BMJ Open

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

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

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

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

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2020-039087 on 7 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open

Acupuncture for chronic cancer-related pain: a systematic review and network meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039087
Article Type:	Protocol
Date Submitted by the Author:	03-Apr-2020
Complete List of Authors:	Yang, Jiao; Chengdu University of Traditional Chinese Medicine Shierqiao Campus, Liang, Fan-rong; Chengdu University of Traditional Chinese Medicine, Acu-moxibustion and Tuina school; Chengdu University of Traditional Chinese Medicine qianhua, zheng; Chengdu University of Traditional Chinese Medicine Shierqiao Campus guixing, xu; Chengdu University of TCM, ; zihan, yin ying, cheng; Chengdu University of TCM, ; Sun, Sheng; Chengdu University of Traditional Chinese Medicine Shierqiao Campus Chen, Jiao; Chengdu University of Traditional Chinese Medicine Zhao, Ling; Chengdu University of Traditional Chinese Medicine, College of Acupuncture and Moxibustion and Tuina
Keywords:	Anaesthesia in oncology < ANAESTHETICS, COMPLEMENTARY MEDICINE, Pain management < ANAESTHETICS

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2020-039087 on 7 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Acupuncture for chronic cancer-related pain: a systematic review and network meta-analysis protocol

Jiao Yang[a1], Guixing Xu[a1], Zihan Yin[a1], Ying Cheng[a], Mingsheng Sun[a], Qianhua Zheng[a], Jiao Chen[a], Fan-rong Liang[a*], Ling Zhao[a*]

[a] School of Acu-Mox and Tuina, Chengdu University of Traditional Chinese Medicine, Chengdu, 610075, China

[1]Jiao Yang , Guixing Xu and Zihan Yin contributed equally to this work.

[*]Fan-rong Liang and Ling Zhao are correspondence authors.

Correspondence author at: Chengdu University of Traditional Chinese Medicine, 37 Shierqiao Road, Chengdu, China.

E-mail addresses: acuresearch@126.com (FRL), zhaoling@cdutcm.edu.cn (LZ).

For peer review only

ABSTRACT

Introduction Chronic cancer-related pain is one of the most commonly excruciating symptoms which can be caused by the cancer itself (by the primary tumor or by metastases) or by its treatment (surgery, chemotherapy, and radiotherapy). Although multiple clinical trials and systematic reviews have suggested that acupuncture could be effective in treating chronic cancer-related pain, the comparative efficacy and safety of these acupuncture methods remains unclear. We, therefore, perform this study to evaluate and rank the efficacy and safety of different acupuncture methods for chronic cancer-related pain.

Methods and analysis Seven databases will be searched, including Cochrane Library, MEDLINE, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP) and Chinese Biomedical Literature Database (CBM) from their inception to March 2020.The primary outcomes is the change of pain intensity. Bayesian network meta-analysis will be conducted using software R3.5.1. Finally, we will use the Grading of Recommendations Assessment, Development and Evaluation System (GRADE) to assess the quality of evidence.

Ethics and dissemination Ethical approval is not required for literature-based studies. The results will be disseminated through peer-reviewed publication.

PROSPERO registration number CRD42020165747

Strengths and limitations of this study

►This study will be the first to compare the efficacy and safety of various acupuncture methods in the treatment of chronic cancer-related pain using Bayesian network meta-analysis.

► The quality of evidence will be assessed by the Grading of Recommendations Assessment, Development, and Evaluation system(GRADE).

► The study will be strictly carried out according to the recommendation of Cochrane handbook for systematic reviews of interventions.

► We will only retrieve data from Chinese and English databases which could limit available data or result in language bias.

