical University, Hangzhou, China

#These authors contributed equally to this work.

\*Corresponding author

Jianqiao Fang, Department of Neurobiology and Acupuncture Research, The Third Clinical Medical College, Zhejiang Chinese Medical University, Key Laboratory of Acupuncture and Neurology of Zhejiang Province, NO.548 Binwen Road, Hangzhou, 310053, China

E-mail: [fangjianqiao7532@163.com](mailto:fangjianqiao7532@163.com)

ORCID IDs: Zhiyuan Bian 0000-0002-4420-9047; Jie Yu 0000-0002-9225-1901; Mingqi Tu 0000-0002-6048-8111; Jianqiao Fang 0000-0003-4499-0352

Word count: 2988

## ABSTRACT

**Introduction** Postherpetic neuralgia (PHN) is the most common sequela of herpes zoster, and often refractory to guideline-recommended treatments. Acupuncture therapy, a widely applied complementary-alternative treatment, may help in the management of PHN. Diverse types of acupuncture therapy for PHN have been proposed, however, their comparative efficacies remain unclear. This study protocol plans to compare the efficacy and safety of different acupuncture therapies for PHN.

**Methods and analysis** Databases including MEDLINE, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), VIP Database, Wanfang Database, WHO International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov, Chinese Clinical Trial Register (ChiCTR) and OpenGrey will be searched from their inception to July 2021. Randomised controlled trials (RCTs) assessing the effectiveness of acupuncture therapy on the management of PHN will be selected. The primary outcome is pain intensity. Secondary outcomes include negative emotions, sleep condition, quality of life and adverse events. Reviewers will conduct study selection, data extraction and risk of bias assessment procedures. Then, standard pair-wised meta-analysis and Bayesian network meta-analysis will be performed (if applicable). The Confidence in Network Meta-Analysis (CINeMA) application will be used to assess the confidence in the evidence for the primary outcome.

**Ethics and dissemination** All data used for this study will be extracted from published RCTs, thus, no ethical approval will be required. The results of this systematic review will be disseminated through peer-reviewed journal and conference presentation.

**PROSPERO registration number** CRD42020219576

**Keywords:** acupuncture therapy, postherpetic neuralgia, systematic review, network meta-analysis

### Strengths and limitations of this study

- ▶ This study will be the first Bayesian network meta-analysis comparing various acupuncture therapies in the management of postherpetic neuralgia (PHN).
- ▶ Our study will comprehensively evaluate the multi-therapeutic effects of acupuncture therapy for patients with PHN on pain intensity, emotional symptoms, sleep quality as well as life quality, which may provide more practical suggestions for clinical decision-making.
- ▶ Our study will focus on the methods of acupuncture treatment, without consideration of acupoints selection or specific details of manual techniques.
- ▶ We will only search Chinese and English databases, which may result in language bias.

## INTRODUCTION

Postherpetic neuralgia (PHN) is neuropathic pain which occurs after an eruptive phase of herpes zoster (HZ), as its most common clinical sequela.<sup>1</sup> Definitions of PHN are not consistent across studies, ranging from  $\geq 1$  to  $\geq 6$  months after the rash.<sup>2</sup> Compared with acute HZ-associated pain (pain preceding or accompanying the visible cutaneous manifestation) which resolves within a month, PHN may continue for months even years.<sup>3,4</sup> A systematic review showed the incidence rate of HZ ranged from 3 to 5/1000 person-years globally, with 5% to more than 30% HZ patients progressing to PHN.<sup>5</sup> A series of risk factors for PHN are commonly reported, including advanced age, female gender, severe immunosuppression, severe rash and pain in acute zoster episode. Physical comorbidities such as autoimmune conditions and diabetes, may also associate with increased risk of PHN.<sup>6-8</sup> Patients with PHN prominently complain about continuous or intermittent spontaneous pain (eg, aching pain, burning pain, stabbing, shooting), and may co-present hyperalgesia, allodynia and other abnormal sensation (eg, anaesthesia, vibration).<sup>9</sup> In addition, persistent pain can lead to negative emotions, sleep disorders and lowered life quality of patients and even their families, which causes a heavy burden of health care at both the individual and societal levels.<sup>10-12</sup>

Several systemic and topical treatments are listed in guidelines for the management of PHN (either exclusive for PHN or specific mention to PHN in neuropathic pain context).<sup>13-16</sup> Antiepileptic drugs gabapentin and pregabalin, tricyclic antidepressants (TCAs) and topical lidocaine are recommended as first-line treatments. Treatment for PHN is often required for long periods, thus side effect profiles of antiepileptic drugs and TCAs may become troublesome, especially for elderly patients who are dealing with other age-related issues.<sup>17</sup> Lidocaine patch may only cause mild skin reaction, and is considered well tolerated and safe even in long-term treatment.<sup>18,19</sup> Opioids and tramadol are recommended as second-line or third-line options in latest guidelines, with uncertain long-term efficacy and safety.<sup>1</sup> Topical use of capsaicin is listed as second-line or third-line therapy, either capsaicin 0.075% cream or capsaicin 8% patch can be chosen, however, its use may be limited by localized pain during the application.<sup>20</sup> In general, given the refractory nature of neuropathic pain, conventional medications only provide modest effect on pain relief for PHN.<sup>21</sup> Interventional therapy, either involving invasive delivery of

1  
2  
3  
4 drugs or ablation/modulation of related nerves, is proposed in the management of neuropathic  
5 pain and often considered after failure of standard pharmacologic treatments.<sup>22</sup> However,  
6 evidence of interventional treatments specific for PHN patients is generally insufficient, and  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Acupuncture therapy, based on stimulation to acupoints (specific locations on the body), is not only favourable in Asia-Pacific, but also gains increasing popularity in Europa and America.<sup>25-</sup>  
<sup>27</sup> It is one of major components of traditional Chinese medicine (TCM), which has been used in the management of various pain conditions including PHN as an complementary-alternative treatment.<sup>28-31</sup> With a substantial number of clinical trials carried out in China, diverse acupuncture approaches have been reported either singly or in combination when treating PHN, such as manual acupuncture, moxibustion, electro-acupuncture, firing needling and bloodletting.<sup>31</sup> These methods most likely have different effects on pain reduction, given the distinct mechanisms they involved with in both TCM theory and neurophysiological processes.  
<sup>32 33</sup>In recent years, systematic reviews and meta-analyses have shown a potential positive effect of acupuncture therapy for PHN patients on pain relief with few reported adverse events.<sup>34-36</sup> However, these studies either combined all relative methods as acupuncture therapy when conducting data syntheses, or evaluate the effect of only single type of acupuncture therapy, thus, their results may not be sufficient to reflect the distinct effects of diverse acupuncture methods. With the majority of existing studies focus on the comparison between acupuncture therapy and conventional pharmacological treatment, the relative treatment effects of different acupuncture therapies for PHN are poorly understood, which may cause confusion for clinical practitioners. To this end, it is necessary to further explore the relative effectiveness of different acupuncture therapies for PHN.

Network meta-analysis (NMA), as an extension of standard pairwise meta-analysis, compares multiple interventions simultaneously, which can be used to obtain the potential optimal option among different treatments.<sup>37</sup> Therefore, we plan to conduct NMA to evaluate the effectiveness and safety of different acupuncture therapies (and their combinations) for PHN.

### **Objective**

The overall purpose of this study is to assess the effectiveness and safety of different



1  
2  
3  
4 acupuncture therapies in the treatment of PHN based on existing clinical trials. By using the  
5 systematic review and NMA methods, we will primarily focus on the efficacy of acupuncture  
6 therapies on pain relief when treating PHN. We will also compare their effect on negative  
7 emotions, sleep condition as well as life quality and evaluate treatment safety to provide a  
8 comprehensive view for clinical practice.  
9  
10  
11  
12

## 13 **METHODS**

14  
15 We will perform a systematic review and NMA guided by the Checklist of Items to Include  
16 When Reporting a Systematic Review Involving a Network Meta-analysis.<sup>38</sup> This study  
17 protocol will be presented according to the Preferred Reporting Items for Systematic Reviews  
18 and Meta-Analyses Protocols (PRISMA-P) statement.<sup>39</sup> The protocol has been registered on  
19 PROSPERO.  
20  
21  
22  
23  
24

### 25 **Eligibility criteria**

#### 26 Types of studies

27  
28 This review will only include randomised controlled trials (RCTs) reported in English or  
29 Chinese with a parallel-group design. Cross-over trials, quasi-RCTs, cluster RCTs or any other  
30 types of non-RCTs will be excluded.  
31  
32  
33  
34

#### 35 Types of participants

36  
37 Participants will include patients who meet the diagnostic criteria of PHN according to the  
38 definition by the American Academy of Family Physicians,<sup>40</sup> which is pain persist from 30 days  
39 to more than six months after the HZ lesions have healed, or any other accepted diagnostic  
40 guidelines. There will be no restrictions on age, sex or nationality of participants.  
41  
42  
43  
44

#### 45 Types of interventions

46  
47 In this review, we define acupuncture therapy as acupoint-stimulated techniques guided by  
48 TCM theory. Therefore, we will include any of the following treatments: manual acupuncture,  
49 electro-acupuncture, warm needling, fire needling, pressing needling, transcutaneous electrical  
50 acupoint stimulation, moxibustion, bloodletting, cupping, acupoint catgut embedding, acupoint  
51 injection or a combination of any two or three of these methods. Therapies related to acupoint  
52 defined in a non-traditional way such as auricular acupuncture and wrist-ankle acupuncture will  
53 be excluded.  
54  
55  
56  
57  
58  
59  
60

## Types of control groups

Studies using either conventional medication, sham-acupuncture or placebo in the control groups, as well as studies comparing different types of acupuncture therapies will be included. However, studies comparing different acupoints prescriptions or different manual needling techniques with the same type of acupuncture method will be excluded.

## Types of outcome measurements

### *Primary outcome(s)*

Our primary aim is to evaluate the efficacy on pain control. According to preliminary searches of relevant articles, measurements of pain intensity is reported in most cases. While other profiles of pain control such as onset of pain relief time are not frequently reported.<sup>35</sup> Therefore, we will choose pain intensity as main outcome of interest, which is measured by Numerical Rating Scale (NRS), Visual Analogue Scale (VAS), Verbal Rating Scale (VRS), Average Daily Pain Score (ADPS) or other validated scales.

### *Secondary outcome(s)*

To comprehensively assess the effect of acupuncture therapies for PHN, following outcomes will be analysed in our study:

1. Negative emotions such as anxiety and depression measured by Hamilton Anxiety Scale (HAMA), self-rating anxiety scale (SAS) self-rating depression scale (SDS) or other validated scales.
2. Sleep quality measured by Pittsburgh Sleep Quality Index (PSQI) or other validated scales.
3. Life quality measured by Quality of Life scale (QOL) or other validated scales.
4. Adverse events occurred during the treatment period.

## **Data sources and search strategy**

We will identify clinical studies by searching the following databases: MEDLINE (via PubMed), EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), VIP Database and Wanfang Database, WHO International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov and Chinese Clinical Trial Register (ChiCTR). We will also search grey literature in OpenGrey database. Search dates will be from the inception of these databases to July 31st, 2021, with the

1  
2  
3  
4 searching languages limited to either English or Chinese. Search terms used in our review will  
5 be a combination of medical subject headings terms (MeSH) and free-text terms, which can be  
6 categorised into three groups: clinical condition (eg, “postherpetic neuralgia”, “zoster herpes”,  
7 “shingles”, etc.), interventions (eg, “acupuncture”, “moxibustion”, “electroacupuncture”, “fire  
8 needling”, etc.), study design (eg, “randomised controlled trial”, “RCT”, “clinical trial”, etc.).  
9 We will adjust search terms for each database. The search strategy for PubMed is shown in the  
10 appendix 1. In addition, reference lists of included studies will be examined to identify potential  
11 eligible studies.  
12  
13  
14  
15  
16  
17  
18

### 19 **Study selection**

20  
21 Bibliographic information of search results in each database and additional records will be  
22 combined and imported into NoteExpress 3.2.0. After deduplication, two independent  
23 reviewers (ZYB and JY) will screen titles and abstracts of identified studies to remove  
24 irrelevant ones. Full texts of remaining studies will be downloaded for further assessment  
25 according to the inclusion criteria. Reviewers will try to identify duplicate data of same trials  
26 from different publications, and contact study authors for clarification when needed.  
27 Discrepancies on study selection will be resolved by discussion, or when no consensus reached,  
28 a third reviewer (JQF) will be consulted for arbitration. Excluded studies will be recorded with  
29 reasons of exclusion. The process of selection will be shown in a PRISMA flow chart.  
30  
31  
32  
33  
34  
35  
36  
37  
38

### 39 **Data extraction**

40  
41 Two independent reviewers (MQT and JMH) will use a pre-designed data collection form to  
42 extract data from included studies. The following information will be collected: publication  
43 information (publication year, first author), characteristics of the study population (sample size,  
44 age, sex, duration of PHN), details of intervention (type of acupuncture therapies, acupoints  
45 selection, needle retention time, frequency and duration of treatment sessions), details of  
46 comparator (drug names, dosage, frequency, treatment duration), outcomes (data and time point  
47 of outcome measures, adverse events and dropouts). Any disagreement will be solved through  
48 discussion or consulting a third reviewer (JQF).  
49  
50  
51  
52  
53  
54  
55

56 For multi-arm studies where report different types acupuncture interventions (or comparators) ,  
57 data from all relevant arms will be extracted. When comparators involve sham acupuncture  
58  
59  
60

1  
2  
3  
4 methods, types of sham acupuncture and other items same as in acupuncture interventions will  
5  
6 be recorded.

7  
8 Means and standard deviations (SDs) of change scores between baseline and after treatment  
9  
10 (defined as baseline scores minus outcome scores) will be collected for each outcome. When  
11  
12 studies fail to report data on change from baseline, means and SDs at before and after the  
13  
14 treatment will be extracted, then we will calculate the mean change in each arm and the SD of  
15  
16 the changes.<sup>41</sup> For studies where outcomes are reported in multiple time points after the  
17  
18 treatment, data of outcomes assessed at the first time point after the complete treatment regimen  
19  
20 will be used.

21  
22 For studies where SDs of the outcome are not reported, missing SDs will be calculated from  
23  
24 standard errors (SEs), confidence intervals (CIs), t statistics and P values. Additionally, in  
25  
26 studies only reporting median and interquartile ranges (IQR), means and SDs will be calculated  
27  
28 by using specific formula.<sup>42</sup> If these data are not presented, we will contact the corresponding  
29  
30 authors of original studies to obtain the missing data. After these steps, studies with insufficient  
31  
32 data to conduct quantitative synthesis will be excluded for meta-analysis.

### 33 **Risk of bias assessment**

34  
35 We will assess the risk of bias of included studies using the Cochrane tool RoB 2, which  
36  
37 identifies bias in following domains: randomization process, deviations from intended  
38  
39 interventions, missing outcome data, measurement of the outcome, and selection of the reported  
40  
41 result.<sup>43</sup> Pain intensity, as the main outcome of interest, will be selected as the result to assess.  
42  
43 The assessment will be done in relation to the assignment to the intervention (intention-to-treat  
44  
45 effect). Two reviewers (BJL and RHS) will independently answer the signalling questions of  
46  
47 each domain. Then, a judgement into “low”, “some concerns” or “high” risk of bias will be  
48  
49 made depending on the responses to these questions and finally reaching an overall risk-of-bias  
50  
51 judgement. Disagreements during the assessment will be resolved by discussion, and a third  
52  
53 reviewer (JQF) will be consult where necessary.

