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

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ABSTRACT

Introduction Postherpetic neuralgia (PHN) is the most common sequela of herpes zoster, and often refractory to guideline-recommended treatments. Acupuncture therapy, a wildly 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.[1] Definitions of PHN are not consistent across studies, ranging from ≥1 to ≥6 months after the rash.[2] 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.[3 4] 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.[5] 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.[6-8] 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). [9] 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.[10-12]

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).[13-16] 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.[17] Lidocaine patch may only cause mild skin reaction, and is considered well tolerated and safe even in long-term treatment.[18 19] Opioids and tramadol are recommended as second-line or third-line options in latest guidelines, with uncertain long-term efficacy and safety.[1] 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.[20] In general, given the refractory nature of neuropathic pain, conventional medications only provide modest effect on pain relief for PHN.[21] 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 pharmacologic treatments.[22] However, evidence of interventional treatments specific for PHN patients is generally insufficient, and invasive procedures are often associated with safety concerns.[23 24]

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.[25-27] 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.[28–31] 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.[31] These methods most likely have different effects on pain reduction, given the distinct mechanisms they involved with in both TCM theory and neurophysiological processes.[32 33]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.[34-36] 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.[37] 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

acupuncture therapies in the treatment of PHN based on existing clinical trials. By using the systematic review and NMA methods, we will primarily focus on the efficacy of acupuncture therapies on pain relief when treating PHN. We will also compare their effect on negative emotions, sleep condition as well as life quality 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.[38] This study protocol will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.[39] 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,[40] which is pain persist from 30 days to more than six months after the HZ lesions have healed, or any other accepted diagnostic guidelines. There will be no restrictions on age, sex or nationality of participants.

Types of interventions

In this review, we define acupuncture therapy as acupoint-stimulated techniques guided by TCM theory. Therefore, we will include any of the following treatments: manual acupuncture, electro-acupuncture, 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. Therapies related to acupoint defined in a non-traditional way such as auricular acupuncture and wrist-ankle acupuncture will be excluded.

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 primarily 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.[35] 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

searching languages limited to either English or Chinese. Search terms used in our review will be a combination of medical subject headings terms (MeSH) and free-text terms, which can be categorised into three groups: clinical condition (eg, "postherpetic neuralgia", "zoster herpes", "shingles", etc.), interventions (eg, "acupuncture", "moxibustion", "electroacupuncture", "fire needling", etc.), study design (eg, "randomised controlled trial", "RCT", "clinal trial", etc.). We will adjust search terms for each database. The search strategy for PubMed is shown in the appendix 1. In addition, reference lists of included studies will be examined to identify potential eligible studies.

Study selection

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 titles and abstracts of identified studies to remove irrelevant ones. Full texts of remaining studies will be downloaded for further assessment according to the inclusion criteria. Reviewers will try to identify duplicate data of same trials from different publications, and contact study authors for clarification when needed. Discrepancies on study selection will be resolved by discussion, or when no consensus reached, a third reviewer (JQF) will be consulted for arbitration. Excluded studies will be recorded with reasons of exclusion. The process of selection will be shown in a PRISMA flow chart.

Data extraction

Two independent reviewers (MQT and JMH) will use a pre-designed data collection form to extract data from 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, acupoints selection, needle retention time, frequency and duration of treatment sessions), details of comparator (drug names, dosage, frequency, treatment duration), outcomes (data and time point of outcome measures, adverse events and dropouts). Any disagreement will be solved through discussion or consulting a third reviewer (JQF).

For multi-arm studies where report different types 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 same as in 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 change from baseline, means and SDs at before and after the treatment will be extracted, then we will calculate the mean change in each arm and the SD of the changes.[41] For studies where outcomes are reported in multiple time points after the treatment, data of outcomes assessed at the first time point after the complete treatment regimen will be used.