►The quality of the pooled effects will be affected by original trials

For peer review only

INTRODUCTION

Chronic cancer-related pain is one of the most common symptoms in cancer patients,[1] which includes chronic cancer pain and chronic post-cancer treatment pain.[2] Studies showed that the incidence of chronic cancer-related pain is established to be 33% for patients after curative treatment, 59% for patients undergoing anticancer treatment and 64% for patients with metastatic, advanced or terminal disease.[3 4] Particularly, pain is highly prevalent at early ages in certain cancer types such as pancreatic cancer (44%) and head and neck cancer (40%).[5] It could lead to mood disturbance, dyspepsia and poor quality of life.[6 7] These symptoms caused by chronic cancer-related pain could make the things worse. In terms of treatment approach, the WHO analgesic ladder recommends opioid therapy on the basis of pain intensity.[8] However, over half of all cancer patients still suffering intolerable pain,[9] the inadequate management of chronic cancer-related pain have a significant harmful impact on quality of life for patients[10] and may lead to increased healthcare costs.[11]Moreover, many patients develop adverse effects from analgesic regimen, such as constipation, nausea, drowsiness, confusion, and hallucinations.[12 13] Each adverse effect requires a careful assessment and treatment strategy, and increase patients' financial burden.[14] Therefore, it is necessary to explore other forms of alternative therapies which are both safe and effective in relieving chronic cancer-related pain. The United States and Europe have developed guidelines on complementary and alternative medicine (CAM) for chronic cancer-related pain ,[15] most patients use CAM as an adjunct therapy along with the conventional treatments.[16] As one of CAM treatments, acupuncture plays an important role in the treatment of pain.[17-19] In recent years, various acupuncture methods has been widely used in treating chronic cancer-related pain and adverse effects related to the cancer treatments.[20-22] Most National Cancer Institute-designated comprehensive cancer centers have begun offering acupuncture. In addition, A systematic review showed that acupuncture and/or acupressure is significantly associated with reduce chronic cancer-related pain and decrease the use of analgesics.[21] A randomized control trial indicates the efficacy of auricular acupuncture for patients receiving chemotherapy.[22] However, due to the diversity of acupuncture approach, its relative effectiveness have not yet been studied and explained. Clinicians are confused about how to choose the optimal acupuncture method for chronic cancer-related pain.

Studies showed that the rankings of different treatments can be provided by using the network

meta-analysis (NMA) to analyze the direct and indirect randomized data. [23 24] Therefore, we conducted this network meta-analysis to comprehensively evaluate the effectiveness of various acupuncture therapies for chronic cancer-related pain.

Objective

The purpose of this study is to compare the efficacy and safety of existing acupuncture methods for the treatment of chronic cancer-related pain through NMA and systematic review.

METHODS

This protocol will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement and the Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.[25 26] The research has been registered on PROSPERO (supplementary file 1 for PRISMA-P checklist).

Criteria for including studies in this review

Types of studies

The review will include randomised controlled trials (RCTs) that were reported in English or Chinese without any regional restrictions. The first period of randomised cross-over trials will be included. Non-RCTs reviews, case report, animal experimental studies, expert experience, conference article and duplicated publications will be excluded.

Types of participants

We will include patients with chronic cancer-related pain which includes chronic cancer pain and chronic post-cancer treatment pain, regardless of the cancer type. Trials that studied chronic cancer-related pain mixed with other types of pain and trials studied chronic post-cancer surgery pain will be excluded.

Types of interventions

We will define acupuncture and related therapies in this review as acupoint-based therapy, regardless of needling techniques and stimulation method, including manual acupuncture, electro-acupuncture, auricular (ear) acupuncture, acupressure, acupoint application, moxibustion, catgut embedding, transcutaneous electrical acupoint stimulation, acupoint injection, et.al . We will rule out interventions without stimulating the acupoint.

Types of control groups

For peer review only

Treatments in the comparison groups can be sham-acupuncture, placebo, pharmacotherapy or no additional intervention to usual care. Studies compared different types of acupoint-based therapy will be included.

Types of outcome measures

Studies reporting one or more of the following outcomes will be included.

Primary outcomes

The change of pain intensity will be measured by a visual analogue scale (VAS),[27-29] McGill Pain Questionnaire(MPQ),[30 31] Brief Pain Inventory(BPI)[32] or other validated outcome measures.

Secondary outcomes

(1) Quality of life measured by validated scales including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQC30), the General Version of the Functional Assessment of Cancer Therapy (FACT-G), the Edmonton Symptom Assessment System (ESAS) or other validated scales.[33]

(2) Consumption of analgesics including opioids and non-opioids.[34]

(3) Frequency of breakthrough pain and rescue medication use or dosage.

(4) Side effects of analgesic regimen, such as nausea and vomiting, constipation, and cognitive deficits.