### 54 **Data synthesis**

55  
56 We will perform NMA as primary method for data synthesis. Additionally, standard pairwise  
57  
58 meta-analyses will be conducted and the results will be compared with those from the NMA.  
59  
60

1  
2  
3  
4 For each outcome, mean difference (MD) on the change score will be considered as the  
5 measures of relative treatment effects. When trials use different measurement scales for a  
6 certain outcome, standardised mean difference (SMD) will be calculated. We will use odds  
7 ratio (OR) to investigate adverse events data as the measure of treatment safety.  
8  
9

10  
11 When two or more studies comparing the same pair of interventions exist for an outcome, the  
12 standard meta-analysis will be performed. Random-effects models will be fitted in Stata 15.1.  
13 The effect size will be estimated with 95% confidence interval (CI). We will use  $I^2$  statistic to  
14 quantify heterogeneity of the results in same treatment comparisons.<sup>44</sup> If the  $I^2$  value is greater  
15 than 75% which indicates the existing of high heterogeneity, and meanwhile no main source  
16 of heterogeneity is found, we will provide a narrative summary without conducting data  
17 synthesis.<sup>45</sup>  
18  
19

20  
21 We will perform network meta-analyses to compare multiple interventions simultaneously. For  
22 each outcome, network plots of all included comparisons will be generated using Stata 15.1,  
23 interventions will be represented by nodes, and each line between two nodes means that direct  
24 comparison between two interventions is available. Studies that are not connected to the  
25 network will be exclude from network meta-analyses. Sizes of the nodes and lines are  
26 proportional to the number of included studies. We will conduct the NMA within a Bayesian  
27 hierarchical framework in OpenBUGS 3.2.3. Random effects models with vague priors will be  
28 fitted and Markov Chain Monte Carlo (MCMC) method will be employed to obtain the pooled  
29 treatment effect with 95% credible interval (CrI). Three MCMC chains with different sets of  
30 initial values will be run simultaneously. For each initial values, a total of 60,000 times of  
31 simulation will be conducted after 10,000 times of simulation being discarded as the burn-in  
32 period, and convergence will be checked visually as well as assessed by the Gelman-Rubin  
33 statistic.<sup>46</sup> To assess the model fit, the posterior mean residual deviance will be calculated and  
34 compared with the number of data points in the model.<sup>47</sup> We will obtain the ranking  
35 probabilities of all included interventions using the surface under the cumulative ranking curve  
36 (SUCRA) analysis in Stata V.15.1.<sup>48</sup>  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

56 Clinical and methodological heterogeneity will be assessed by examining the characteristics  
57 and design of the included studies. The transitivity assumption for NMA will be evaluated by  
58  
59  
60

1  
2  
3  
4 reviewing the distribution of potential effect modifiers (participant characteristics: age, pain  
5 severity at baseline; interventions: treatment duration; study design: risk of bias) across  
6 comparisons. We will also assess statistical heterogeneity by calculating between-study  
7 standard deviation ( $\tau^2$ ), with larger  $\tau^2$  value indicates higher level of heterogeneity among  
8 studies. We will evaluate global inconsistency of treatment network by comparing the  
9 consistency model with an inconsistency model, and for each closed loop, node-splitting  
10 method will be used to assess local inconsistency.<sup>49 50</sup>

### 17 **Additional analyses**

18  
19 We will perform network meta-regression using a random effects model to examine the  
20 influence of potential effect modifiers (eg, average age of participants, duration of PHN, pain  
21 severity at baseline, treatment duration) on the main outcome. If sufficient studies are available,  
22 we will also perform sensitivity analysis by excluding trials rated as high risk of bias to ensure  
23 robustness of primary findings. Furthermore, the presence of potential reporting bias will be  
24 inspected by using comparison-adjusted funnel plot.<sup>51</sup>

### 31 **Credibility of the evidence**

32  
33 We plan to evaluate credibility of the evidence from NMA using the Confidence in Network  
34 Meta-Analysis (CINeMA) web application for the primary outcome.<sup>52</sup> Two reviewers (GI and  
35 YYX) will independently assess the following domains: within-study bias, across-study bias,  
36 indirectness, imprecision, heterogeneity and incoherence. Disagreements will be solved by  
37 discuss or consulting to a third reviewer (JQF). Confidence in the results will be graded as  
38 “high”, “moderate”, “low” and “very low”.

### 44 **Patient and public involvement**

45  
46 No patients or public will be involved in this study.

### 48 **DISCUSSION**

49  
50 Patients with PHN usually undergo persistent pain, and many of them complain about other  
51 clinical symptoms such as anxiety, depression and sleep disorder, which are frequent in general  
52 neuropathic pain condition.<sup>53</sup> Although plenty of recommendations has been made on  
53 pharmacologic therapy, it is widely considered that many PHN patients do not achieve  
54 satisfactory pain relief or discontinue treatment due to adverse effects.<sup>54</sup> Acupuncture therapy  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 is proposed as potential beneficial in the management of neuropathic pain, and is generally safe  
5 when operated by competent practitioners.<sup>55 56</sup> Besides, acupuncture therapy may help with  
6 negative emotion and sleep disorder, which would provide additional benefits for patients in  
7 usually long-term treatment.<sup>57 58</sup> In clinical practice for PHN, diverse acupuncture methods are  
8 available, and with variations of other treatment characteristics (eg, acupoints selection,  
9 treatment duration), standardized clinical strategy of acupuncture for PHN has not been fully  
10 established. The clinical practice guideline of acupuncture for HZ, launched by the WHO's  
11 Western Pacific Regional Office, recommended the use of fire needling, electro-acupuncture  
12 and bloodletting in PHN phase, and suggested the combined use of two or more methods is  
13 more beneficial.<sup>59</sup> However, there is still less knowledge on the relative effectiveness of these  
14 acupuncture methods and their integrated use. NMA, a technique to integrate direct and indirect  
15 comparisons integrate across a set of multiple variables, can be used for comparing efficacies  
16 of multiple treatments simultaneously in a single analysis.<sup>60</sup> In recent years, NMA has been  
17 increasingly conducted to compare the efficacies of different acupuncture methods for many  
18 diseases such as knee osteoarthritis, myofascial pain syndrome, chronic fatigue syndrome,<sup>61-63</sup>  
19 To the best of our knowledge, this study will be the first network meta-analysis of acupuncture  
20 therapies for the treatment of PHN. We sincerely hope that our results will offer credible  
21 evidence and contribute to more proper use of acupuncture therapy for treating PHN.

#### 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 **ETHICS AND DISSEMINATION**

40 This study will not collect confidential patient data, thus no ethical approval needed. The  
41 findings will be disseminated through peer-reviewed publication and conference presentation.  
42  
43  
44

45  
46  
47 **Acknowledgements** Not applicable

48  
49 **Author contributions** ZYB and JY conceived this study and wrote the manuscript. MQT and  
50 BJJ developed the search strategy. JMH, GI, RHS and YYX provided methodological advice.  
51 YLJ, XFH and JQF revised the manuscript. All authors have reviewed this protocol and  
52 approved the final manuscript.  
53  
54

55  
56  
57 **Funding** This study is supported by Key Plan of Zhejiang Province Traditional Chinese  
58 Medicine Prevention and Treatment of Major Disease of the Health and Family Planning  
59  
60



Commission of Zhejiang Province (No.2018ZY008). The funders had no role on the design of this study.

**Competing interests** None declared

## REFERENCES

1. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *N Engl J Med* 2014;371:1526-33. doi:10.1056/NEJMcp1403062
2. CDC (Centers for Disease Control and Prevention). Prevention of herpes zoster: recommendations of the advisory committee on immunization practices (ACIP). CDC. 2008 <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e0515a1.htm>
3. Gan EY, Tian EA, Tey HL. Management of herpes zoster and post-herpetic neuralgia. *Am J Clin Dermatol* 2013;14:77-85. doi:10.1007/s40257-013-0011-2
4. Dworkin RH, Gnann JW Jr, Oaklander AL, *et al.* Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. *J Pain* 2008;9(1 Suppl 1):S37-44. doi:10.1016/j.jpain.2007.10.008
5. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open* 2014;4:e004833. doi:10.1136/bmjopen-2014-004833
6. Choo PW, Galil K, Donahue JG, *et al.* Risk factors for postherpetic neuralgia. *Arch Intern Med.* 1997;157:1217-24.
7. Forbes HJ, Thomas SL, Smeeth L, *et al.* A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016;157:30-54. doi:10.1097/j.pain.0000000000000307
8. Forbes HJ, Bhaskaran K, Thomas SL, *et al.* Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: A cohort study. *Neurology* 2016;87:94-102. doi:10.1212/WNL.0000000000002808
9. Schutzer-Weissmann J, Farquhar-Smith P. Post-herpetic neuralgia - a review of current management and future directions. *Expert Opin Pharmacother* 2017;18:1739-50. doi:10.1080/14656566.2017.1392508



10. Oster G, Harding G, Dukes E, *et al.* Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. *J Pain* 2005;6:356-63. doi:10.1016/j.jpain.2005.01.359
11. Mauskopf J, Austin R, Dix L, *et al.* The Nottingham Health Profile as a measure of quality of life in zoster patients: convergent and discriminant validity. *Qual Life Res* 1994;3:431-5. doi:10.1007/BF00435395
12. Weinke T, Glogger A, Bertrand I, *et al.* The societal impact of herpes zoster and postherpetic neuralgia on patients, life partners, and children of patients in Germany. *ScientificWorldJournal* 2014;2014:749698. doi:10.1155/2014/749698
13. Dubinsky RM, Kabbani H, El-Chami Z, *et al.* Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2004;63:959-65. doi:10.1212/01.wnl.0000140708.62856.72
14. Attal N, Cruccu G, Baron R, *et al.* EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17:1113-e88. doi:10.1111/j.1468-1331.2010.02999.x
15. Dworkin RH, O'Connor AB, Backonja M, *et al.* Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132:237-51. doi:10.1016/j.pain.2007.08.033
16. Dworkin RH, O'Connor AB, Audette J, *et al.* Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* 2010;85:S3-14. doi:10.4065/mcp.2009.0649
17. Hadley GR, Gayle JA, Ripoll J, *et al.* Post-herpetic Neuralgia: a Review [published correction appears in *Curr Pain Headache Rep* 2016 Apr;20:28]. *Curr Pain Headache Rep* 2016;20:17. doi:10.1007/s11916-016-0548-x
18. Wilhelm IR, Tzabazis A, Likar R, *et al.* Long-term treatment of neuropathic pain with a 5% lidocaine medicated plaster. *Eur J Anaesthesiol* 2010;27:169-73. doi:10.1097/EJA.0b013e328330e989
19. Bursi R, Piana C, Grevel J, *et al.* Evaluation of the Population Pharmacokinetic Properties

- of Lidocaine and its Metabolites After Long-Term Multiple Applications of a Lidocaine Plaster in Post-Herpetic Neuralgia Patients. *Eur J Drug Metab Pharmacokinet* 2017;42:801-14. doi:10.1007/s13318-017-0400-7
20. Argoff CE. Review of current guidelines on the care of postherpetic neuralgia. *Postgrad Med* 2011;123:134-42. doi:10.3810/pgm.2011.09.2469
21. Wright ME, Rizzolo D. An update on the pharmacologic management and treatment of neuropathic pain. *JAAPA* 2017;30:13-7. doi:10.1097/01.JAA.0000512228.23432.f7
22. Dworkin RH, O'Connor AB, Kent J, *et al.* Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain* 2013;154:2249-61. doi:10.1016/j.pain.2013.06.004
23. Colloca L, Ludman T, Bouhassira D, *et al.* Neuropathic pain. *Nat Rev Dis Primers* 2017;3:17002. doi:10.1038/nrdp.2017.2.
24. Lin CS, Lin YC, Lao HC, *et al.* Interventional Treatments for Postherpetic Neuralgia: A Systematic Review. *Pain Physician* 2019;22:209-28.
25. Wiesener S, Falkenberg T, Hegyi G, *et al.* Legal status and regulation of complementary and alternative medicine in Europe. *Forsch Komplementmed* 2012;19 Suppl 2:29-36. doi:10.1159/000343125
26. Bückner B, Groenewold M, Schoefer Y, *et al.* The use of complementary alternative medicine (CAM) in 1 001 German adults: results of a population-based telephone survey. *Gesundheitswesen* 2008;70:e29-36. doi:10.1055/s-2008-1081505
27. Zhang Y, Lao L, Chen H, *et al.* Acupuncture Use among American Adults: What Acupuncture Practitioners Can Learn from National Health Interview Survey 2007?. *Evid Based Complement Alternat Med* 2012;2012:710750. doi:10.1155/2012/710750
28. Fu LM, Li JT, Wu WS. Randomized controlled trials of acupuncture for neck pain: systematic review and meta-analysis. *J Altern Complement Med* 2009;15:133-45. doi:10.1089/acm.2008.0135
29. Witt C, Brinkhaus B, Jena S, *et al.* Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet* 2005;366:136-43. doi:10.1016/S0140-6736(05)66871-7
30. Vickers AJ, Cronin AM, Maschino AC, *et al.* Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med* 2012;172:1444-53.

- doi:10.1001/archinternmed.2012.3654
31. Chen LK, Arai H, Chen LY, *et al.* Looking back to move forward: a twenty-year audit of herpes zoster in Asia-Pacific. *BMC Infect Dis* 2017;17:213. doi:10.1186/s12879-017-2198-y
  32. Deng H, Shen X. The mechanism of moxibustion: ancient theory and modern research. *Evid Based Complement Alternat Med* 2013;2013:379291. doi:10.1155/2013/379291.
  33. Wang QY, Qu YY, Feng CW, *et al.* Analgesic mechanism of acupuncture on neuropathic pain. *Zhongguo Zhen Jiu* 2020;40:907-12. doi:10.13703/j.0255-2930.20190927-k0003
  34. Wang Y, Li W, Peng W, *et al.* Acupuncture for postherpetic neuralgia: Systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e11986. doi:10.1097/MD.00000000000011986
  35. Pei W, Zeng J, Lu L, *et al.* Is acupuncture an effective postherpetic neuralgia treatment? A systematic review and meta-analysis. *J Pain Res* 2019;12:2155-65. doi:10.2147/JPR.S199950
  36. Liu YJ, Zhang QA, Wu YY, *et al.* Meta-analysis for efficacy and safety of electroacupuncture in treating postherpetic neuralgia. *J Guangzhou Univ Tradit Chin Med* 2020;37:2472-80.
  37. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med* 2017;12:103-111. doi:10.1007/s11739-016-1583-7
  38. Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84. doi:10.7326/M14-2385
  39. Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1. doi:10.1186/2046-4053-4-1
  40. Fashner J, Bell AL. Herpes zoster and postherpetic neuralgia: prevention and management. *Am Fam Physician* 2011;83:1432-1437.
  41. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, *et al.* *Cochrane Handbook for*

- 1  
2  
3  
4 Systematic Reviews of Interventions version 6.1. Cochrane, 2020. Available from  
5 www.training.cochrane.org/handbook.  
6  
7  
8 42. Wan X, Wang W, Liu J, *et al.* Estimating the sample mean and standard deviation from  
9 the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*  
10 2014;14:135. doi:10.1186/1471-2288-14-135  
11  
12  
13 43. Sterne JAC, Savović J, Page MJ, *et al.* Rob 2: a revised tool for assessing risk of bias in  
14 randomised trials. *BMJ* 2019;366:14898. doi:10.1136/bmj.14898  
15  
16  
17 44. Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses.  
18 *BMJ* 2003;327:557-60. doi:10.1136/bmj.327.7414.557  
19  
20  
21 45. Melsen WG, Bootsma MC, Rovers MM, *et al.* The effects of clinical and statistical  
22 heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect*  
23 2014;20:123-129. doi:10.1111/1469-0691.12494  
24  
25  
26  
27 46. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Statist*  
28 *Sci* 1992;7:457-72. doi: 10.1214/ss/1177011136.  
29  
30  
31 47. Dias S, Ades A, Welton N, *et al.* *Network meta-analysis for decision-making*. Chichester,  
32 UK: John Wiley & Sons, Ltd 2018.  
33  
34  
35 48. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works  
36 without resampling methods. *BMC Med Res Methodol* 2015;15:58. doi:10.1186/s12874-  
37 015-0060-8  
38  
39  
40 49. Dias S, Welton NJ, Sutton AJ, *et al.* Evidence synthesis for decision making 4:  
41 inconsistency in networks of evidence based on randomized controlled trials. *Med Decis*  
42 *Making* 2013;33:641-56. doi:10.1177/0272989X12455847  
43  
44  
45  
46 50. Dias S, Welton NJ, Caldwell DM, *et al.* Checking consistency in mixed treatment  
47 comparison meta-analysis. *Stat Med* 2010;29:932-44. doi:10.1002/sim.3767  
48  
49  
50 51. Chaimani A, Higgins JP, Mavridis D, *et al.* Graphical tools for network meta-analysis in  
51 STATA. *PLoS One* 2013;8:e76654. doi:10.1371/journal.pone.0076654  
52  
53  
54 52. Salanti G, Del Giovane C, Chaimani A, *et al.* Evaluating the quality of evidence from a  
55 network meta-analysis. *PLoS One* 2014;9:e99682. doi:10.1371/journal.pone.0099682  
56  
57  
58 53. Colloca L, Ludman T, Bouhassira D, *et al.* Neuropathic pain. *Nat Rev Dis Primers*  
59  
60