For studies where SDs of the outcome are not reported, missing SDs will be calculated from standard errors (SEs), confidence intervals (CIs), t statistics and P values. Additionally, in studies only reporting median and interquartile ranges (IQR), means and SDs will be calculated by using specific formula.[42] If these data are not presented, we will contact the corresponding authors of original studies to obtain the missing data. After these steps, studies with insufficient data to conduct quantitative synthesis will be excluded for meta-analysis.

Risk of bias assessment

We will assess the risk of bias of included studies using the Cochrane tool RoB 2, which identifies bias in following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[43] Pain intensity, as the main outcome of interest, will be selected as the result to assess. The assessment will be done in relation to the assignment to the intervention (intention-to-treat effect). Two reviewers (BJL and RHS) will independently answer the signalling questions of each domain. Then, a judgement into "low", "some concerns" or "high" risk of bias will be made depending on the responses to these questions and finally reaching an overall risk-of-bias judgement. Disagreements during the assessment will be resolved by discussion, and a third reviewer (JQF) will be consult where necessary.

Data synthesis

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

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

When two or more studies comparing the same pair of interventions exist for an outcome, the standard meta-analysis will be performed. Random-effects models will be fitted in Stata 15.1. The effect size will be estimated with 95% confidence interval (CI). We will use I^2 statistic to quantify heterogeneity of the results in same treatment comparisons.[44] If the I^2 value is greater than 75% which indicates the existing of high heterogeneity, and meanwhile no main source o1f heterogeneity is found, we will provide a narrative summary without conducting data synthesis.[45]

We will perform network meta-analyses to compare multiple interventions simultaneously. For each outcome, network plots of all included comparisons will be generated using Stata 15.1, interventions will be represented by nodes, and each line between two nodes means that direct comparison between two interventions is available. Studies that are not connected to the network will be exclude from network meta-analyses. Sizes of the nodes and lines are proportional to the number of included studies. We will conduct the NMA within a Bayesian hierarchical framework in OpenBUGS 3.2.3. Random effects models with vague priors will be fitted and Markov Chain Monte Carlo (MCMC) method will be employed to obtain the pooled treatment effect with 95% credible interval (CrI). Three MCMC chains with different sets of initial values will be run simultaneously. For each initial values, a total of 60,000 times of simulation will be conducted after 10,000 times of simulation being discarded as the burn-in period, and convergence will be checked visually as well as assessed by the Gelman-Rubin statistic. [46] To assess the model fit, the posterior mean residual deviance will be calculated and compared with the number of data points in the model.[47] We will obtain the ranking probabilities of all included interventions using the surface under the cumulative ranking curve (SUCRA) analysis in Stata V.15.1.[48]

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

reviewing the distribution of potential effect modifiers (participant characteristics: age, pain severity at baseline; interventions: treatment duration; study design: risk of bias) across comparisons. We will also assess statistical heterogeneity by calculating between-study standard deviation (τ^2), with larger τ^2 value indicates higher level of heterogeneity among studies. We will evaluate global inconsistency of treatment network by comparing the consistency model with an inconsistency model, and for each closed loop, node-splitting method will be used to assess local inconsistency. [49 50]

Additional analyses

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, treatment duration) on the main outcome. If sufficient studies are available, we will also perform sensitivity analysis by excluding trials rated as high risk of bias to ensure robustness of primary findings. Furthermore, the presence of potential reporting bias will be inspected by using comparison-adjusted funnel plot.[51]

Credibility of the evidence

We plan to evaluate credibility of the evidence from NMA using the Confidence in Network Meta-Analysis (CINeMA) web application for the primary outcome.[52] 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 discuss or consulting to 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 undergo persistent pain, and many of them complain about other clinical symptoms such as anxiety, depression and sleep disorder, which are frequent in general neuropathic pain condition.[53] Although plenty of recommendations has been made on pharmacologic therapy, it is widely considered that many PHN patients do not achieve satisfactory pain relief or discontinue treatment due to adverse effects.[54] Acupuncture therapy

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

ETHICS AND DISSEMINATION

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

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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.

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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. Bücker 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.0000000000011986
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

Systematic Reviews of Interventions version 6.1. Cochrane, 2020. Available from www.training.cochrane.org/handbook.