(5) Safety of the acupoint-based therapies, including adverse events and withdrawals for any reasons.

Search methods for identification of studies

The following databases will be searched from their inception to February2020: Cochrane Library, MEDLINE, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), Chinese Biomedical Literature Database (CBM), World Health Organization Clinical Trials Registry, Chinese clinical registry, ClinicalTrials.gov, and reference lists of articles to identify additional studies.

The following medical search headings (MeSH) will be used: "cancer", "tumor" , "carcinoma" , "neoplasms", "pain", "analgesia", "acupuncture", "electro acupuncture", "auriculotherapy", "acupoint", "needle" , "acupoint catgut embedding", "wrist-ankle acupuncture", "moxibustion", "scalp acupuncture", "transcutaneous electrical acupoint stimulation"," acupoint

injection", "randomized controlled trial"," randomised controlled", "randomised, controlled", "clinical trial". Chinese translations of these search terms will be used for the Chinese databases. The search strategy for MEDLINE is shown in table 1.

Table 1 Search strategy in MEDLINE (Ovid SP).

Number	Search Items
1	exp Acupuncture Therapy
2	exp Medicine, East Asian Traditional
3	Acupuncture
4	(acupuncture or acupoint* or electroacupuncture or electro-acupuncture or meridian* or moxibustion* or "traditional chinese medicine" or "traditional oriental medicine" or auriculotherapy or needle or "acupoint catgut embedding" or "wrist-ankle acupuncture" or "scalp acupuncture" or "transcutaneous electrical acupoint stimulation" or " acupoint injection").mp.
5	Or 1-4
6	exp Neoplasms
7	(neoplasm* or cancer* or carcino* or malignan* or tumor* or tumour*).mp.
8	Or 6-7
9	exp Pain/
10	pain*.mp.
11	exp Analgesia
12	(analges* or nocicept* or neuropath*).mp.
13	Or 9-12
14	13 and 8 and 5
15	randomized controlled trial.pt.
16	controlled clinical trial.pt.
17	randomized.ab.
18	placebo.ab
19	drug therapy.fs

For peer review only

20	randomly.ab.
21	trial.ab.
22	groups.ab.
23	Or 15-22
24	exp animals/ not humans.sh.
25	23 not 24
26	25 and 14

For peer revi

Data collection and analysis

Selection of studies

Two reviewers (Jiao Yang and GuiXing Xu) will screen all hits independently based on the titles and abstracts. Full texts will be downloaded for further evaluation when necessary. At the next stage, the reviewers will examine the full text articles according to the inclusion criteria. A third reviewer (Qianhua Zheng) will be consulted to resolve any disagreement by discussion and consensus. The selection procedure will be shown in a PRISMA flow chart (Fig.1)

Data extraction and management

Two independent reviewers(ZiHan Yin and MingSheng Sun) will extract information using a pre-designed form including: (1) identification information (publication year, first author); (2) general information (country, study type, number of centres, sample size, study design); (3) participants (type and/or stage of cancer, age, sex, pain intensity before treatment); (4) interventions (type of acupuncture, acupuncture points selection, treatment frequency/session/duration); (5) comparator (if there is any, details of the treatment including name, dosage, frequency and course); (6) outcomes (data and time points for each measurement, safety).

We will try to contact corresponding authors for missing data or clarification for unclear information. Any disagreements will be arbitrated by a third reviewer (Ling Zhao). Cross-check of all data will be done by ZHY and MSS and transferred into RevMan software (V.5.3).

Quality assessment

Two or more independent reviews (Ying Cheng and Jiao Chen) will appraise the quality of the included trials using the risk of bias tool developed by the Cochrane Collaboration.[35] We will

appraise each study in terms of selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), selective reporting bias and other bias. Trials will be evaluated and classified into three levels: low risk, high risk and unclear. Any disagreements will be arbitrated by a third reviewer (Ling Zhao).

The GRADE system will be used to grading the quality of the evidence for main outcomes.[36] Two reviewers will use the GRADE system to independently assess the quality of evidence for each outcome. Evidence quality will be rated 'high', 'moderate', 'low' or 'very low' according to the GRADE rating standards. The quality of evidence of a specific study will be assessed according to the risk of bias, inconsistency, indirectness, imprecision and publication bias.