- 2017;3:17002. doi:10.1038/nrdp.2017.2
54. Dworkin RH, Panarites CJ, Armstrong EP, *et al.* Is treatment of postherpetic neuralgia in the community consistent with evidence-based recommendations?. *Pain* 2012;153:869-875. doi:10.1016/j.pain.2012.01.015
55. Maccone A, Otis JAD. Neuropathic Pain. *Semin Neurol* 2018;38:644-653. doi:10.1055/s-0038-1673679
56. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med* 2002;136:374-383. doi:10.7326/0003-4819-136-5-200203050-00010
57. Goyata SL, Avelino CC, Santos SV, *et al.* Effects from acupuncture in treating anxiety: integrative review. *Rev Bras Enferm* 2016; 69:602-9. doi:10.1590/0034-7167.2016690325i
58. Shergis JL, Ni X, Jackson ML, *et al.* A systematic review of acupuncture for sleep quality in people with insomnia. *Complement Ther Med* 2016;26:11-20. doi:10.1016/j.ctim.2016.02.007
59. Liu ZS, Peng WN, Liu BY, *et al.* Clinical practice guideline of acupuncture for herpes zoster. *Chin J Integr Med* 2013;19:58-67. doi:10.1007/s11655-013-1191-y
60. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331(7521):897-900. doi:10.1136/bmj.331.7521.897
61. Corbett MS, Rice SJ, Madurasinghe V, *et al.* Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: network meta-analysis. *Osteoarthritis Cartilage* 2013;21:1290-1298. doi:10.1016/j.joca.2013.05.007
62. Li X, Wang R, Xing X, *et al.* Acupuncture for Myofascial Pain Syndrome: A Network Meta-Analysis of 33 Randomized Controlled Trials. *Pain Physician* 2017;20:E883-902.
63. Wang T, Xu C, Pan K, *et al.* Acupuncture and moxibustion for chronic fatigue syndrome in traditional Chinese medicine: a systematic review and meta-analysis. *BMC Complement Altern Med* 2017;17:163. doi:10.1186/s12906-017-1647-x

Appendix 1  
Search strategy in PubMed

Order	search items
#1	MeSH Terms: "Neuralgia, Postherpetic"
#2	Title/Abstract: "postherpetic neuralgia" OR "post-herpetic neuralgia" OR "PHN" OR "herpes zoster" OR "shingles"
#3	#1 OR #2
#4	MeSH Terms: "Acupuncture Therapy" OR "Acupuncture" OR "Moxibustion" OR "Cupping Therapy" OR "Bloodletting" OR "Electroacupuncture"
#5	Title/Abstract: "acupuncture" OR "electroacupuncture" OR "moxibustion" OR "moxa" OR "cupping" OR "bloodletting" OR "blood-letting" OR "pricking blood" OR "pyonex" OR "acupressure" OR "needle" OR "needles" OR "needling" OR "acupoint" OR "acupoints" OR "meridian" OR "meridians"
#6	#4 OR #5
#7	Publication Type: "Randomized Controlled Trial"
#8	MeSH Terms: "Randomized Controlled Trials as Topic"
#9	Title/Abstract: "randomized" OR "randomly" OR "RCT" OR "trial"
#10	#7 OR #8 OR #9
#11	#3 AND #6 AND #10

# Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	NA

1 **Registration**

2  
3  
4 [#2](#) If registered, provide the name of the registry (such as 2  
5  
6 PROSPERO) and registration number  
7  
8

9 **Authors**

10  
11  
12  
13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all 1  
14  
15 protocol authors; provide physical mailing address of  
16  
17 corresponding author  
18

19  
20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the 12  
21  
22 guarantor of the review  
23  
24

25 **Amendments**

26  
27  
28  
29 [#4](#) If the protocol represents an amendment of a previously NA  
30  
31 completed or published protocol, identify as such and list  
32  
33 changes; otherwise, state plan for documenting important  
34  
35 protocol amendments  
36  
37

38 **Support**

39  
40  
41  
42 **Sources** [#5a](#) Indicate sources of financial or other support for the review 12-13  
43

44  
45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor 12-13  
46

47  
48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), 13  
49  
50 funder  
51 if any, in developing the protocol  
52

53 **Introduction**

54  
55  
56  
57 **Rationale** [#6](#) Describe the rationale for the review in the context of what is 4-5  
58



1		already known	
2			
3			
4	Objectives	<a href="#">#7</a> Provide an explicit statement of the question(s) the review will	5-6
5		address with reference to participants, interventions,	
6		comparators, and outcomes (PICO)	
7			
8			
9			
10			
11	<b>Methods</b>		
12			
13			
14	Eligibility criteria	<a href="#">#8</a> Specify the study characteristics (such as PICO, study design,	6-7
15		setting, time frame) and report characteristics (such as years	
16		considered, language, publication status) to be used as	
17		criteria for eligibility for the review	
18			
19			
20			
21			
22			
23			
24	Information	<a href="#">#9</a> Describe all intended information sources (such as electronic	7-8
25		databases, contact with study authors, trial registers or other	
26	sources	grey literature sources) with planned dates of coverage	
27			
28			
29			
30			
31			
32	Search strategy	<a href="#">#10</a> Present draft of search strategy to be used for at least one	7-8
33		electronic database, including planned limits, such that it	
34		could be repeated	
35			
36			
37			
38			
39	Study records -	<a href="#">#11a</a> Describe the mechanism(s) that will be used to manage	8
40		records and data throughout the review	
41	data management		
42			
43			
44			
45	Study records -	<a href="#">#11b</a> State the process that will be used for selecting studies (such	8
46		as two independent reviewers) through each phase of the	
47	selection process	review (that is, screening, eligibility and inclusion in meta-	
48		analysis)	
49			
50			
51			
52			
53			
54	Study records -	<a href="#">#11c</a> Describe planned method of extracting data from reports	8-9
55		(such as piloting forms, done independently, in duplicate), any	
56	data collection		
57			
58			
59			
60			

1	process		processes for obtaining and confirming data from investigators	
2				
3				
4	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	8-9
5			(such as PICO items, funding sources), any pre-planned data	
6			assumptions and simplifications	
7				
8				
9				
10				
11	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	8-9
12				
13	prioritization		including prioritization of main and additional outcomes, with	
14			rationale	
15				
16				
17				
18				
19	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	9
20				
21	individual studies		individual studies, including whether this will be done at the	
22			outcome or study level, or both; state how this information will	
23			be used in data synthesis	
24				
25				
26				
27				
28				
29	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively	10
30			synthesised	
31				
32				
33				
34	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	9-11
35			planned summary measures, methods of handling data and	
36			methods of combining data from studies, including any	
37			planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
38				
39				
40				
41				
42				
43				
44	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	11
45			sensitivity or subgroup analyses, meta-regression)	
46				
47				
48				
49	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type	10
50			of summary planned	
51				
52				
53				
54				
55	Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as	11
56			publication bias across studies, selective reporting within	
57				
58				
59				
60				

studies)

1  
2  
3  
4 Confidence in [#17](#) Describe how the strength of the body of evidence will be  
5  
6 cumulative assessed (such as GRADE)  
7  
8 evidence  
9

11

10  
11 The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative  
12  
13 Commons Attribution License CC-BY. This checklist was completed on 19. August 2021 using  
14  
15 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with  
16  
17 [Penelope.ai](#)  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# BMJ Open

## Acupuncture therapies for postherpetic neuralgia: a protocol for a systematic review and Bayesian network meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056632.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Dec-2021
Complete List of Authors:	<p>Bian, Zhiyuan; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Yu, Jie; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province; Affiliated Hangzhou First People's Hospital Zhejiang University School of Medicine, Department of Acupuncture and Massage</p> <p>Tu, Mingqi; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Liao, Binjun; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Huang, Jingmei; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Izumoji, Genki; Zhejiang Chinese Medical University, International Education College</p> <p>Sun, Ruohan; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Xu, Yunyun; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Jiang, Yongliang; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>He, Xiaofen; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Fang, Jian-Qiao; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p>
<b>Primary Subject Heading</b>:	Complementary medicine
Secondary Subject Heading:	Neurology

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Keywords:	COMPLEMENTARY MEDICINE, Neurological pain < NEUROLOGY, PAIN MANAGEMENT

SCHOLARONE™  
Manuscripts

# Acupuncture therapies for postherpetic neuralgia : a protocol for a systematic review and Bayesian network meta-analysis

Zhiyuan Bian,<sup>1</sup> # Jie Yu,<sup>2</sup> # Mingqi Tu,<sup>1</sup> Binjun Liao,<sup>1</sup> Jingmei Huang,<sup>1</sup> Genki Izumoji,<sup>3</sup> Ruohan Sun,<sup>1</sup> Yunyun Xu,<sup>1</sup> Yongliang Jiang,<sup>1</sup> Xiaofen He,<sup>1</sup> Jianqiao Fang<sup>1</sup> \*

<sup>1</sup> Department of Neurobiology and Acupuncture Research, The Third Clinical Medical College, Zhejiang Chinese Medical University, Key Laboratory of Acupuncture and Neurology of Zhejiang Province, Hangzhou, China

<sup>2</sup> Department of Acupuncture and Massage, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine. Hangzhou, China

<sup>3</sup> International Education College, Zhejiang Chinese Medical University, Hangzhou, China

#These authors contributed equally to this work.

\*Corresponding author

Jianqiao Fang, Department of Neurobiology and Acupuncture Research, The Third Clinical Medical College, Zhejiang Chinese Medical University, Key Laboratory of Acupuncture and Neurology of Zhejiang Province, NO.548 Binwen Road, Hangzhou, 310053, China

E-mail: [fangjianqiao7532@163.com](mailto:fangjianqiao7532@163.com)

ORCID IDs: Zhiyuan Bian 0000-0002-4420-9047; Jie Yu 0000-0002-9225-1901; Mingqi Tu 0000-0002-6048-8111; Jianqiao Fang 0000-0003-4499-0352

Word count: 2997

## ABSTRACT

**Introduction** Postherpetic neuralgia (PHN) is the most common sequela of herpes zoster, and it is often refractory to guideline-recommended treatments. Acupuncture therapy, a widely applied complementary-alternative treatment, may help in the management of PHN. Diverse types of acupuncture therapy for PHN have been proposed, however, their comparative efficacies remain unclear. This study protocol plans to compare the efficacy and safety of different acupuncture therapies for PHN.

**Methods and analysis** Databases including MEDLINE, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Database, China National Knowledge Infrastructure, VIP Database, Wanfang Database, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, Chinese Clinical Trial Register and OpenGrey will be searched from their inception to December 2021. Randomised controlled trials (RCTs) assessing the effectiveness of acupuncture therapy on the management of PHN will be selected. The primary outcome is pain intensity. Secondary outcomes include negative emotions, sleep condition, quality of life and adverse events. Reviewers will conduct study selection, data extraction and risk of bias assessment procedures. Then, standard pair-wised meta-analysis and Bayesian network meta-analysis will be performed (if applicable). The Confidence in Network Meta-Analysis application will be used to assess the confidence in the evidence for the primary outcome.

**Ethics and dissemination** All data used for this study will be extracted from published RCTs, thus, no ethical approval will be required. The results of this systematic review will be disseminated through peer-reviewed journal and conference presentation.

**PROSPERO registration number** CRD42020219576

**Keywords:** acupuncture therapy, postherpetic neuralgia, systematic review, network meta-analysis

### Strengths and limitations of this study

- ▶ This study will be the first Bayesian network meta-analysis comparing various acupuncture therapies in the management of postherpetic neuralgia (PHN).
- ▶ Our study will comprehensively evaluate the effects of acupuncture therapy on pain intensity, emotional symptoms, sleep quality, and life quality for patients with PHN.
- ▶ Our study will focus on the methods of acupuncture treatment, without consideration of acupoints selection or specific details of manual techniques.
- ▶ We will only search Chinese and English databases, which may result in language bias.



## INTRODUCTION

Postherpetic neuralgia (PHN) is defined as a neuropathic pain that occurs after an eruptive phase of herpes zoster (HZ), as its most common clinical sequela.<sup>1</sup> Definitions of PHN are not consistent across studies, with its occurrence ranging from  $\geq 1$  to  $\geq 6$  months after the rash.<sup>2</sup> Compared with acute HZ-associated pain (pain preceding or accompanying the visible cutaneous manifestation), which resolves within a month, PHN may persist for months, even years.<sup>3-4</sup> A systematic review showed that the incidence rate of HZ ranged from 3 to 5/1000 person-years globally, with 5% to more than 30% of patients with HZ progressing to PHN.<sup>5</sup> Several risk factors for PHN are commonly reported, including advanced age, female sex, severe immunosuppression, severe rash, and pain in acute zoster episode. Physical comorbidities, such as autoimmune conditions and diabetes, may also be associated with an increased risk of PHN.<sup>6-8</sup> Patients with PHN prominently complain about continuous or intermittent spontaneous pain (eg, aching pain, burning pain, stabbing, shooting) and may co-present with hyperalgesia, allodynia, and other abnormal sensations (eg, anaesthesia, vibration).<sup>9</sup> In addition, persistent pain can lead to negative emotions, sleep disorders, and lowered quality of life of patients and their families, which causes a heavy burden of health care at both the individual and societal levels.<sup>10-12</sup>

Several systemic and topical treatments are listed in the guidelines for the management of PHN (either exclusive for PHN or specific mention to PHN in neuropathic pain context).<sup>13-16</sup> Antiepileptic drugs gabapentin and pregabalin, tricyclic antidepressants (TCAs), and topical lidocaine are recommended as first-line treatments. PHN often requires long-term treatment; thus, side effect profiles of antiepileptic drugs and TCAs may become dangerous, especially for elderly patients who are dealing with other age-related issues.<sup>17</sup> Lidocaine patch may only cause mild skin reaction and is well tolerated and safe even in long-term treatment.<sup>18-19</sup> Opioids and tramadol are recommended as second-line or third-line options in latest guidelines, with uncertain long-term efficacy and safety.<sup>1</sup> Topical use of capsaicin is listed as second-line or third-line therapy, and either capsaicin 0.075% cream or capsaicin 8% patch can be selected. However, its use may be limited by localised pain during the application.<sup>20</sup> In general, given the refractory nature of neuropathic pain, conventional medications only

1  
2  
3  
4 provide modest effect on pain relief for PHN.<sup>21</sup> Interventional therapy, either involving  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

provide modest effect on pain relief for PHN.<sup>21</sup> Interventional therapy, either involving  
invasive delivery of drugs or ablation/modulation of related nerves, is proposed in the  
management of neuropathic pain and often considered after failure of standard  
pharmacological treatments.<sup>22</sup> However, evidence of interventional treatments specific for  
patients with PHN is generally insufficient, and invasive procedures are often associated with  
safety concerns.<sup>23 24</sup>

Acupuncture therapy, based on stimulation to acupoints (specific locations on the body), not  
only is favourable in Asia-Pacific but also gains increasing popularity in Europe and  
America.<sup>25-27</sup> It is one of the major components of traditional Chinese medicine (TCM), which  
has been used in the management of various pain conditions, including PHN, as a  
complementary alternative treatment.<sup>28-31</sup> With a substantial number of clinical trials  
conducted in China, diverse acupuncture approaches have been reported either singly or in  
combination when treating PHN, such as manual acupuncture, moxibustion,  
electroacupuncture, firing needling, and bloodletting.<sup>31</sup> These methods most likely have  
different effects on pain reduction, given their distinct mechanisms in both TCM theory and  
neurophysiological processes.<sup>32 33</sup> In recent years, systematic reviews and meta-analyses have  
shown a potential positive effect of acupuncture therapy for patients with PHN on pain relief  
with few reported adverse events.<sup>34-36</sup> However, these studies either combined all relative  
methods as acupuncture therapy when conducting data syntheses or evaluated the effect of  
only a single type of acupuncture therapy. Thus, their results may not be sufficient to reflect  
the distinct effects of diverse acupuncture methods. With the majority of existing studies  
focusing on the comparison between acupuncture therapy and conventional pharmacological  
treatment, the relative treatment effects of different acupuncture therapies for PHN are poorly  
understood, which may cause confusion for clinical practitioners. To this end, it is necessary  
to further explore the relative effectiveness of different acupuncture therapies for PHN.

Network meta-analysis (NMA), as an extension of standard pairwise meta-analysis, compares  
multiple interventions simultaneously, which can be used to obtain the potential optimal  
option among different treatments.<sup>37</sup> Therefore, we plan to perform NMA to evaluate the  
effectiveness and safety of different acupuncture therapies (and their combinations) for PHN.

## Objective

The overall purpose of this study is to assess the effectiveness and safety of different acupuncture therapies in the treatment of PHN based on existing clinical trials. Using a systematic review and NMA methods, we will primarily focus on the efficacy of acupuncture therapies for pain relief when treating PHN. We will also compare their effect on negative emotions, sleep condition, and quality of life and evaluate treatment safety to provide a comprehensive view for clinical practice.