42. 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
43. 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
44. 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
45. 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
46. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Statist Sci* 1992;7:457-72. doi: 10.1214/ss/1177011136.
47. Dias S, Ades A, Welton N, *et al*. *Network meta-analysis for decision-making*. Chichester, UK: John Wiley & Sons, Ltd 2018.
48. 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
49. 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
50. 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
51. 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
52. 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
53. Colloca L, Ludman T, Bouhassira D, *et al*. Neuropathic pain. *Nat Rev Dis Primers*

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. Macone 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-Preporting 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
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	NA

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	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	#5a	Indicate sources of financial or other support for the review	12-13
Sponsor	#5b	Provide name for the review funder and / or sponsor	12-13
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	13
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	4-5

		already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5-6
Methods			
Eligibility criteria	#8	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	#9	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	#10	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	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	8-9

process		processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	9-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	11

		studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

BMJ Open

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

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

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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 wildly 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.[1] Definitions of PHN are not consistent across studies, with its occurrence ranging from ≥1 to ≥6 months after the rash.[2] 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.[3 4] 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.[5] 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.[6-8] 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).[9] 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.[10-12]

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).[13-16] 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.[17] Lidocaine patch may only cause mild skin reaction and is well tolerated and safe even in long-term treatment.[18 19] Opioids and tramadol are recommended as second-line or third-line options in latest guidelines, with uncertain long-term efficacy and safety.[1] 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.[20] In general, given the refractory nature of neuropathic pain, conventional medications only

provide modest effect on pain relief for PHN.[21] 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.[22] However, evidence of interventional treatments specific for patients with PHN is generally insufficient, and invasive procedures are often associated with safety concerns.[23 24]

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.[25-27] 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.[28–31] 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.[31] These methods most likely have different effects on pain reduction, given their distinct mechanisms in both TCM theory and neurophysiological processes.[32 33] 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.[34-36] 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.[37] 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.[38] This study protocol will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.[39] 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,[40] 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.

Therapies related to acupoints defined in a non-traditional way, such as auricular acupuncture and wrist-ankle acupuncture, will be excluded.

Types of control groups

Studies using either conventional medication or placebo in the control groups and studies comparing different types of acupuncture therapies will be included. However, studies comparing different acupoint 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 pain control efficacy. According to preliminary searches of relevant articles, measurements of pain intensity have been reported in most cases. Other profiles of pain control, such as onset of pain relief time, are not frequently reported.[35] Therefore, we will select pain intensity as the main outcome of interest. Pain intensity is usually presented by a score on a range between no pain to maximum pain, with higher number indicating more severe pain, using the Visual Analogue Scale, Numerical Rating Scale, Verbal Rating Scale, Average Daily Pain Score, or other validated scales.

Secondary outcome(s)

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

1. Negative emotions, such as anxiety and depression, measured using the Hamilton Anxiety Scale, Self-Rating Anxiety Scale, Self-Rating Depression Scale, or other validated scales.

2. Sleep quality measured using the Pittsburgh Sleep Quality Index or other validated scales.

3. Quality of life measured using the Quality of Life scale or other validated scales.

4. Adverse events occurring 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, 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 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

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.[41]

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.[42] For studies where outcomes are reported at multiple time points after the treatment, data of outcomes assessed at the first time point after the complete treatment regimen will be used.

For studies where SDs of the outcome are not reported, missing SDs will be calculated from standard errors, confidence intervals (CIs), t-statistics, and P values. Additionally, in studies reporting only the median and interquartile ranges, means and SDs will be calculated using a specific formula.[43] If these data are not presented, we will contact the corresponding authors of original studies to obtain the missing data. After these steps, studies with insufficient data for quantitative synthesis will be excluded from the meta-analysis.