Assessment of similarity and consistency

An assessment of similarity and consistency will be performed to produce a credible and valid result. Since it is difficult to determine similarity using statistical analysis, the assessment will be based on clinical and methodological characteristics including study designs, participant characteristics, and interventions. We will conduct the Z test to check the consistency, and the *P*-value will be calculated to confirm whether there are inconsistencies among the comparison of direct and indirect. If the $P > 0.05$, there is no statistical significance, so the comparison of direct and indirect is consistency; on the contrary, inconsistency is considered.

Network meta-analysis

Efficacy data will be synthesized and statistically analyzed in R3.5.1with the Bayesian method.[37] Dichotomous data will be investigated by using a risk ratio with 95% CIs. For continuous outcomes, data will be analyzed by using a standard mean difference with 95% CIs or a weighted mean difference. The weighted mean difference will be used for the same scale or the same assessment instrument; standard mean difference will be used for different assessment tools.

The contribution of different designs to the final effect size of the network meta-analysis will be evaluated by net-heat plots. The acupoint-based therapies will be ranked by using P-score that measures the extent of certainty when treatment is better than control. A P-score equals 100% when a treatment is certain to be the best and 0% of a P-score indicates a treatment to be the worst.

Assessment of heterogeneity

Clinical and methodological heterogeneity will be evaluated by closely checking the features of the participants, interventions and outcomes of the inclusive studies and comparing fit of the fixed effect model and random effect model. Statistical heterogeneity will be assessed by the I^2 index. Values of I^2<50% will indicate that heterogeneity is not salient for the cases that we explore, otherwise, substantial heterogeneity will be considered.[37] Meta-analysis will be performed after removal of studies where main or unacceptable sources of heterogeneity were derived. Furthermore, if the source of heterogeneity cannot be explored, a narrative review will be provided.

Sensitivity analysis and subgroup analysis

A network meta-regression will be performed to explore sources of heterogeneity using a random effects network meta-regression model. If sufficient evidence is available, we will conduct subgroup analyses based on cancer types and degree of pain. In order to obtain a stable conclusion, a sensitivity analysis will be conducted to remove effects of trials with small sample size and remove studies rated as high risk of bias based on accounting of methodological quality. These steps will be crucial to ensure the accuracy and depth of inferences from results.

Patients and public involvement

There was no patients or public will be directly involved in this review. Only data already existent in the literature and the aforementioned sources will be used for this study.

DISCUSSION

Pain is often accompanied by cancer patients and represents a major challenge for both clinicians and patients.[38] More than one third of patients with cancer rating their pain as moderate to severe in nature.[39] In most National Cancer Institution, acupuncture has a decisive role in the treatment of chronic cancer-related pain, but acupuncture therapies for chronic cancer-related pain are diverse. Clinicians are confused to select the optimal way. However, exploring the most suitable acupuncture methods may not only increase financial burden but also waste medical resources. NMA can be used to integrate direct and indirect comparisons across a set of multiple variables, it can help to evaluate the comparative efficacy and safety of various acupuncture methods.[40 41] Based on the type of single study, we will conduct a rigorous analysis of multiple inclusion criteria and quality scores for results evaluated by GRADE.[42]

To the best of our knowledge, this study will be the first SR and NMA to investigate

acupuncture therapies for chronic cancer-related pain. Based on evidence of comparative effectiveness and safety, the NMA is expected to provide a ranking of these methods for cancer patients suffering from pain. Moreover, the NMA may assist patients, physicians and clinical research investigators to choose the most appropriate acupuncture method. Finally, we sincerely hope that our results will offer credible evidence for the clinicians and encourage wider application of acupuncture for chronic cancer-related pain.

Ethics and dissemination

The results will be disseminated through peer-review journals or conference reports. There are no ethical considerations related to the agreement, since no private data will be included in the SR. We will not endanger the individual's privacy or compromise their rights.

Acknowledgements

None

Contributions

Jiao Yang, Zihan Yin and Ling Zhao conceived this study. Jiao Yang, Guixing Xu and Zihan Yin will develop the study protocol and will implement the systematic review under the supervision of Jiao Chen and Qianhua Zheng. Guixing Xu will provide the statistical analysis plan of the study and will conduct data analysis. Ying Cheng and Mingsheng Sun will perform the study search, screening, and extraction of data whereas Fanrong Liang will review the work. Jiao Yang, Zihan Yin and Guixing Xu wrote the first manuscript draft and all authors gave input to the final draft of the protocol.