## METHODS

We will perform a systematic review and NMA guided by the Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.<sup>38</sup> This study protocol will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.<sup>39</sup> The protocol has been registered on PROSPERO.

### Eligibility criteria

#### Types of studies

This review will only include randomised controlled trials (RCTs) reported in English or Chinese with a parallel-group design. Cross-over trials, quasi-RCTs, cluster RCTs, or any other types of non-RCTs will be excluded.

#### Types of participants

Participants will include patients who meet the diagnostic criteria of PHN according to the definition by the American Academy of Family Physicians,<sup>40</sup> which is pain persisting from 30 days to more than 6 months after the HZ lesions have healed, or any other accepted diagnostic guidelines. There will be no restrictions on age, sex, or nationality of the participants.

#### Types of interventions

In this review, we define acupuncture therapy as an acupoint-stimulated technique guided by the TCM theory. Therefore, we will include any of the following treatments: manual acupuncture, electroacupuncture, warm needling, fire needling, pressing needling, transcutaneous electrical acupoint stimulation, moxibustion, bloodletting, cupping, acupoint catgut embedding, acupoint injection, or a combination of any two or three of these methods.

1  
2  
3  
4 Therapies related to acupoints defined in a non-traditional way, such as auricular acupuncture  
5 and wrist-ankle acupuncture, will be excluded.  
6

7  
8 Types of control groups

9  
10 Studies using either conventional medication or placebo in the control groups and studies  
11 comparing different types of acupuncture therapies will be included. However, studies  
12 comparing different acupoint prescriptions or different manual needling techniques with the  
13 same type of acupuncture method will be excluded.  
14  
15

16  
17 Types of outcome measurements

18  
19 *Primary outcome(s)*

20  
21 Our primary aim is to evaluate pain control efficacy. According to preliminary searches of  
22 relevant articles, measurements of pain intensity have been reported in most cases. Other  
23 profiles of pain control, such as onset of pain relief time, are not frequently reported.<sup>35</sup>  
24  
25 Therefore, we will select pain intensity as the main outcome of interest. Pain intensity is  
26 usually presented by a score on a range between no pain to maximum pain, with higher  
27 number indicating more severe pain, using the Visual Analogue Scale, Numerical Rating  
28 Scale, Verbal Rating Scale, Average Daily Pain Score, or other validated scales.  
29  
30  
31  
32  
33

34  
35 *Secondary outcome(s)*

36  
37 To comprehensively assess the effect of acupuncture therapies for PHN, the following  
38 outcomes will be analysed in our study:  
39

- 40 1. Negative emotions, such as anxiety and depression, measured using the Hamilton Anxiety  
41 Scale, Self-Rating Anxiety Scale, Self-Rating Depression Scale, or other validated scales.  
42
- 43 2. Sleep quality measured using the Pittsburgh Sleep Quality Index or other validated scales.  
44
- 45 3. Quality of life measured using the Quality of Life scale or other validated scales.  
46
- 47 4. Adverse events occurring during the treatment period.  
48  
49

#### 50 **Data sources and search strategy**

51  
52 We will identify clinical studies by searching the following databases: MEDLINE (via  
53 PubMed), EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Database,  
54 China National Knowledge Infrastructure, VIP Database, Wanfang Database, WHO  
55 International Clinical Trials Registry Platform, ClinicalTrials.gov, and Chinese Clinical Trial  
56  
57  
58  
59  
60

Register. We will also search for grey literature in the OpenGrey database. Search dates will be from the inception of these databases to 31 December 2021 with the search languages limited to either English or Chinese. Search terms used in our review will be a combination of medical subject headings terms and free-text terms, which can be categorised into three groups: clinical condition (eg, ‘postherpetic neuralgia’, ‘zoster herpes’, ‘shingles’), interventions (eg, ‘acupuncture’, ‘moxibustion’, ‘electroacupuncture’, ‘fire needling’), and study design (eg, ‘randomised controlled trial’, ‘RCT’, ‘clinical trial’). We adjusted the search terms for each database. The search strategy for PubMed is presented in table 1. In addition, reference lists of the included studies will be examined to identify potentially eligible studies.

Table 1 Search strategy in PubMed

Order	search items
#1	MeSH Terms: “Neuralgia, Postherpetic”
#2	Title/Abstract: “postherpetic neuralgia” OR “post-herpetic neuralgia” OR “PHN” OR “herpes zoster” OR “shingles”
#3	#1 OR #2
#4	MeSH Terms: “Acupuncture Therapy” OR “Acupuncture” OR “Moxibustion” OR “Cupping Therapy” OR “Bloodletting” OR “Electroacupuncture”
#5	Title/Abstract: “acupuncture” OR “electroacupuncture” OR “moxibustion” OR “moxa” OR “cupping” OR “bloodletting” OR “blood-letting” OR “pricking blood” OR “pyonex” OR “acupressure” OR “needle” OR “needles” OR “needling” OR “acupoint” OR “acupoints” OR “meridian” OR “meridians”
#6	#4 OR #5
#7	Publication Type: “Randomized Controlled Trial”
#8	MeSH Terms: “Randomized Controlled Trials as Topic”
#9	Title/Abstract: “randomized” OR “randomly” OR “RCT” OR “trial”
#10	#7 OR #8 OR #9
#11	#3 AND #6 AND #10

### Study selection

The bibliographic information of search results in each database and additional records will

1  
2  
3  
4 be combined and imported into NoteExpress 3.2.0. After deduplication, two independent  
5 reviewers (ZYB and JY) will screen the titles and abstracts of the identified studies to remove  
6 irrelevant ones. Full texts of the remaining studies will be downloaded for further assessment  
7 according to the inclusion criteria. Reviewers will try to identify duplicate data from the same  
8 trials from different publications and contact study authors for clarification when needed.  
9 Discrepancies in study selection will be resolved by discussion, or when no consensus is  
10 reached, a third reviewer (JQF) will be consulted for arbitration. Excluded studies will be  
11 recorded for reasons of exclusion. The Preferred Reporting Items for Systematic review and  
12 Meta-Analysis (PRISMA) flowchart of the study selection process is shown in figure 1.<sup>41</sup>

### 21 **Data extraction**

22  
23 Two independent reviewers (MQT and JMH) will use a pre-designed data collection form to  
24 extract data from the included studies. The following information will be collected:  
25 publication information (publication year, first author), characteristics of the study population  
26 (sample size, age, sex, duration of PHN), details of intervention (type of acupuncture  
27 therapies, acupoint selection, needle retention time, frequency, and duration of treatment  
28 sessions), details of the comparator (drug names, dosage, frequency, treatment duration), and  
29 outcomes (data and time point of outcome measures, adverse events, and dropouts). Any  
30 disagreement will be solved through discussion or consultation with a third reviewer (JQF).

31  
32 For multi-arm studies that report different types of acupuncture interventions (or  
33 comparators), data from all relevant arms will be extracted. When comparators involve sham  
34 acupuncture methods, types of sham acupuncture and other items, similar to acupuncture  
35 interventions, will be recorded.

36  
37 Means and standard deviations (SDs) of change scores between baseline and after treatment  
38 (defined as baseline scores minus outcome scores) will be collected for each outcome. When  
39 studies fail to report data on changes from baseline and means and SDs before and after the  
40 treatment will be extracted, we will calculate the mean change in each arm and the SD of the  
41 changes.<sup>42</sup> For studies where outcomes are reported at multiple time points after the treatment,  
42 data of outcomes assessed at the first time point after the complete treatment regimen will be  
43 used.

1  
2  
3  
4 For studies where SDs of the outcome are not reported, missing SDs will be calculated from  
5 standard errors, confidence intervals (CIs), t-statistics, and P values. Additionally, in studies  
6 reporting only the median and interquartile ranges, means and SDs will be calculated using a  
7 specific formula.<sup>43</sup> If these data are not presented, we will contact the corresponding authors  
8 of original studies to obtain the missing data. After these steps, studies with insufficient data  
9 for quantitative synthesis will be excluded from the meta-analysis.  
10  
11  
12  
13  
14

### 15 **Risk of bias assessment**

16  
17 We will assess the risk of bias of included studies using the Cochrane tool RoB 2, which  
18 identifies bias in the following domains: randomisation process, deviations from intended  
19 interventions, missing outcome data, measurement of the outcome, and selection of the  
20 reported result.<sup>44</sup> Pain intensity, as the main outcome of interest, will be selected as the result  
21 to assess. The assessment will be performed in relation to the assignment to the intervention  
22 (intention-to-treat effect). Two reviewers (BJL and RHS) will independently answer the  
23 signalling questions of each domain. Subsequently, a judgement into 'low', 'some concerns'  
24 or 'high' risk of bias will be made depending on the responses to these questions, finally  
25 reaching an overall risk-of-bias judgement. Disagreements during the assessment will be  
26 resolved by discussion, and a third reviewer (JQF) will be consulted where necessary.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36

### 37 **Data synthesis**

38  
39 We will perform NMA as the primary method for data synthesis. Additionally, standard  
40 pairwise meta-analyses will be performed, and the results will be compared with those from  
41 the NMA. For each outcome, the mean difference (MD) of the change score will be  
42 considered the measure of relative treatment effects. When trials use different measurement  
43 scales for a certain outcome, the standardised MD will be calculated. We will use the odds  
44 ratio to investigate adverse event data as a measure of treatment safety.  
45  
46  
47  
48  
49

50  
51 When two or more studies comparing the same pair of interventions exist for an outcome, a  
52 standard meta-analysis will be performed. Random-effects models will be fitted using Stata  
53 15.1. The effect size will be estimated with a 95% CI. We will use the I<sup>2</sup> statistic to quantify  
54 the heterogeneity of the results in the same treatment comparisons.<sup>45</sup> If the I<sup>2</sup> value is greater  
55 than 75%, which indicates the existence of high heterogeneity, and no main source of  
56  
57  
58  
59  
60



1  
2  
3  
4 heterogeneity is found, we will provide a narrative summary without conducting data  
5 synthesis.<sup>46</sup>  
6

7 We will perform network meta-analyses to simultaneously compare multiple interventions.  
8  
9 For each outcome, network plots of all included comparisons will be generated using Stata  
10 15.1, where interventions are represented by nodes, and each line between two nodes means  
11 that a direct comparison between two interventions is available. Studies that are not connected  
12 to the network will be excluded from network meta-analyses. The sizes of the nodes and lines  
13 are proportional to the number of included studies. We will conduct NMA within a Bayesian  
14 hierarchical framework in OpenBUGS 3.2.3. Random-effects models with vague priors will  
15 be fitted, and the Markov Chain Monte Carlo (MCMC) method will be employed to obtain  
16 the pooled treatment effect, with a 95% credible interval. Three MCMC chains with different  
17 sets of initial values will be run simultaneously. For each initial value, 60,000 simulations will  
18 be conducted after discarding 10,000 simulations as the burn-in period, and convergence will  
19 be assessed visually and using the Gelman–Rubin statistic.<sup>47</sup> To assess the model fit, the  
20 posterior mean residual deviance will be calculated and compared with the number of data  
21 points in the model.<sup>48</sup> We will obtain the ranking probabilities of all included interventions  
22 using the surface under the cumulative ranking curve analysis in Stata 15.1.<sup>49</sup>  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35

36 Clinical and methodological heterogeneity will be assessed by examining the characteristics  
37 and design of the included studies. The transitivity assumption for NMA will be evaluated by  
38 reviewing the distribution of potential effect modifiers (participant characteristics: age, pain  
39 severity at baseline; interventions: treatment duration; study design: risk of bias) across  
40 comparisons. We will also assess statistical heterogeneity by calculating the between-study  
41 SD ( $\tau^2$ ), with a larger  $\tau^2$  value indicating a higher level of heterogeneity among studies. We  
42 will evaluate the global inconsistency of the treatment network by comparing the consistency  
43 model with an inconsistency model; for each closed loop, the node-splitting method will be  
44 used to assess local inconsistency.<sup>50 51</sup>  
45  
46  
47  
48  
49  
50  
51  
52  
53

#### 54 **Additional analyses**

55  
56 We will perform network meta-regression using a random-effects model to examine the  
57 influence of potential effect modifiers (eg, average age of participants, duration of PHN, pain  
58  
59  
60



1  
2  
3  
4 severity at baseline, treatment duration) on the main outcome. If sufficient studies are  
5 available, we will also perform sensitivity analysis by excluding trials rated as a high risk of  
6 bias to ensure the robustness of the primary findings. Furthermore, the presence of potential  
7 reporting bias will be inspected using a comparison-adjusted funnel plot.<sup>52</sup>  
8  
9

### 10 11 **Credibility of the evidence**

12  
13 We plan to evaluate credibility of the evidence from NMA using the Confidence in Network  
14 Meta-Analysis web application for the primary outcome.<sup>53</sup> Two reviewers (GI and YYX) will  
15 independently assess the following domains: within-study bias, across-study bias,  
16 indirectness, imprecision, heterogeneity, and incoherence. Disagreements will be solved by  
17 discussion or consultation with a third reviewer (JQF). Confidence in the results will be  
18 graded as 'high', 'moderate', 'low', and 'very low'.  
19  
20  
21  
22  
23  
24

### 25 **Patient and public involvement**

26  
27 No patients or public will be involved in this study.  
28

## 29 **DISCUSSION**

30  
31 Patients with PHN usually experience persistent pain, and many of them complain about other  
32 clinical symptoms, such as anxiety, depression, and sleep disorders, which are frequent in  
33 general neuropathic pain.<sup>54</sup> Although several recommendations have been made on  
34 pharmacological therapy, many patients with PHN do not achieve satisfactory pain relief or  
35 discontinue treatment due to adverse effects.<sup>55</sup> Acupuncture therapy is proposed as potentially  
36 beneficial in the management of neuropathic pain and is generally safe when operated by  
37 competent practitioners.<sup>56 57</sup> Moreover, acupuncture therapy may help with negative emotions  
38 and sleep disorders, which would provide additional benefits for patients in usually long-term  
39 treatment.<sup>58 59</sup> In clinical practice for PHN, diverse acupuncture methods are available, and  
40 with variations of other treatment characteristics (eg, acupoint selection, treatment duration),  
41 standardised clinical strategy of acupuncture for PHN has not been fully established. The  
42 clinical practice guidelines of acupuncture for HZ, launched by the WHO's Western Pacific  
43 Regional Office, recommended the use of fire needling, electroacupuncture, and bloodletting  
44 in the PHN phase and suggested that the combined use of two or more methods is more  
45 beneficial.<sup>60</sup> However, there is still little knowledge on the relative effectiveness of these  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 acupuncture methods and their integrated use. NMA, a technique to integrate direct and  
5 indirect comparisons across a set of multiple variables, can be used for comparing efficacies  
6 of multiple treatments simultaneously in a single analysis.<sup>61</sup> In recent years, NMA has been  
7 increasingly performed to compare the efficacies of different acupuncture methods for many  
8 diseases, such as knee osteoarthritis, myofascial pain syndrome, and chronic fatigue  
9 syndrome.<sup>62-64</sup> To the best of our knowledge, this is the first Bayesian NMA of acupuncture  
10 therapies for the treatment of PHN. We sincerely hope that our results will offer credible  
11 evidence and contribute to the proper use of acupuncture therapy for treating PHN.  
12  
13  
14  
15  
16  
17  
18

### 19 **ETHICS AND DISSEMINATION**

20  
21 This study will not collect confidential patient data, thus no ethical approval needed. The  
22 findings will be disseminated through peer-reviewed publication and conference presentation.  
23  
24  
25

26  
27 **Acknowledgements** We would like to thank Editage (www.editage.com) for English  
28 language editing.  
29

30  
31 **Author contributions** ZYB and JY conceived this study and wrote the manuscript. MQT and  
32 BJJ developed the search strategy. JMH, GI, RHS and YYX provided methodological advice.  
33 YLJ, XFH and JQF revised the manuscript. All authors have reviewed this protocol and  
34 approved the final manuscript.  
35  
36  
37

38  
39 **Funding** This study is supported by Key Plan of Zhejiang Province Traditional Chinese  
40 Medicine Prevention and Treatment of Major Disease of the Health and Family Planning  
41 Commission of Zhejiang Province (No.2018ZY008). The funders had no role on the design of  
42 this study.  
43  
44  
45

46  
47 **Competing interests** None declared  
48  
49

### 50 **REFERENCES**

- 51  
52  
53 1. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *N Engl J Med*  
54 2014;371:1526-33. doi:10.1056/NEJMcp1403062  
55  
56 2. CDC (Centers for Disease Control and Prevention). Prevention of herpes zoster:  
57 recommendations of the advisory committee on immunization practices (ACIP). CDC.  
58  
59  
60