Risk of bias assessment

We will assess the risk of bias of included studies using the Cochrane tool RoB 2, which identifies bias in the following domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[44] Pain intensity, as the main outcome of interest, will be selected as the result to assess. The assessment will be performed in relation to the assignment to the intervention (intention-to-treat effect). Two reviewers (BJL and RHS) will independently answer the signalling questions of each domain. Subsequently, a judgement into 'low', 'some concerns' or 'high' risk of bias will be made depending on the responses to these questions, finally reaching an overall risk-of-bias judgement. Disagreements during the assessment will be resolved by discussion, and a third reviewer (JQF) will be consulted where necessary.

Data synthesis

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

When two or more studies comparing the same pair of interventions exist for an outcome, a standard meta-analysis will be performed. Random-effects models will be fitted using Stata 15.1. The effect size will be estimated with a 95% CI. We will use the I^2 statistic to quantify the heterogeneity of the results in the same treatment comparisons.[45] If the I^2 value is greater than 75%, which indicates the existence of high heterogeneity, and no main source of

heterogeneity is found, we will provide a narrative summary without conducting data synthesis.[46]

We will perform network meta-analyses to simultaneously compare multiple interventions. For each outcome, network plots of all included comparisons will be generated using Stata 15.1, where interventions are represented by nodes, and each line between two nodes means that a direct comparison between two interventions is available. Studies that are not connected to the network will be excluded from network meta-analyses. The sizes of the nodes and lines are proportional to the number of included studies. We will conduct NMA within a Bayesian hierarchical framework in OpenBUGS 3.2.3. Random-effects models with vague priors will be fitted, and the Markov Chain Monte Carlo (MCMC) method will be employed to obtain the pooled treatment effect, with a 95% credible interval. Three MCMC chains with different sets of initial values will be run simultaneously. For each initial value, 60,000 simulations will be conducted after discarding 10,000 simulations as the burn-in period, and convergence will be assessed visually and using the Gelman–Rubin statistic.[47] To assess the model fit, the posterior mean residual deviance will be calculated and compared with the number of data points in the model.[48] We will obtain the ranking probabilities of all included interventions using the surface under the cumulative ranking curve analysis in Stata 15.1.[49]

Clinical and methodological heterogeneity will be assessed by examining the characteristics and design of the included studies. The transitivity assumption for NMA will be evaluated by reviewing the distribution of potential effect modifiers (participant characteristics: age, pain severity at baseline; interventions: treatment duration; study design: risk of bias) across comparisons. We will also assess statistical heterogeneity by calculating the between-study SD (τ^2), with a larger τ^2 value indicating a higher level of heterogeneity among studies. We will evaluate the global inconsistency of the treatment network by comparing the consistency model with an inconsistency model; for each closed loop, the node-splitting method will be used to assess local inconsistency. [50 51]

Additional analyses

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, treatment duration) on the main outcome. 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.[52]

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.[53] 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.[54] 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.[55] Acupuncture therapy is proposed as potentially beneficial in the management of neuropathic pain and is generally safe when operated by competent practitioners.[56 57] Moreover, acupuncture therapy may help with negative emotions and sleep disorders, which would provide additional benefits for patients in usually long-term treatment.[58 59] In clinical practice for PHN, diverse acupuncture methods are available, and with variations of other treatment characteristics (eg, acupoint selection, treatment duration), standardised clinical strategy of acupuncture for PHN has not been fully established. The clinical practice guidelines of acupuncture for HZ, launched by the WHO's Western Pacific Regional Office, recommended the use of fire needling, electroacupuncture, and bloodletting in the PHN phase and suggested that the combined use of two or more methods is more beneficial.[60] However, there is still little knowledge on the relative effectiveness of these

acupuncture methods and their integrated use. NMA, a technique to integrate direct and indirect comparisons across a set of multiple variables, can be used for comparing efficacies of multiple treatments simultaneously in a single analysis.[61] In recent years, NMA has been increasingly performed to compare the efficacies of different acupuncture methods for many diseases, such as knee osteoarthritis, myofascial pain syndrome, and chronic fatigue syndrome.[62-64] To the best of our knowledge, this is the first Bayesian NMA of acupuncture therapies for the treatment of PHN. We sincerely hope that our results will offer credible evidence and contribute to the proper use of acupuncture therapy for treating PHN.