- 2008 <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e0515a1.htm>
3. Gan EY, Tian EA, Tey HL. Management of herpes zoster and post-herpetic neuralgia. *Am J Clin Dermatol* 2013;14:77-85. doi:10.1007/s40257-013-0011-2
  4. Dworkin RH, Gnann JW Jr, Oaklander AL, *et al.* Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. *J Pain* 2008;9(1 Suppl 1):S37-44. doi:10.1016/j.jpain.2007.10.008
  5. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open* 2014;4:e004833. doi:10.1136/bmjopen-2014-004833
  6. Choo PW, Galil K, Donahue JG, *et al.* Risk factors for postherpetic neuralgia. *Arch Intern Med.* 1997;157:1217-24.
  7. Forbes HJ, Thomas SL, Smeeth L, *et al.* A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016;157:30-54. doi:10.1097/j.pain.0000000000000307
  8. Forbes HJ, Bhaskaran K, Thomas SL, *et al.* Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: A cohort study. *Neurology* 2016;87:94-102. doi:10.1212/WNL.0000000000002808
  9. Schutzer-Weissmann J, Farquhar-Smith P. Post-herpetic neuralgia - a review of current management and future directions. *Expert Opin Pharmacother* 2017;18:1739-50. doi:10.1080/14656566.2017.1392508
  10. Oster G, Harding G, Dukes E, *et al.* Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. *J Pain* 2005;6:356-63. doi:10.1016/j.jpain.2005.01.359
  11. Mauskopf J, Austin R, Dix L, *et al.* The Nottingham Health Profile as a measure of quality of life in zoster patients: convergent and discriminant validity. *Qual Life Res* 1994;3:431-5. doi:10.1007/BF00435395
  12. Weinke T, Glogger A, Bertrand I, *et al.* The societal impact of herpes zoster and postherpetic neuralgia on patients, life partners, and children of patients in Germany. *ScientificWorldJournal* 2014;2014:749698. doi:10.1155/2014/749698

- 1  
2  
3  
4 13. Dubinsky RM, Kabbani H, El-Chami Z, *et al.* Practice parameter: treatment of  
5  
6 postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee  
7  
8 of the American Academy of Neurology. *Neurology* 2004;63:959-65.  
9  
10 doi:10.1212/01.wnl.0000140708.62856.72
- 11  
12 14. Attal N, Cruccu G, Baron R, *et al.* EFNS guidelines on the pharmacological treatment of  
13  
14 neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17:1113-e88.  
15  
16 doi:10.1111/j.1468-1331.2010.02999.x
- 17  
18 15. Dworkin RH, O'Connor AB, Backonja M, *et al.* Pharmacologic management of  
19  
20 neuropathic pain: evidence-based recommendations. *Pain* 2007;132:237-51.  
21  
22 doi:10.1016/j.pain.2007.08.033
- 23  
24 16. Dworkin RH, O'Connor AB, Audette J, *et al.* Recommendations for the pharmacological  
25  
26 management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*  
27  
28 2010;85:S3-14. doi:10.4065/mcp.2009.0649
- 29  
30 17. Hadley GR, Gayle JA, Ripoll J, *et al.* Post-herpetic Neuralgia: a Review [published  
31  
32 correction appears in *Curr Pain Headache Rep* 2016 Apr;20:28]. *Curr Pain Headache*  
33  
34 *Rep* 2016;20:17. doi:10.1007/s11916-016-0548-x
- 35  
36 18. Wilhelm IR, Tzabazis A, Likar R, *et al.* Long-term treatment of neuropathic pain with a  
37  
38 5% lidocaine medicated plaster. *Eur J Anaesthesiol* 2010;27:169-73.  
39  
40 doi:10.1097/EJA.0b013e328330e989
- 41  
42 19. Bursi R, Piana C, Grevel J, *et al.* Evaluation of the Population Pharmacokinetic  
43  
44 Properties of Lidocaine and its Metabolites After Long-Term Multiple Applications of a  
45  
46 Lidocaine Plaster in Post-Herpetic Neuralgia Patients. *Eur J Drug Metab Pharmacokinet*  
47  
48 2017;42:801-14. doi:10.1007/s13318-017-0400-7
- 49  
50 20. Argoff CE. Review of current guidelines on the care of postherpetic neuralgia. *Postgrad*  
51  
52 *Med* 2011;123:134-42. doi:10.3810/pgm.2011.09.2469
- 53  
54 21. Wright ME, Rizzolo D. An update on the pharmacologic management and treatment of  
55  
56 neuropathic pain. *JAAPA* 2017;30:13-7. doi:10.1097/01.JAA.0000512228.23432.f7
- 57  
58 22. Dworkin RH, O'Connor AB, Kent J, *et al.* Interventional management of neuropathic  
59  
60 pain: NeuPSIG recommendations. *Pain* 2013;154:2249-61.

- 1  
2  
3  
4 doi:10.1016/j.pain.2013.06.004  
5  
6 23. Colloca L, Ludman T, Bouhassira D, *et al.* Neuropathic pain. *Nat Rev Dis Primers*  
7 2017;3:17002. doi:10.1038/nrdp.2017.2.  
8  
9 24. Lin CS, Lin YC, Lao HC, *et al.* Interventional Treatments for Postherpetic Neuralgia: A  
10 Systematic Review. *Pain Physician* 2019;22:209-28.  
11  
12 25. Wiesener S, Falkenberg T, Hegyi G, *et al.* Legal status and regulation of complementary  
13 and alternative medicine in Europe. *Forsch Komplementmed* 2012;19 Suppl 2:29-36.  
14 doi:10.1159/000343125  
15  
16 26. Bückner B, Groenewold M, Schoefer Y, *et al.* The use of complementary alternative  
17 medicine (CAM) in 1 001 German adults: results of a population-based telephone  
18 survey. *Gesundheitswesen* 2008;70:e29-36. doi:10.1055/s-2008-1081505  
19  
20 27. Zhang Y, Lao L, Chen H, *et al.* Acupuncture Use among American Adults: What  
21 Acupuncture Practitioners Can Learn from National Health Interview Survey 2007?.  
22 *Evid Based Complement Alternat Med* 2012;2012:710750. doi:10.1155/2012/710750  
23  
24 28. Fu LM, Li JT, Wu WS. Randomized controlled trials of acupuncture for neck pain:  
25 systematic review and meta-analysis. *J Altern Complement Med* 2009;15:133-45.  
26 doi:10.1089/acm.2008.0135  
27  
28 29. Witt C, Brinkhaus B, Jena S, *et al.* Acupuncture in patients with osteoarthritis of the  
29 knee: a randomised trial. *Lancet* 2005;366:136-43. doi:10.1016/S0140-6736(05)66871-7  
30  
31 30. Vickers AJ, Cronin AM, Maschino AC, *et al.* Acupuncture for chronic pain: individual  
32 patient data meta-analysis. *Arch Intern Med* 2012;172:1444-53.  
33 doi:10.1001/archinternmed.2012.3654  
34  
35 31. Chen LK, Arai H, Chen LY, *et al.* Looking back to move forward: a twenty-year audit of  
36 herpes zoster in Asia-Pacific. *BMC Infect Dis* 2017;17:213.  
37 doi:10.1186/s12879-017-2198-y  
38  
39 32. Deng H, Shen X. The mechanism of moxibustion: ancient theory and modern research.  
40 *Evid Based Complement Alternat Med* 2013;2013:379291. doi:10.1155/2013/379291.  
41  
42 33. Wang QY, Qu YY, Feng CW, *et al.* Analgesic mechanism of acupuncture on  
43 neuropathic pain. *Zhongguo Zhen Jiu* 2020;40:907-12.  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- doi:10.13703/j.0255-2930.20190927-k0003
- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
34. Wang Y, Li W, Peng W, *et al.* Acupuncture for postherpetic neuralgia: Systematic review and meta-analysis. *Medicine (Baltimore)* 2018;97:e11986. doi:10.1097/MD.00000000000011986
35. Pei W, Zeng J, Lu L, *et al.* Is acupuncture an effective postherpetic neuralgia treatment? A systematic review and meta-analysis. *J Pain Res* 2019;12:2155-65. doi:10.2147/JPR.S199950
36. Liu YJ, Zhang QA, Wu YY, *et al.* Meta-analysis for efficacy and safety of electroacupuncture in treating postherpetic neuralgia. *J Guangzhou Univ Tradit Chin Med* 2020;37:2472–80.
37. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med* 2017;12:103-111. doi:10.1007/s11739-016-1583-7
38. Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84. doi:10.7326/M14-2385
39. Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1. doi:10.1186/2046-4053-4-1
40. Fashner J, Bell AL. Herpes zoster and postherpetic neuralgia: prevention and management. *Am Fam Physician* 2011;83:1432-1437.
41. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097. doi:10.1371/journal.pmed.1000097
42. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, *et al.* *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1. Cochrane, 2020. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).
43. Wan X, Wang W, Liu J, *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*

- 2014;14:135. doi:10.1186/1471-2288-14-135
44. Sterne JAC, Savović J, Page MJ, *et al.* Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi:10.1136/bmj.l4898
45. Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60. doi:10.1136/bmj.327.7414.557
46. Melsen WG, Bootsma MC, Rovers MM, *et al.* The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect* 2014;20:123-129. doi:10.1111/1469-0691.12494
47. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Statist Sci* 1992;7:457-72. doi: 10.1214/ss/1177011136
48. Dias S, Ades A, Welton N, *et al.* *Network meta-analysis for decision-making*. Chichester, UK: John Wiley & Sons, Ltd 2018.
49. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015;15:58. doi:10.1186/s12874-015-0060-8
50. Dias S, Welton NJ, Sutton AJ, *et al.* Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013;33:641-56. doi:10.1177/0272989X12455847
51. Dias S, Welton NJ, Caldwell DM, *et al.* Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932-44. doi:10.1002/sim.3767
52. Chaimani A, Higgins JP, Mavridis D, *et al.* Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;8:e76654. doi:10.1371/journal.pone.0076654
53. Salanti G, Del Giovane C, Chaimani A, *et al.* Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9:e99682. doi:10.1371/journal.pone.0099682
54. Colloca L, Ludman T, Bouhassira D, *et al.* Neuropathic pain. *Nat Rev Dis Primers* 2017;3:17002. doi:10.1038/nrdp.2017.2
55. Dworkin RH, Panarites CJ, Armstrong EP, *et al.* Is treatment of postherpetic neuralgia in the community consistent with evidence-based recommendations?. *Pain* 2012;153:869-875. doi:10.1016/j.pain.2012.01.015



- 1  
2  
3  
4 56. Macone A, Otis JAD. Neuropathic Pain. *Semin Neurol* 2018;38:644-653.  
5 doi:10.1055/s-0038-1673679  
6  
7  
8 57. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med*  
9 2002;136:374-383. doi:10.7326/0003-4819-136-5-200203050-00010  
10  
11 58. Goyata SL, Avelino CC, Santos SV, *et al.* Effects from acupuncture in treating anxiety:  
12 integrative review. *Rev Bras Enferm* 2016; 69:602-9.  
13 doi:10.1590/0034-7167.2016690325i  
14  
15  
16  
17 59. Shergis JL, Ni X, Jackson ML, *et al.* A systematic review of acupuncture for sleep  
18 quality in people with insomnia. *Complement Ther Med* 2016;26:11-20.  
19 doi:10.1016/j.ctim.2016.02.007  
20  
21  
22  
23 60. Liu ZS, Peng WN, Liu BY, *et al.* Clinical practice guideline of acupuncture for herpes  
24 zoster. *Chin J Integr Med* 2013;19:58-67. doi:10.1007/s11655-013-1191-y  
25  
26  
27 61. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments:  
28 combining direct and indirect evidence. *BMJ* 2005;331(7521):897-900.  
29 doi:10.1136/bmj.331.7521.897  
30  
31  
32  
33 62. Corbett MS, Rice SJ, Madurasinghe V, *et al.* Acupuncture and other physical treatments  
34 for the relief of pain due to osteoarthritis of the knee: network meta-analysis.  
35 *Osteoarthritis Cartilage* 2013;21:1290-1298. doi:10.1016/j.joca.2013.05.007  
36  
37  
38  
39 63. Li X, Wang R, Xing X, *et al.* Acupuncture for Myofascial Pain Syndrome: A Network  
40 Meta-Analysis of 33 Randomized Controlled Trials. *Pain Physician* 2017;20:E883-902.  
41  
42  
43 64. Wang T, Xu C, Pan K, *et al.* Acupuncture and moxibustion for chronic fatigue syndrome  
44 in traditional Chinese medicine: a systematic review and meta-analysis. *BMC*  
45 *Complement Altern Med* 2017;17:163. doi:10.1186/s12906-017-1647-x  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure legend

Figure 1 PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis.

For peer review only

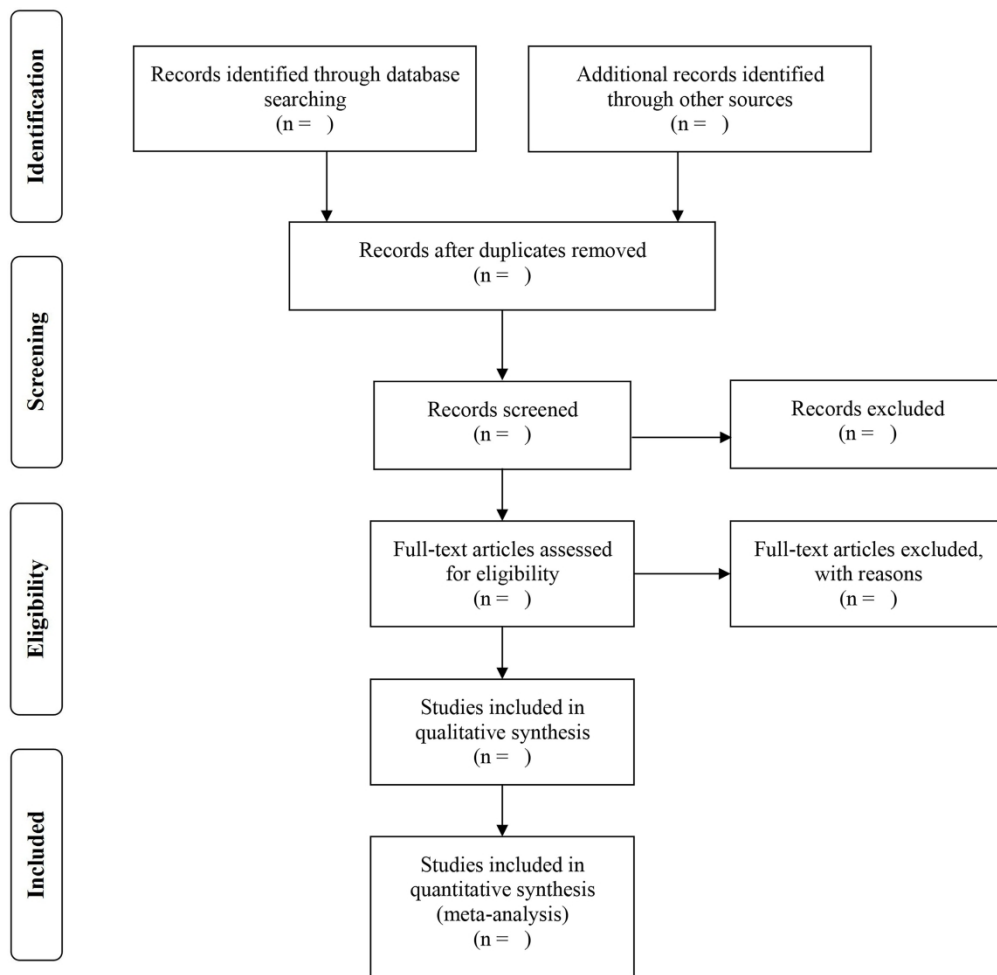


Figure 1 PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis.