ETHICS AND DISSEMINATION

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

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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.

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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. Bücker 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.0000000000011986
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.
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

56. Macone A, Otis JAD. Neuropathic Pain. *Semin Neurol* 2018;38:644-653. doi:10.1055/s-0038-1673679

57. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med* 2002;136:374-383. doi:10.7326/0003-4819-136-5-200203050-00010

58. 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

59. 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

60. 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

61. 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

62. 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

63. 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.

64. 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

Figure legend

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

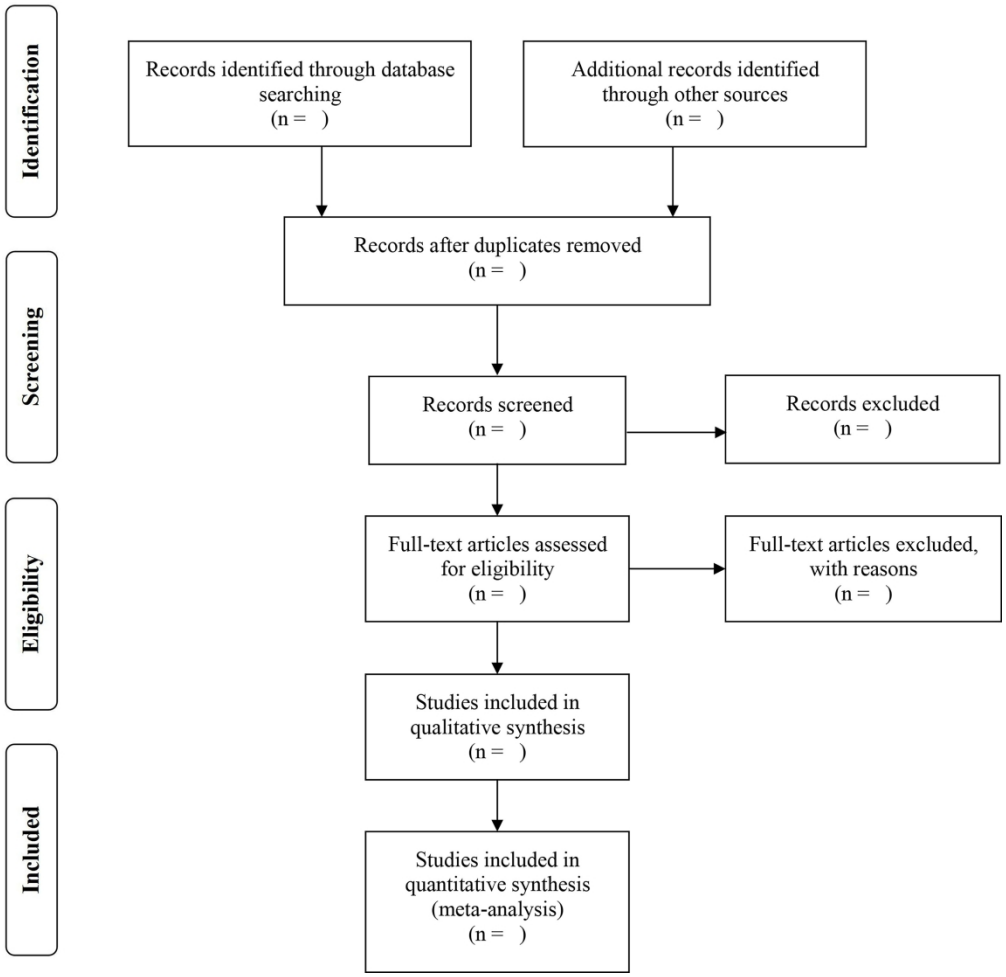

Figure 1 PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis.