279x271mm (300 x 300 DPI)

# Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preorting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	NA
<b>Registration</b>			
	<a href="#">#2</a>	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
<b>Authors</b>			
Contact	<a href="#">#3a</a>	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	<a href="#">#3b</a>	Describe contributions of protocol authors and identify the	13

guarantor of the review

## Amendments

<a href="#">#4</a>	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
--------------------	---	----

## Support

Sources	<a href="#">#5a</a>	Indicate sources of financial or other support for the review	13
Sponsor	<a href="#">#5b</a>	Provide name for the review funder and / or sponsor	13
Role of sponsor or funder	<a href="#">#5c</a>	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	13

## Introduction

Rationale	<a href="#">#6</a>	Describe the rationale for the review in the context of what is already known	4-5
Objectives	<a href="#">#7</a>	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6

## Methods

Eligibility criteria	<a href="#">#8</a>	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	<a href="#">#9</a>	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	<a href="#">#10</a>	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8
Study records - data management	<a href="#">#11a</a>	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Study records -	<a href="#">#11b</a>	State the process that will be used for selecting studies (such	8-9

1	selection process		as two independent reviewers) through each phase of the	
2			review (that is, screening, eligibility and inclusion in meta-	
3			analysis)	
4				
5	Study records -	<a href="#">#11c</a>	Describe planned method of extracting data from reports	9
6	data collection		(such as piloting forms, done independently, in duplicate),	
7	process		any processes for obtaining and confirming data from	
8			investigators	
9				
10				
11				
12	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	9-10
13			(such as PICO items, funding sources), any pre-planned data	
14			assumptions and simplifications	
15				
16				
17	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	9-10
18	prioritization		including prioritization of main and additional outcomes, with	
19			rationale	
20				
21				
22				
23	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	10
24	individual studies		individual studies, including whether this will be done at the	
25			outcome or study level, or both; state how this information will	
26			be used in data synthesis	
27				
28				
29				
30	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively	10-11
31			synthesised	
32				
33	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	10-11
34			planned summary measures, methods of handling data and	
35			methods of combining data from studies, including any	
36			planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
37				
38				
39				
40	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	11-12
41			sensitivity or subgroup analyses, meta-regression)	
42				
43				
44	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type	10-11
45			of summary planned	
46				
47				
48	Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as	12
49			publication bias across studies, selective reporting within	
50			studies)	
51				
52				
53	Confidence in	<a href="#">#17</a>	Describe how the strength of the body of evidence will be	12
54	cumulative		assessed (such as GRADE)	
55	evidence			
56				
57				
58				
59				
60				

1 The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative  
2 Commons Attribution License CC-BY. This checklist was completed on 19. August 2021 using  
3 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with  
4 [Penelope.ai](#)  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

# BMJ Open

## Acupuncture therapies for postherpetic neuralgia: a protocol for a systematic review and Bayesian network meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056632.R2
Article Type:	Protocol
Date Submitted by the Author:	01-Feb-2022
Complete List of Authors:	<p>Bian, Zhiyuan; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Yu, Jie; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province; Affiliated Hangzhou First People's Hospital Zhejiang University School of Medicine, Department of Acupuncture and Massage</p> <p>Tu, Mingqi; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Liao, Binjun; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Huang, Jingmei; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Izumoji, Genki; Zhejiang Chinese Medical University, International Education College</p> <p>Sun, Ruohan; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Xu, Yunyun; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Jiang, Yongliang; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>He, Xiaofen; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p> <p>Fang, Jian-Qiao; Zhejiang Chinese Medical University Third Clinical College, Department of Neurobiology and Acupuncture Research, Key Laboratory of Acupuncture and Neurology of Zhejiang Province</p>
<b>Primary Subject Heading</b>:	Complementary medicine
Secondary Subject Heading:	Neurology

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Keywords:	COMPLEMENTARY MEDICINE, Neurological pain < NEUROLOGY, PAIN MANAGEMENT

SCHOLARONE™  
Manuscripts



# Acupuncture therapies for postherpetic neuralgia : a protocol for a systematic review and Bayesian network meta-analysis

Zhiyuan Bian,<sup>1</sup> # Jie Yu,<sup>2</sup> # Mingqi Tu,<sup>1</sup> Binjun Liao,<sup>1</sup> Jingmei Huang,<sup>1</sup> Genki Izumoji,<sup>3</sup> Ruohan Sun,<sup>1</sup> Yunyun Xu,<sup>1</sup> Yongliang Jiang,<sup>1</sup> Xiaofen He,<sup>1</sup> Jianqiao Fang<sup>1</sup> \*

<sup>1</sup> Department of Neurobiology and Acupuncture Research, The Third Clinical Medical College, Zhejiang Chinese Medical University, Key Laboratory of Acupuncture and Neurology of Zhejiang Province, Hangzhou, China

<sup>2</sup> Department of Acupuncture and Massage, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine. Hangzhou, China

<sup>3</sup> International Education College, Zhejiang Chinese Medical University, Hangzhou, China

#These authors contributed equally to this work.

\*Corresponding author

Jianqiao Fang, Department of Neurobiology and Acupuncture Research, The Third Clinical Medical College, Zhejiang Chinese Medical University, Key Laboratory of Acupuncture and Neurology of Zhejiang Province, NO.548 Binwen Road, Hangzhou, 310053, China

E-mail: [fangjianqiao7532@163.com](mailto:fangjianqiao7532@163.com)

ORCID IDs: Zhiyuan Bian 0000-0002-4420-9047; Jie Yu 0000-0002-9225-1901; Mingqi Tu 0000-0002-6048-8111; Jianqiao Fang 0000-0003-4499-0352

Word count: 3205

## ABSTRACT

**Introduction** Postherpetic neuralgia (PHN) is the most common sequela of herpes zoster, and it is often refractory to guideline-recommended treatments. Acupuncture therapy, a widely applied complementary-alternative treatment, may help in the management of PHN. Diverse types of acupuncture therapy for PHN have been proposed, however, their comparative efficacies remain unclear. This study protocol plans to compare the efficacy and safety of different acupuncture therapies for PHN.

**Methods and analysis** Databases including MEDLINE, EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Database, China National Knowledge Infrastructure, VIP Database, Wanfang Database, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, Chinese Clinical Trial Register and OpenGrey will be searched from their inception to January 2022. Randomised controlled trials (RCTs) assessing the effectiveness of acupuncture therapy on the management of PHN will be selected. The primary outcome is pain intensity. Secondary outcomes include negative emotions, sleep condition, quality of life and adverse events. Reviewers will conduct study selection, data extraction and risk of bias assessment procedures. Then, standard pair-wised meta-analysis and Bayesian network meta-analysis will be performed (if applicable). The Confidence in Network Meta-Analysis application will be used to assess the confidence in the evidence for the primary outcome.

**Ethics and dissemination** All data used for this study will be extracted from published RCTs, thus, no ethical approval will be required. The results of this systematic review will be disseminated through peer-reviewed journal and conference presentation.

**PROSPERO registration number** CRD42020219576

**Keywords:** acupuncture therapy, postherpetic neuralgia, systematic review, network meta-analysis

### Strengths and limitations of this study

- ▶ This study will be the first Bayesian network meta-analysis comparing various acupuncture therapies in the management of postherpetic neuralgia (PHN).
- ▶ Our study will comprehensively evaluate the effects of acupuncture therapy on pain intensity, emotional symptoms, sleep quality, and life quality for patients with PHN.
- ▶ Our study will focus on the methods of acupuncture treatment, without consideration of acupoints selection or specific details of manual techniques.
- ▶ We will only search Chinese and English databases, which may result in language bias.

## INTRODUCTION

Postherpetic neuralgia (PHN) is defined as a neuropathic pain that occurs after an eruptive phase of herpes zoster (HZ), as its most common clinical sequela.<sup>1</sup> Definitions of PHN are not consistent across studies, with its occurrence ranging from  $\geq 1$  to  $\geq 6$  months after the rash.<sup>2</sup> Compared with acute HZ-associated pain (pain preceding or accompanying the visible cutaneous manifestation), which resolves within a month, PHN may persist for months, even years.<sup>3-4</sup> A systematic review showed that the incidence rate of HZ ranged from 3 to 5/1000 person-years globally, with 5% to more than 30% of patients with HZ progressing to PHN.<sup>5</sup> Several risk factors for PHN are commonly reported, including advanced age, female sex, severe immunosuppression, severe rash, and pain in acute zoster episode. Physical comorbidities, such as autoimmune conditions and diabetes, may also be associated with an increased risk of PHN.<sup>6-8</sup> Patients with PHN prominently complain about continuous or intermittent spontaneous pain (eg, aching pain, burning pain, stabbing, shooting) and may co-present with hyperalgesia, allodynia, and other abnormal sensations (eg, anaesthesia, vibration).<sup>9</sup> In addition, persistent pain can lead to negative emotions, sleep disorders, and lowered quality of life of patients and their families, which causes a heavy burden of health care at both the individual and societal levels.<sup>10-12</sup>

Several systemic and topical treatments are listed in the guidelines for the management of PHN (either exclusive for PHN or specific mention to PHN in neuropathic pain context).<sup>13-16</sup> Antiepileptic drugs gabapentin and pregabalin, tricyclic antidepressants (TCAs), and topical lidocaine are recommended as first-line treatments. PHN often requires long-term treatment; thus, side effect profiles of antiepileptic drugs and TCAs may become dangerous, especially for elderly patients who are dealing with other age-related issues.<sup>17</sup> Lidocaine patch may only cause mild skin reaction and is well tolerated and safe even in long-term treatment.<sup>18-19</sup> Opioids and tramadol are recommended as second-line or third-line options in latest guidelines, with uncertain long-term efficacy and safety.<sup>1</sup> Topical use of capsaicin is listed as second-line or third-line therapy, and either capsaicin 0.075% cream or capsaicin 8% patch can be selected. However, its use may be limited by localised pain during the application.<sup>20</sup> In general, given the refractory nature of neuropathic pain, conventional medications only

1  
2  
3  
4 provide modest effect on pain relief for PHN.<sup>21</sup> Interventional therapy, either involving  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

provide modest effect on pain relief for PHN.<sup>21</sup> Interventional therapy, either involving  
invasive delivery of drugs or ablation/modulation of related nerves, is proposed in the  
management of neuropathic pain and often considered after failure of standard  
pharmacological treatments.<sup>22</sup> However, evidence of interventional treatments specific for  
patients with PHN is generally insufficient, and invasive procedures are often associated with  
safety concerns.<sup>23 24</sup>

Acupuncture therapy, based on stimulation to acupoints (specific locations on the body), not  
only is favourable in Asia-Pacific but also gains increasing popularity in Europe and  
America.<sup>25-27</sup> It is one of the major components of traditional Chinese medicine (TCM), which  
has been used in the management of various pain conditions, including PHN, as a  
complementary alternative treatment.<sup>28-31</sup> With a substantial number of clinical trials  
conducted in China, diverse acupuncture approaches have been reported either singly or in  
combination when treating PHN, such as manual acupuncture, moxibustion,  
electroacupuncture, firing needling, and bloodletting.<sup>31</sup> These methods most likely have  
different effects on pain reduction, given their distinct mechanisms in both TCM theory and  
neurophysiological processes.<sup>32 33</sup> In recent years, systematic reviews and meta-analyses have  
shown a potential positive effect of acupuncture therapy for patients with PHN on pain relief  
with few reported adverse events.<sup>34-36</sup> However, these studies either combined all relative  
methods as acupuncture therapy when conducting data syntheses or evaluated the effect of  
only a single type of acupuncture therapy. Thus, their results may not be sufficient to reflect  
the distinct effects of diverse acupuncture methods. With the majority of existing studies  
focusing on the comparison between acupuncture therapy and conventional pharmacological  
treatment, the relative treatment effects of different acupuncture therapies for PHN are poorly  
understood, which may cause confusion for clinical practitioners. To this end, it is necessary  
to further explore the relative effectiveness of different acupuncture therapies for PHN.

Network meta-analysis (NMA), as an extension of standard pairwise meta-analysis, compares  
multiple interventions simultaneously, which can be used to obtain the potential optimal  
option among different treatments.<sup>37</sup> Therefore, we plan to perform NMA to evaluate the  
effectiveness and safety of different acupuncture therapies (and their combinations) for PHN.

## Objective

The overall purpose of this study is to assess the effectiveness and safety of different acupuncture therapies in the treatment of PHN based on existing clinical trials. Using a systematic review and NMA methods, we will primarily focus on the efficacy of acupuncture therapies for pain relief when treating PHN. We will also compare their effect on negative emotions, sleep condition, and quality of life and evaluate treatment safety to provide a comprehensive view for clinical practice.

## METHODS

We will perform a systematic review and NMA guided by the Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.<sup>38</sup> This study protocol will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.<sup>39</sup> The protocol has been registered on PROSPERO (registration number CRD42020219576).

### Eligibility criteria

#### Types of studies

This review will only include randomised controlled trials (RCTs) reported in English or Chinese with a parallel-group design. Cross-over trials, quasi-RCTs, cluster RCTs, or any other types of non-RCTs will be excluded.

#### Types of participants

Participants will include patients who meet the diagnostic criteria of PHN according to the definition by the American Academy of Family Physicians,<sup>40</sup> which is pain persisting from 30 days to more than 6 months after the HZ lesions have healed, or any other accepted diagnostic guidelines. There will be no restrictions on age, sex, or nationality of the participants.

#### Types of interventions

In this review, we define acupuncture therapy as an acupoint-stimulated technique guided by the TCM theory. Therefore, we will include any of the following treatments: manual acupuncture, electroacupuncture, warm needling, fire needling, pressing needling, transcutaneous electrical acupoint stimulation, moxibustion, bloodletting, cupping, acupoint catgut embedding, acupoint injection, or a combination of any two or three of these methods.

1  
2  
3  
4 Therapies related to acupoints defined in a non-traditional way, such as auricular acupuncture  
5 and wrist-ankle acupuncture, will be excluded.  
6

#### 7 8 Types of control groups

9  
10 Studies using either conventional medication or placebo in the control groups and studies  
11 comparing different types of acupuncture therapies will be included. However, studies  
12 comparing different acupoint prescriptions or different manual needling techniques with the  
13 same type of acupuncture method will be excluded. We will also exclude studies using sham  
14 acupuncture in the control groups, as sham acupuncture is widely considered not inert, which  
15 may cause confusion when compare with various types of acupuncture therapies.<sup>41</sup>  
16  
17  
18  
19

#### 20 21 Types of outcome measurements

##### 22 23 *Primary outcome(s)*

24  
25 Our primary aim is to evaluate pain control efficacy. According to preliminary searches of  
26 relevant articles, measurements of pain intensity have been reported in most cases. Other  
27 profiles of pain control, such as onset of pain relief time, are not frequently reported.<sup>35</sup>  
28  
29 Therefore, we will select pain intensity as the main outcome of interest. Pain intensity is  
30 usually presented by a score on a range between no pain to maximum pain, with higher  
31 number indicating more severe pain, using the Visual Analogue Scale, Numerical Rating  
32 Scale, Verbal Rating Scale, Average Daily Pain Score, or other validated scales.  
33  
34  
35  
36  
37

##### 38 39 *Secondary outcome(s)*

40  
41 To comprehensively assess the effect of acupuncture therapies for PHN, the following  
42 outcomes will be analysed in our study:  
43

- 44 1. Negative emotions, such as anxiety and depression, measured using the Hamilton Anxiety  
45 Scale, Self-Rating Anxiety Scale, Self-Rating Depression Scale, or other validated scales.  
46
- 47 2. Sleep quality measured using the Pittsburgh Sleep Quality Index or other validated scales.  
48
- 49 3. Quality of life measured using the Quality of Life scale or other validated scales.  
50
- 51 4. Adverse events occurring during the treatment period.  
52

#### 53 54 **Data sources and search strategy**

55  
56 We will identify clinical studies by searching the following databases: MEDLINE (via  
57 PubMed), EMBASE, Cochrane Library, Web of Science, Chinese Biomedical Database,  
58  
59  
60

China National Knowledge Infrastructure, VIP Database, Wanfang Database, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, and Chinese Clinical Trial Register. We will also search for grey literature in the OpenGrey database. Search dates will be from the inception of these databases to 31 January 2022 with the search languages limited to either English or Chinese. Search terms used in our review will be a combination of medical subject headings terms and free-text terms, which can be categorised into three groups: clinical condition (eg, ‘postherpetic neuralgia’, ‘zoster herpes’, ‘shingles’), interventions (eg, ‘acupuncture’, ‘moxibustion’, ‘electroacupuncture’, ‘fire needling’), and study design (eg, ‘randomised controlled trial’, ‘RCT’, ‘clinical trial’). We adjusted the search terms for each database. The search strategy for PubMed is presented in table 1. In addition, reference lists of the included studies will be examined to identify potentially eligible studies.

Table 1 Search strategy in PubMed

Order	search items
#1	MeSH Terms: “Neuralgia, Postherpetic”
#2	Title/Abstract: “postherpetic neuralgia” OR “post-herpetic neuralgia” OR “PHN” OR “herpes zoster” OR “shingles”
#3	#1 OR #2
#4	MeSH Terms: “Acupuncture Therapy” OR “Acupuncture” OR “Cupping Therapy” OR “Bloodletting”
#5	Title/Abstract: “acupuncture” OR “electroacupuncture” OR “moxibustion” OR “moxa” OR “cupping” OR “bloodletting” OR “blood-letting” OR “pricking blood” OR “pyonex” OR “acupressure” OR “needle” OR “needles” OR “needling” OR “acupoint” OR “acupoints” OR “meridian” OR “meridians”
#6	#4 OR #5
#7	Publication Type: “Randomized Controlled Trial”
#8	MeSH Terms: “Randomized Controlled Trials as Topic”
#9	Title/Abstract: “randomized” OR “randomly” OR “RCT” OR “trial”
#10	#7 OR #8 OR #9
#11	#3 AND #6 AND #10



## Study selection

The bibliographic information of search results in each database and additional records will be combined and imported into NoteExpress 3.2.0. After deduplication, two independent reviewers (ZYB and JY) will screen the titles and abstracts of the identified studies to remove irrelevant ones. Full texts of the remaining studies will be downloaded for further assessment according to the inclusion criteria. Reviewers will try to identify duplicate data from the same trials from different publications and contact study authors for clarification when needed. Discrepancies in study selection will be resolved by discussion, or when no consensus is reached, a third reviewer (JQF) will be consulted for arbitration. Excluded studies will be recorded for reasons of exclusion. The Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flowchart of the study selection process is shown in figure 1.<sup>42</sup>

## Data extraction

Two independent reviewers (MQT and JMH) will use a pre-designed data collection form to extract data from the included studies. The following information will be collected: publication information (publication year, first author), characteristics of the study population (sample size, age, sex, duration of PHN), details of intervention (type of acupuncture therapies, acupoint selection, needle retention time, frequency, and duration of treatment sessions), details of the comparator (drug names, dosage, frequency, treatment duration), and outcomes (data and time point of outcome measures, adverse events, and dropouts). Any disagreement will be solved through discussion or consultation with a third reviewer (JQF).

For multi-arm studies that report different types of acupuncture interventions (or comparators), data from all relevant arms will be extracted. When comparators involve sham acupuncture methods, types of sham acupuncture and other items, similar to acupuncture interventions, will be recorded.

Means and standard deviations (SDs) of change scores between baseline and after treatment (defined as baseline scores minus outcome scores) will be collected for each outcome. When studies fail to report data on changes from baseline and means and SDs before and after the treatment will be extracted, we will calculate the mean change in each arm and the SD of the changes.<sup>43</sup> For studies where outcomes are reported at multiple time points after the treatment,

1  
2  
3  
4 data of outcomes assessed at the first time point after the complete treatment regimen will be  
5 used.

6  
7 For studies where SDs of the outcome are not reported, missing SDs will be calculated from  
8 standard errors, confidence intervals (CIs), t-statistics, and P values. Additionally, in studies  
9 reporting only the median and interquartile ranges, means and SDs will be calculated using a  
10 specific formula.<sup>44</sup> If these data are not presented, we will contact the corresponding authors  
11 of original studies to obtain the missing data. After these steps, studies with insufficient data  
12 for quantitative synthesis will be excluded from the meta-analysis.  
13  
14  
15  
16  
17  
18

### 19 **Risk of bias assessment**

20  
21 We will assess the risk of bias of included studies using the Cochrane tool RoB 2, which  
22 identifies bias in the following domains: randomisation process, deviations from intended  
23 interventions, missing outcome data, measurement of the outcome, and selection of the  
24 reported result.<sup>45</sup> Pain intensity, as the main outcome of interest, will be selected as the result  
25 to assess. The assessment will be performed in relation to the assignment to the intervention  
26 (intention-to-treat effect). Two reviewers (BJL and RHS) will independently answer the  
27 signalling questions of each domain. Subsequently, a judgement into 'low', 'some concerns'  
28 or 'high' risk of bias will be made depending on the responses to these questions, finally  
29 reaching an overall risk-of-bias judgement. Disagreements during the assessment will be  
30 resolved by discussion, and a third reviewer (JQF) will be consulted where necessary.  
31  
32  
33  
34  
35  
36  
37  
38  
39

### 40 **Data synthesis**

41  
42 We will perform NMA as the primary method for data synthesis. Additionally, standard  
43 pairwise meta-analyses will be performed, and the results will be compared with those from  
44 the NMA. For each outcome, the mean difference (MD) of the change score will be  
45 considered the measure of relative treatment effects. When trials use different measurement  
46 scales for a certain outcome, the standardised MD will be calculated. We will use the odds  
47 ratio to investigate adverse event data as a measure of treatment safety.  
48  
49  
50  
51  
52  
53

54 When two or more studies comparing the same pair of interventions exist for an outcome, a  
55 standard meta-analysis will be performed. Random-effects models will be fitted using Stata  
56 15.1. The effect size will be estimated with a 95% CI. We will use the I<sup>2</sup> statistic to quantify  
57  
58  
59  
60

1  
2  
3  
4 the heterogeneity of the results in the same treatment comparisons.<sup>46</sup> If the  $I^2$  value is greater  
5 than 75%, which indicates the existence of high heterogeneity, and no main source of  
6 heterogeneity is found, we will provide a narrative summary without conducting data  
7 synthesis.<sup>47</sup>  
8  
9

10  
11 We will perform network meta-analyses to simultaneously compare multiple interventions.  
12 For each outcome, network plots of all included comparisons will be generated using Stata  
13 15.1, where interventions are represented by nodes, and each line between two nodes means  
14 that a direct comparison between two interventions is available. Studies that are not connected  
15 to the network will be excluded from network meta-analyses. The sizes of the nodes and lines  
16 are proportional to the number of included studies. We will conduct NMA within a Bayesian  
17 hierarchical framework in OpenBUGS 3.2.3. Random-effects models with vague priors will  
18 be fitted, and the Markov Chain Monte Carlo (MCMC) method will be employed to obtain  
19 the pooled treatment effect, with a 95% credible interval. Three MCMC chains with different  
20 sets of initial values will be run simultaneously. For each initial value, 60,000 simulations will  
21 be conducted after discarding 10,000 simulations as the burn-in period, and convergence will  
22 be assessed visually and using the Gelman–Rubin statistic.<sup>48</sup> To assess the model fit, the  
23 posterior mean residual deviance will be calculated and compared with the number of data  
24 points in the model.<sup>49</sup> We will obtain the ranking probabilities of all included interventions  
25 using the surface under the cumulative ranking curve analysis in Stata 15.1.<sup>50</sup>  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39

40 Clinical and methodological heterogeneity will be assessed by examining the characteristics  
41 and design of the included studies. The transitivity assumption for NMA will be evaluated by  
42 reviewing the distribution of potential effect modifiers (participant characteristics: age, pain  
43 severity at baseline; interventions: treatment duration; study design: risk of bias) across  
44 comparisons. We will also assess statistical heterogeneity by calculating the between-study  
45 SD ( $\tau^2$ ), with a larger  $\tau^2$  value indicating a higher level of heterogeneity among studies. We  
46 will evaluate the global inconsistency of the treatment network by comparing the consistency  
47 model with an inconsistency model; for each closed loop, the node-splitting method will be  
48 used to assess local inconsistency.<sup>51 52</sup>  
49  
50  
51  
52  
53  
54  
55  
56  
57

### 58 **Additional analyses**

59  
60

We will perform network meta-regression using a random-effects model to examine the influence of potential effect modifiers (eg, average age of participants, duration of PHN, pain severity at baseline) on the main outcome. As dose of acupuncture treatment is an important factor that can influence treatment efficacy, a subgroup analysis involving different dosage of the acupuncture therapies on the main outcome will be performed. The concept of adequate acupuncture dose has been introduced in several systematic reviews.<sup>53 54</sup> Accordingly, we will define a 'high dosage' of acupuncture treatment when both the following criteria are met: (1) the treatment frequency is  $\geq 2$  sessions a week, and (2) the total number of treatment sessions is  $\geq 12$ .<sup>55</sup> When only one of (1) or (2) is met, the treatment will be defined as 'medium dosage', and when neither of them are met, the treatment will be defined as 'low dosage'. If sufficient studies are available, we will also perform sensitivity analysis by excluding trials rated as a high risk of bias to ensure the robustness of the primary findings. Furthermore, the presence of potential reporting bias will be inspected using a comparison-adjusted funnel plot.<sup>56</sup>

### **Credibility of the evidence**

We plan to evaluate credibility of the evidence from NMA using the Confidence in Network Meta-Analysis web application for the primary outcome.<sup>57</sup> Two reviewers (GI and YYX) will independently assess the following domains: within-study bias, across-study bias, indirectness, imprecision, heterogeneity, and incoherence. Disagreements will be solved by discussion or consultation with a third reviewer (JQF). Confidence in the results will be graded as 'high', 'moderate', 'low', and 'very low'.

### **Patient and public involvement**

No patients or public will be involved in this study.

### **DISCUSSION**

Patients with PHN usually experience persistent pain, and many of them complain about other clinical symptoms, such as anxiety, depression, and sleep disorders, which are frequent in general neuropathic pain.<sup>58</sup> Although several recommendations have been made on pharmacological therapy, many patients with PHN do not achieve satisfactory pain relief or discontinue treatment due to adverse effects.<sup>59</sup> Acupuncture therapy is proposed as potentially

1  
2  
3  
4 beneficial in the management of neuropathic pain and is generally safe when operated by  
5 competent practitioners.<sup>60 61</sup> Moreover, acupuncture therapy may help with negative emotions  
6 and sleep disorders, which would provide additional benefits for patients in usually long-term  
7 treatment.<sup>62 63</sup>

8  
9  
10  
11 In clinical practice for PHN, diverse acupuncture methods are available, and in many trials,  
12 the integrated use of two or more acupuncture methods have been reported. The existing  
13 systematic reviews are generally focusing on comparing a single type of acupuncture therapy  
14 with pharmacologic therapy, while the effects of integrated use of different acupuncture  
15 methods are poorly investigated. The clinical practice guidelines of acupuncture for HZ,  
16 launched by the WHO's Western Pacific Regional Office, recommended the use of fire  
17 needling, electroacupuncture, and bloodletting in the PHN phase and suggested that the  
18 combined use of two or more methods is more beneficial.<sup>64</sup> However, there is still little  
19 knowledge on the relative effectiveness of these acupuncture methods and their integrated  
20 use, which causes confusion for the selection of these methods. NMA, a technique to integrate  
21 direct and indirect comparisons across a set of multiple variables, can be used for comparing  
22 efficacies of multiple treatments simultaneously in a single analysis.<sup>65</sup> Our NMA will clearly  
23 define the types of included acupuncture therapy and their integrated use, to comprehensively  
24 evaluate their effects in the management of PHN. In recent years, NMA has been increasingly  
25 performed to compare the efficacies of different acupuncture methods for many diseases, such  
26 as knee osteoarthritis, myofascial pain syndrome, and chronic fatigue syndrome.<sup>66-68</sup> To the  
27 best of our knowledge, this study will be the first Bayesian NMA of acupuncture therapies for  
28 the treatment of PHN. We sincerely hope that our results will offer credible evidence and  
29 contribute to the proper use of acupuncture therapy for treating PHN.

#### 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 **ETHICS AND DISSEMINATION**

49 This study will not collect confidential patient data, thus no ethical approval needed. The  
50 findings will be disseminated through peer-reviewed publication and conference presentation.  
51  
52  
53  
54

55  
56 **Acknowledgements** We would like to thank Editage ([www.editage.com](http://www.editage.com)) for English  
57 language editing.  
58  
59  
60

**Author contributions** ZYB and JY conceived this study and wrote the manuscript. MQT and BJL developed the search strategy. JMH, GI, RHS and YYX provided methodological advice. YLJ, XFH and JQF revised the manuscript. All authors have reviewed this protocol and approved the final manuscript.

**Funding** This study is supported by Key Plan of Zhejiang Province Traditional Chinese Medicine Prevention and Treatment of Major Disease of the Health and Family Planning Commission of Zhejiang Province (No.2018ZY008). The funders had no role on the design of this study.

**Competing interests** None declared

## REFERENCES

1. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *N Engl J Med* 2014;371:1526-33. doi:10.1056/NEJMcp1403062
2. CDC (Centers for Disease Control and Prevention). Prevention of herpes zoster: recommendations of the advisory committee on immunization practices (ACIP). CDC. 2008 <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr57e0515a1.htm>
3. Gan EY, Tian EA, Tey HL. Management of herpes zoster and post-herpetic neuralgia. *Am J Clin Dermatol* 2013;14:77-85. doi:10.1007/s40257-013-0011-2
4. Dworkin RH, Gnann JW Jr, Oaklander AL, *et al.* Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. *J Pain* 2008;9(1 Suppl 1):S37-44. doi:10.1016/j.jpain.2007.10.008
5. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open* 2014;4:e004833. doi:10.1136/bmjopen-2014-004833
6. Choo PW, Galil K, Donahue JG, *et al.* Risk factors for postherpetic neuralgia. *Arch Intern Med.* 1997;157:1217-24.
7. Forbes HJ, Thomas SL, Smeeth L, *et al.* A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016;157:30-54. doi:10.1097/j.pain.0000000000000307

- 1  
2  
3  
4 8. Forbes HJ, Bhaskaran K, Thomas SL, *et al.* Quantification of risk factors for postherpetic  
5  
6 neuralgia in herpes zoster patients: A cohort study. *Neurology* 2016;87:94-102.  
7  
8 doi:10.1212/WNL.0000000000002808
- 9  
10 9. Schutzer-Weissmann J, Farquhar-Smith P. Post-herpetic neuralgia - a review of current  
11  
12 management and future directions. *Expert Opin Pharmacother* 2017;18:1739-50.  
13  
14 doi:10.1080/14656566.2017.1392508
- 15  
16 10. Oster G, Harding G, Dukes E, *et al.* Pain, medication use, and health-related quality of  
17  
18 life in older persons with postherpetic neuralgia: results from a population-based survey.  
19  
20 *J Pain* 2005;6:356-63. doi:10.1016/j.jpain.2005.01.359
- 21  
22 11. Mauskopf J, Austin R, Dix L, *et al.* The Nottingham Health Profile as a measure of  
23  
24 quality of life in zoster patients: convergent and discriminant validity. *Qual Life Res*  
25  
26 1994;3:431-5. doi:10.1007/BF00435395
- 27  
28 12. Weinke T, Glogger A, Bertrand I, *et al.* The societal impact of herpes zoster and  
29  
30 postherpetic neuralgia on patients, life partners, and children of patients in Germany.  
31  
32 *ScientificWorldJournal* 2014;2014:749698. doi:10.1155/2014/749698
- 33  
34 13. Dubinsky RM, Kabbani H, El-Chami Z, *et al.* Practice parameter: treatment of  
35  
36 postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee  
37  
38 of the American Academy of Neurology. *Neurology* 2004;63:959-65.  
39  
40 doi:10.1212/01.wnl.0000140708.62856.72
- 41  
42 14. Attal N, Cruccu G, Baron R, *et al.* EFNS guidelines on the pharmacological treatment of  
43  
44 neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17:1113-e88.  
45  
46 doi:10.1111/j.1468-1331.2010.02999.x
- 47  
48 15. Dworkin RH, O'Connor AB, Backonja M, *et al.* Pharmacologic management of  
49  
50 neuropathic pain: evidence-based recommendations. *Pain* 2007;132:237-51.  
51  
52 doi:10.1016/j.pain.2007.08.033
- 53  
54 16. Dworkin RH, O'Connor AB, Audette J, *et al.* Recommendations for the pharmacological  
55  
56 management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*  
57  
58 2010;85:S3-14. doi:10.4065/mcp.2009.0649
- 59  
60 17. Hadley GR, Gayle JA, Ripoll J, *et al.* Post-herpetic Neuralgia: a Review [published