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

		guarantor of the review	
Amendments			
	#4	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	#5a	Indicate sources of financial or other support for the review	13
Sponsor	#5b	Provide name for the review funder and / or sponsor	13
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	13
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	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	#8	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	#9	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	#10	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	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Study records -	#11b	State the process that will be used for selecting studies (such	8-9

selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9-10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11-12
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

BMJ Open

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

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Primary Subject Heading:	Complementary medicine
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Keywords:	COMPLEMENTARY MEDICINE, Neurological pain < NEUROLOGY, PAIN MANAGEMENT

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

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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 wildly 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.[1] Definitions of PHN are not consistent across studies, with its occurrence ranging from ≥1 to ≥6 months after the rash.[2] 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.[3 4] 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.[5] 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.[6-8] 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).[9] 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.[10-12]

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).[13-16] 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.[17] Lidocaine patch may only cause mild skin reaction and is well tolerated and safe even in long-term treatment.[18 19] Opioids and tramadol are recommended as second-line or third-line options in latest guidelines, with uncertain long-term efficacy and safety.[1] 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.[20] In general, given the refractory nature of neuropathic pain, conventional medications only

provide modest effect on pain relief for PHN.[21] 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.[22] However, evidence of interventional treatments specific for patients with PHN is generally insufficient, and invasive procedures are often associated with safety concerns.[23 24]

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.[25-27] 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.[28–31] 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.[31] These methods most likely have different effects on pain reduction, given their distinct mechanisms in both TCM theory and neurophysiological processes.[32 33] 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.[34-36] 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.[37] 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.[38] This study protocol will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.[39] 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,[40] 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.

Therapies related to acupoints defined in a non-traditional way, such as auricular acupuncture and wrist-ankle acupuncture, will be excluded.

Types of control groups

Studies using either conventional medication or placebo in the control groups and studies comparing different types of acupuncture therapies will be included. However, studies comparing different acupoint prescriptions or different manual needling techniques with the same type of acupuncture method will be excluded. We will also exclude studies using sham acupuncture in the control groups, as sham acupuncture is widely considered not inert, which may cause confusion when compare with various types of acupuncture therapies. [41]

Types of outcome measurements

Primary outcome(s)

Our primary aim is to evaluate pain control efficacy. According to preliminary searches of relevant articles, measurements of pain intensity have been reported in most cases. Other profiles of pain control, such as onset of pain relief time, are not frequently reported.[35] Therefore, we will select pain intensity as the main outcome of interest. Pain intensity is usually presented by a score on a range between no pain to maximum pain, with higher number indicating more severe pain, using the Visual Analogue Scale, Numerical Rating Scale, Verbal Rating Scale, Average Daily Pain Score, or other validated scales.

Secondary outcome(s)

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

1. Negative emotions, such as anxiety and depression, measured using the Hamilton Anxiety Scale, Self-Rating Anxiety Scale, Self-Rating Depression Scale, or other validated scales.

2. Sleep quality measured using the Pittsburgh Sleep Quality Index or other validated scales.

3. Quality of life measured using the Quality of Life scale or other validated scales.

4. Adverse events occurring 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,

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.[42]

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.[43] For studies where outcomes are reported at multiple time points after the treatment,

data of outcomes assessed at the first time point after the complete treatment regimen will be used.

For studies where SDs of the outcome are not reported, missing SDs will be calculated from standard errors, confidence intervals (CIs), t-statistics, and P values. Additionally, in studies reporting only the median and interquartile ranges, means and SDs will be calculated using a specific formula.[44] If these data are not presented, we will contact the corresponding authors of original studies to obtain the missing data. After these steps, studies with insufficient data for quantitative synthesis will be excluded from the meta-analysis.

Risk of bias assessment

We will assess the risk of bias of included studies using the Cochrane tool RoB 2, which identifies bias in the following domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[45] Pain intensity, as the main outcome of interest, will be selected as the result to assess. The assessment will be performed in relation to the assignment to the intervention (intention-to-treat effect). Two reviewers (BJL and RHS) will independently answer the signalling questions of each domain. Subsequently, a judgement into 'low', 'some concerns' or 'high' risk of bias will be made depending on the responses to these questions, finally reaching an overall risk-of-bias judgement. Disagreements during the assessment will be resolved by discussion, and a third reviewer (JQF) will be consulted where necessary.

Data synthesis

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

When two or more studies comparing the same pair of interventions exist for an outcome, a standard meta-analysis will be performed. Random-effects models will be fitted using Stata 15.1. The effect size will be estimated with a 95% CI. We will use the I^2 statistic to quantify

the heterogeneity of the results in the same treatment comparisons.[46] If the I^2 value is greater than 75%, which indicates the existence of high heterogeneity, and no main source of heterogeneity is found, we will provide a narrative summary without conducting data synthesis.[47]

We will perform network meta-analyses to simultaneously compare multiple interventions. For each outcome, network plots of all included comparisons will be generated using Stata 15.1, where interventions are represented by nodes, and each line between two nodes means that a direct comparison between two interventions is available. Studies that are not connected to the network will be excluded from network meta-analyses. The sizes of the nodes and lines are proportional to the number of included studies. We will conduct NMA within a Bayesian hierarchical framework in OpenBUGS 3.2.3. Random-effects models with vague priors will be fitted, and the Markov Chain Monte Carlo (MCMC) method will be employed to obtain the pooled treatment effect, with a 95% credible interval. Three MCMC chains with different sets of initial values will be run simultaneously. For each initial value, 60,000 simulations will be conducted after discarding 10,000 simulations as the burn-in period, and convergence will be assessed visually and using the Gelman–Rubin statistic.[48] To assess the model fit, the posterior mean residual deviance will be calculated and compared with the number of data points in the model.[49] We will obtain the ranking probabilities of all included interventions using the surface under the cumulative ranking curve analysis in Stata 15.1.[50]

Clinical and methodological heterogeneity will be assessed by examining the characteristics and design of the included studies. The transitivity assumption for NMA will be evaluated by reviewing the distribution of potential effect modifiers (participant characteristics: age, pain severity at baseline; interventions: treatment duration; study design: risk of bias) across comparisons. We will also assess statistical heterogeneity by calculating the between-study SD (τ^2), with a larger τ^2 value indicating a higher level of heterogeneity among studies. We will evaluate the global inconsistency of the treatment network by comparing the consistency model with an inconsistency model; for each closed loop, the node-splitting method will be used to assess local inconsistency. [51 52]

Additional analyses

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.[53 54] Accordingly, we will define a 'high dosage' of acupuncture treatment when both the following criteria are met: (1) the treatment frequency is ≥2 sessions a week, and (2) the total number of treatment sessions is ≥12.[55] 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.[56]

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.[57] 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.[58] 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.[59] Acupuncture therapy is proposed as potentially

beneficial in the management of neuropathic pain and is generally safe when operated by competent practitioners.[60 61] Moreover, acupuncture therapy may help with negative emotions and sleep disorders, which would provide additional benefits for patients in usually long-term treatment.[62 63]

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

ETHICS AND DISSEMINATION

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

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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.

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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. Bücker 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.0000000000011986

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. 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.
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,

UK: John Wiley & Sons, Ltd 2018.

50. 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
51. 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
52. 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
53. Sun N, Tu JF, Lin LL, et al. Correlation between acupuncture dose and effectiveness in the treatment of knee osteoarthritis: a systematic review. *Acupunct Med* 2019;37:261-7. doi: 10.1136/acupmed-2017-011608.
54. Giovanardi CM, Cinquini M, Aguggia M, et al. Acupuncture vs. Pharmacological Prophylaxis of Migraine: A Systematic Review of Randomized Controlled Trials. *Front Neurol* 2020;11:576272. doi: 10.3389/fneur.2020.576272.
55. Bauer M, McDonald JL, Saunders N. Is acupuncture dose dependent? Ramifications of acupuncture treatment dose within clinical practice and trials. *Integr Med Res* 2020;9:21-7. doi: 10.1016/j.imr.2020.01.003.
56. 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
57. 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
58. Colloca L, Ludman T, Bouhassira D, *et al*. Neuropathic pain. *Nat Rev Dis Primers* 2017;3:17002. doi:10.1038/nrdp.2017.2
59. 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
60. Macone A, Otis JAD. Neuropathic Pain. *Semin Neurol* 2018;38:644-653. doi:10.1055/s-0038-1673679

61. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med* 2002;136:374-383. doi:10.7326/0003-4819-136-5-200203050-00010

62. 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

63. 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

64. 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

65. 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

66. 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

67. 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.