- 1  
2  
3  
4 correction appears in *Curr Pain Headache Rep* 2016 Apr;20:28]. *Curr Pain Headache*  
5  
6 *Rep* 2016;20:17. doi:10.1007/s11916-016-0548-x
- 7  
8 18. Wilhelm IR, Tzabazis A, Likar R, *et al.* Long-term treatment of neuropathic pain with a  
9  
10 5% lidocaine medicated plaster. *Eur J Anaesthesiol* 2010;27:169-73.  
11  
12 doi:10.1097/EJA.0b013e328330e989
- 13  
14 19. Bursi R, Piana C, Grevel J, *et al.* Evaluation of the Population Pharmacokinetic  
15  
16 Properties of Lidocaine and its Metabolites After Long-Term Multiple Applications of a  
17  
18 Lidocaine Plaster in Post-Herpetic Neuralgia Patients. *Eur J Drug Metab Pharmacokinet*  
19  
20 2017;42:801-14. doi:10.1007/s13318-017-0400-7
- 21  
22 20. Argoff CE. Review of current guidelines on the care of postherpetic neuralgia. *Postgrad*  
23  
24 *Med* 2011;123:134-42. doi:10.3810/pgm.2011.09.2469
- 25  
26 21. Wright ME, Rizzolo D. An update on the pharmacologic management and treatment of  
27  
28 neuropathic pain. *JAAPA* 2017;30:13-7. doi:10.1097/01.JAA.0000512228.23432.f7
- 29  
30 22. Dworkin RH, O'Connor AB, Kent J, *et al.* Interventional management of neuropathic  
31  
32 pain: NeuPSIG recommendations. *Pain* 2013;154:2249-61.  
33  
34 doi:10.1016/j.pain.2013.06.004
- 35  
36 23. Colloca L, Ludman T, Bouhassira D, *et al.* Neuropathic pain. *Nat Rev Dis Primers*  
37  
38 2017;3:17002. doi:10.1038/nrdp.2017.2.
- 39  
40 24. Lin CS, Lin YC, Lao HC, *et al.* Interventional Treatments for Postherpetic Neuralgia: A  
41  
42 Systematic Review. *Pain Physician* 2019;22:209-28.
- 43  
44 25. Wiesener S, Falkenberg T, Hegyi G, *et al.* Legal status and regulation of complementary  
45  
46 and alternative medicine in Europe. *Forsch Komplementmed* 2012;19 Suppl 2:29-36.  
47  
48 doi:10.1159/000343125
- 49  
50 26. Bucker B, Groenewold M, Schoefer Y, *et al.* The use of complementary alternative  
51  
52 medicine (CAM) in 1 001 German adults: results of a population-based telephone  
53  
54 survey. *Gesundheitswesen* 2008;70:e29-36. doi:10.1055/s-2008-1081505
- 55  
56 27. Zhang Y, Lao L, Chen H, *et al.* Acupuncture Use among American Adults: What  
57  
58 Acupuncture Practitioners Can Learn from National Health Interview Survey 2007?.  
59  
60 *Evid Based Complement Alternat Med* 2012;2012:710750. doi:10.1155/2012/710750



- 1  
2  
3  
4 28. Fu LM, Li JT, Wu WS. Randomized controlled trials of acupuncture for neck pain:  
5 systematic review and meta-analysis. *J Altern Complement Med* 2009;15:133-45.  
6 doi:10.1089/acm.2008.0135  
7  
8  
9  
10 29. Witt C, Brinkhaus B, Jena S, *et al.* Acupuncture in patients with osteoarthritis of the  
11 knee: a randomised trial. *Lancet* 2005;366:136-43. doi:10.1016/S0140-6736(05)66871-7  
12  
13 30. Vickers AJ, Cronin AM, Maschino AC, *et al.* Acupuncture for chronic pain: individual  
14 patient data meta-analysis. *Arch Intern Med* 2012;172:1444-53.  
15 doi:10.1001/archinternmed.2012.3654  
16  
17  
18 31. Chen LK, Arai H, Chen LY, *et al.* Looking back to move forward: a twenty-year audit of  
19 herpes zoster in Asia-Pacific. *BMC Infect Dis* 2017;17:213.  
20 doi:10.1186/s12879-017-2198-y  
21  
22  
23 32. Deng H, Shen X. The mechanism of moxibustion: ancient theory and modern research.  
24 *Evid Based Complement Alternat Med* 2013;2013:379291. doi:10.1155/2013/379291.  
25  
26  
27 33. Wang QY, Qu YY, Feng CW, *et al.* Analgesic mechanism of acupuncture on  
28 neuropathic pain. *Zhongguo Zhen Jiu* 2020;40:907-12.  
29 doi:10.13703/j.0255-2930.20190927-k0003  
30  
31  
32 34. Wang Y, Li W, Peng W, *et al.* Acupuncture for postherpetic neuralgia: Systematic  
33 review and meta-analysis. *Medicine (Baltimore)* 2018;97:e11986.  
34 doi:10.1097/MD.00000000000011986  
35  
36  
37 35. Pei W, Zeng J, Lu L, *et al.* Is acupuncture an effective postherpetic neuralgia treatment?  
38 A systematic review and meta-analysis. *J Pain Res* 2019;12:2155-65.  
39 doi:10.2147/JPR.S199950  
40  
41  
42 36. Liu YJ, Zhang QA, Wu YY, *et al.* Meta-analysis for efficacy and safety of  
43 electroacupuncture in treating postherpetic neuralgia. *J Guangzhou Univ Tradit Chin*  
44 *Med* 2020;37:2472-80.  
45  
46  
47 37. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern*  
48 *Emerg Med* 2017;12:103-111. doi:10.1007/s11739-016-1583-7  
49  
50  
51 38. Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting  
52 of systematic reviews incorporating network meta-analyses of health care interventions:  
53  
54  
55  
56  
57  
58  
59  
60

- checklist and explanations. *Ann Intern Med* 2015;162:777-84. doi:10.7326/M14-2385
39. Moher D, Shamseer L, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1. doi:10.1186/2046-4053-4-1
40. Fashner J, Bell AL. Herpes zoster and postherpetic neuralgia: prevention and management. *Am Fam Physician* 2011;83:1432-1437.
41. Lund I, Lundeberg T. Are minimal, superficial or sham acupuncture procedures acceptable as inert placebo controls? *Acupunct Med* 2006;24:13-5. doi:10.1136/aim.24.1.13.
42. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097. doi:10.1371/journal.pmed.1000097
43. Higgins JPT, Li T, Deeks JJ. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, *et al.* *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1. Cochrane, 2020. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).
44. Wan X, Wang W, Liu J, *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. doi:10.1186/1471-2288-14-135
45. Sterne JAC, Savović J, Page MJ, *et al.* Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi:10.1136/bmj.l4898
46. Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60. doi:10.1136/bmj.327.7414.557
47. Melsen WG, Bootsma MC, Rovers MM, *et al.* The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect* 2014;20:123-129. doi:10.1111/1469-0691.12494
48. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Statist Sci* 1992;7:457-72. doi:10.1214/ss/1177011136
49. Dias S, Ades A, Welton N, *et al.* *Network meta-analysis for decision-making*. Chichester,

- 1  
2  
3  
4 UK: John Wiley & Sons, Ltd 2018.
- 5  
6 50. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works  
7 without resampling methods. *BMC Med Res Methodol* 2015;15:58.  
8 doi:10.1186/s12874-015-0060-8  
9
- 10  
11 51. Dias S, Welton NJ, Sutton AJ, *et al.* Evidence synthesis for decision making 4:  
12 inconsistency in networks of evidence based on randomized controlled trials. *Med Decis*  
13 *Making* 2013;33:641-56. doi:10.1177/0272989X12455847  
14  
15  
16  
17 52. Dias S, Welton NJ, Caldwell DM, *et al.* Checking consistency in mixed treatment  
18 comparison meta-analysis. *Stat Med* 2010;29:932-44. doi:10.1002/sim.3767  
19  
20  
21 53. Sun N, Tu JF, Lin LL, *et al.* Correlation between acupuncture dose and effectiveness in  
22 the treatment of knee osteoarthritis: a systematic review. *Acupunct Med* 2019;37:261-7.  
23 doi: 10.1136/acupmed-2017-011608.  
24  
25  
26  
27 54. Giovanardi CM, Cinquini M, Aguggia M, *et al.* Acupuncture vs. Pharmacological  
28 Prophylaxis of Migraine: A Systematic Review of Randomized Controlled Trials. *Front*  
29 *Neurol* 2020;11:576272. doi: 10.3389/fneur.2020.576272.  
30  
31  
32  
33 55. Bauer M, McDonald JL, Saunders N. Is acupuncture dose dependent? Ramifications of  
34 acupuncture treatment dose within clinical practice and trials. *Integr Med Res*  
35 2020;9:21-7. doi: 10.1016/j.imr.2020.01.003.  
36  
37  
38  
39 56. Chaimani A, Higgins JP, Mavridis D, *et al.* Graphical tools for network meta-analysis in  
40 STATA. *PLoS One* 2013;8:e76654. doi:10.1371/journal.pone.0076654  
41  
42  
43 57. Salanti G, Del Giovane C, Chaimani A, *et al.* Evaluating the quality of evidence from a  
44 network meta-analysis. *PLoS One* 2014;9:e99682. doi:10.1371/journal.pone.0099682  
45  
46  
47 58. Colloca L, Ludman T, Bouhassira D, *et al.* Neuropathic pain. *Nat Rev Dis Primers*  
48 2017;3:17002. doi:10.1038/nrdp.2017.2  
49  
50  
51 59. Dworkin RH, Panarites CJ, Armstrong EP, *et al.* Is treatment of postherpetic neuralgia in  
52 the community consistent with evidence-based recommendations?. *Pain*  
53 2012;153:869-875. doi:10.1016/j.pain.2012.01.015  
54  
55  
56 60. Macone A, Otis JAD. Neuropathic Pain. *Semin Neurol* 2018;38:644-653.  
57 doi:10.1055/s-0038-1673679  
58  
59  
60

- 1  
2  
3  
4 61. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med*  
5 2002;136:374-383. doi:10.7326/0003-4819-136-5-200203050-00010  
6  
7  
8 62. Goyata SL, Avelino CC, Santos SV, *et al.* Effects from acupuncture in treating anxiety:  
9 integrative review. *Rev Bras Enferm* 2016; 69:602-9.  
10 doi:10.1590/0034-7167.2016690325i  
11  
12  
13 63. Shergis JL, Ni X, Jackson ML, *et al.* A systematic review of acupuncture for sleep  
14 quality in people with insomnia. *Complement Ther Med* 2016;26:11-20.  
15 doi:10.1016/j.ctim.2016.02.007  
16  
17  
18 64. Liu ZS, Peng WN, Liu BY, *et al.* Clinical practice guideline of acupuncture for herpes  
19 zoster. *Chin J Integr Med* 2013;19:58-67. doi:10.1007/s11655-013-1191-y  
20  
21  
22  
23 65. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments:  
24 combining direct and indirect evidence. *BMJ* 2005;331(7521):897-900.  
25 doi:10.1136/bmj.331.7521.897  
26  
27  
28 66. Corbett MS, Rice SJ, Madurasinghe V, *et al.* Acupuncture and other physical treatments  
29 for the relief of pain due to osteoarthritis of the knee: network meta-analysis.  
30 *Osteoarthritis Cartilage* 2013;21:1290-1298. doi:10.1016/j.joca.2013.05.007  
31  
32  
33 67. Li X, Wang R, Xing X, *et al.* Acupuncture for Myofascial Pain Syndrome: A Network  
34 Meta-Analysis of 33 Randomized Controlled Trials. *Pain Physician* 2017;20:E883-902.  
35  
36  
37  
38 68. Wang T, Xu C, Pan K, *et al.* Acupuncture and moxibustion for chronic fatigue syndrome  
39 in traditional Chinese medicine: a systematic review and meta-analysis. *BMC*  
40 *Complement Altern Med* 2017;17:163. doi:10.1186/s12906-017-1647-x  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 Figure legend

5  
6 Figure 1 PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting  
7  
8 Items for Systematic review and Meta-Analysis.  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

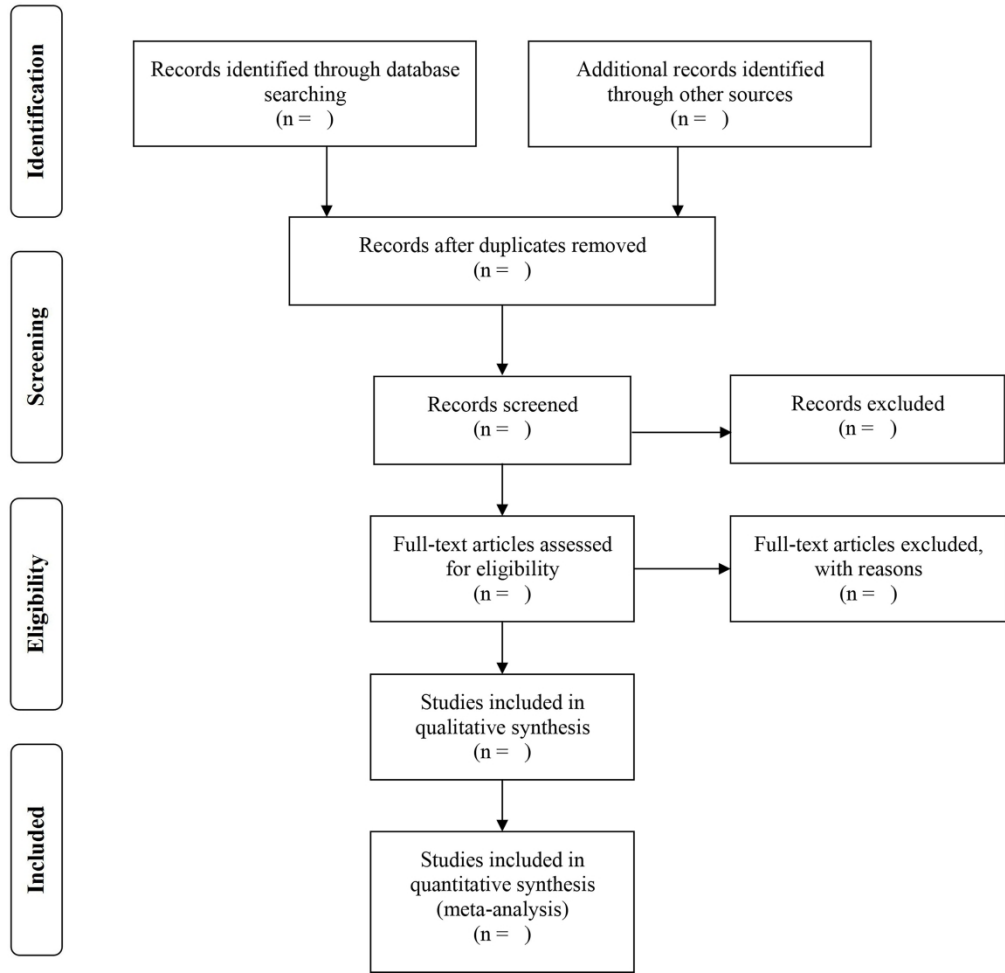


Figure 1 PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis.

279x271mm (300 x 300 DPI)

# Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preorting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	NA
<b>Registration</b>			
	<a href="#">#2</a>	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
<b>Authors</b>			
Contact	<a href="#">#3a</a>	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	<a href="#">#3b</a>	Describe contributions of protocol authors and identify the	14

guarantor of the review

## Amendments

<a href="#">#4</a>	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
--------------------	---	----

## Support

Sources	<a href="#">#5a</a>	Indicate sources of financial or other support for the review	14
Sponsor	<a href="#">#5b</a>	Provide name for the review funder and / or sponsor	14
Role of sponsor or funder	<a href="#">#5c</a>	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	14

## Introduction

Rationale	<a href="#">#6</a>	Describe the rationale for the review in the context of what is already known	4-5
Objectives	<a href="#">#7</a>	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6

## Methods

Eligibility criteria	<a href="#">#8</a>	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	<a href="#">#9</a>	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	<a href="#">#10</a>	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8
Study records - data management	<a href="#">#11a</a>	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records -	<a href="#">#11b</a>	State the process that will be used for selecting studies (such	9



1	selection process		as two independent reviewers) through each phase of the	
2			review (that is, screening, eligibility and inclusion in meta-	
3			analysis)	
4				
5	Study records -	<a href="#">#11c</a>	Describe planned method of extracting data from reports	9
6	data collection		(such as piloting forms, done independently, in duplicate),	
7	process		any processes for obtaining and confirming data from	
8			investigators	
9				
10				
11				
12	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	9-10
13			(such as PICO items, funding sources), any pre-planned data	
14			assumptions and simplifications	
15				
16				
17	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	9-10
18	prioritization		including prioritization of main and additional outcomes, with	
19			rationale	
20				
21				
22				
23	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	10
24	individual studies		individual studies, including whether this will be done at the	
25			outcome or study level, or both; state how this information will	
26			be used in data synthesis	
27				
28				
29				
30	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively	10-11
31			synthesised	
32				
33	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	10-11
34			planned summary measures, methods of handling data and	
35			methods of combining data from studies, including any	
36			planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
37				
38				
39				
40	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	11-12
41			sensitivity or subgroup analyses, meta-regression)	
42				
43				
44	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type	11
45			of summary planned	
46				
47				
48	Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as	12
49			publication bias across studies, selective reporting within	
50			studies)	
51				
52				
53	Confidence in	<a href="#">#17</a>	Describe how the strength of the body of evidence will be	12
54	cumulative		assessed (such as GRADE)	
55	evidence			
56				
57				
58				
59				
60				

1 The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative  
2 Commons Attribution License CC-BY. This checklist was completed on 19. August 2021 using  
3 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with  
4 [Penelope.ai](#)  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60