68. 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

Figure legend

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

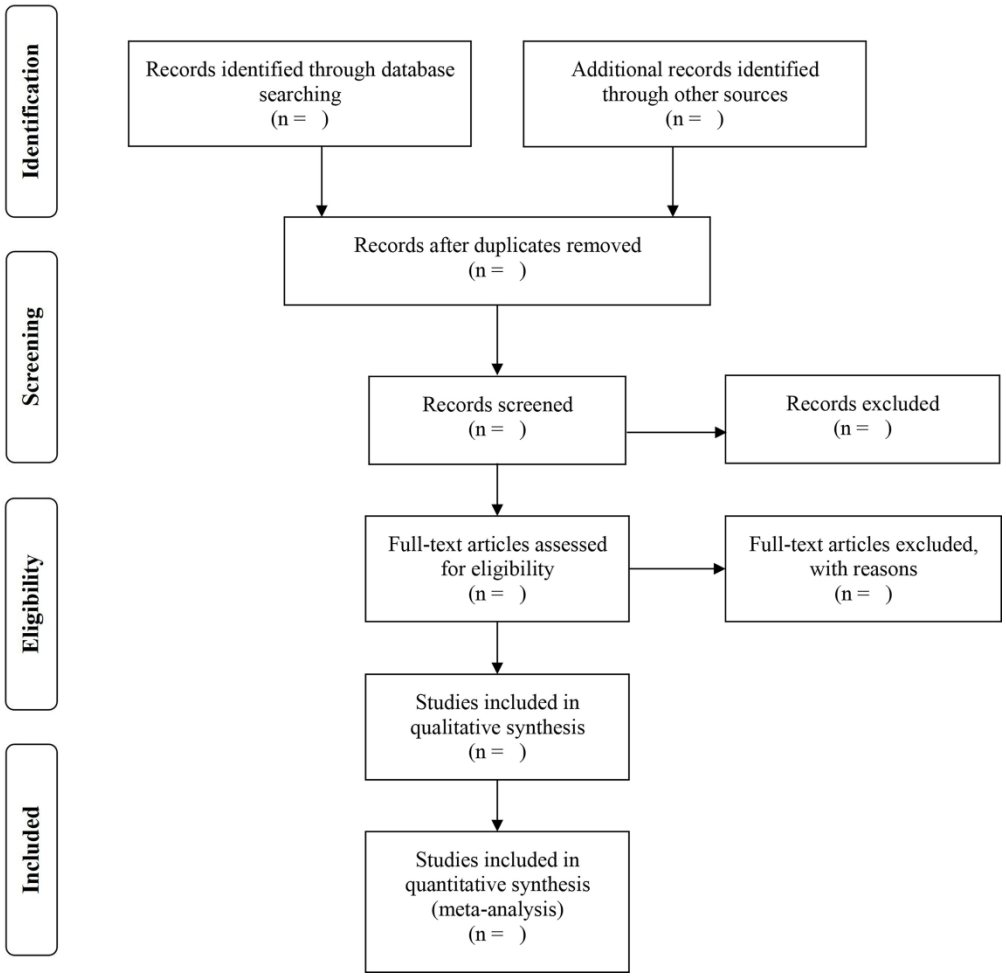

Figure 1 PRISMA flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis.

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

		guarantor of the review	
Amendments			
	#4	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	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	14
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	14
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	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	#8	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	#9	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	#10	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	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records -	#11b	State the process that will be used for selecting studies (such	9

selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9-10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11-12
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12