Funding

This work was financially supported by the National Key Research and Development Program (No.2019YFC1709701), the National Natural Science Foundation of China (No. 81590951, 81973962) and Sichuan Technology Centre (No. 20ZDYF1199，2019YFS0081).

Competing interests

None declared.

Patient consent for publication

Not required.

Provenance and peer review

For peer review only

Not commissioned; externally peer reviewed.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http:// creativecommons. org/ licenses/ by- nc/ 4. 0/.

REFERENCES

1. Sanford NN, Sher DJ, Butler SS, et al. Prevalence of chronic pain among cancer survivors in the United States, 2010-2017. *Cancer* 2019;125:4310-18.
2. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019;160:19-27 doi: 10.1097/j.pain.0000000000001384 [published Online First: 27 December 2018
3. Brown MR, Ramirez JD, Farquhar-Smith P. Pain in cancer survivors. *Br J Pain* 2014;8: 139-53.
4. Van dB-vEM, de Rijke J, Kessels A, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437-49.
5. Burton AW, Fanciullo GJ, Beasley RD, et al. Chronic Pain in the Cancer Survivor: A New Frontier. *Pain Medicine* 2010;8:189-98.
6. Deng G, Cassileth B. Integrative oncology: complementary therapies for pain, anxiety, and mood disturbance. *CA Cancer J Clin* 2005;55:109-16.
7. Hamood R, Hamood H, Merhasin I, et al. Chronic pain and other symptoms among breast cancer survivors: prevalence, predictors, and effects on quality of life. *Breast Cancer Res Treat* 2018;167:157-69.
8. Wiffen PJ, Wee B, Derry S, et al. Opioids for cancer pain-an overview of Cochrane reviews. *Cochrane database syst rev* 2017;7: 1465-1858.
9. Van dB-vEM, de Rijke J, Kessels A, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437-49.
10. Giacalone A, Lleshi A, Zanet E, et al. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. *Cancer* 2012;118:1955-6.
11. Fortner BV, Theodore AO, Russell KP. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain* 2002;3:38-44.
12. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2018;29 (Suppl 4):iv166-iv91.
13. Swarm RA, Abernethy AP, Anghelescu DL, et al. NCCN clinical practice guidelines in Oncology:Adult Cancer Pain(Version3.2019). *JNCCN* 2019;11:992-1034.

For peer review only

14. Ricardo Buenaventura M, Rajive Adlaka M, Nalini Sehgal M. Opioid complications and side effects. *Pain physician* 2008;11:S105-S20.
15. American College of Chest Physicians. New ACCP cancer care guidelines include CAM. *J Altern Complement Med* 2007;13:1049.
16. Richardson MA, Sanders T, Palmer JL, et al. Complementary/Alternative Medicine Use in a Comprehensive Cancer Center and the Implications for Oncology. *J Clin Oncol* 2000; 18: 2505-14.
17. MacPherson H, Vertosick E, Foster N, et al. The persistence of the effects of acupuncture after a course of treatment: a meta-analysis of patients with chronic pain. *Pain* 2017;158:784.
18. Zhao L, Chen J, Li Y, et al. The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial. *JAMA Intern Med* 2017;177:508-15.
19. Zhao L, Li D, Zheng H, et al. Acupuncture as adjunctive therapy for chronic stable angina: a randomized clinical trial. *JAMA Intern Med* 2019;179:1388-97.
20. Hershman DL, Unger JM, Greenlee H, et al. Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. *Jama* 2018;320:167-76 doi: 10.1001/jama.2018.8907[published Online First: 13 July 2018]
21. He Y, Guo X, May BH, et al. Clinical Evidence for Association of Acupuncture and Acupressure With.Improved Cancer Pain: A Systematic Review and Meta-Analysis. *JAMA Oncol*Published Online First:19 December 2019. doi: 10.1001/jamaoncol.2019.5233
22. Ruela LdO, Iunes DH, Nogueira DA, et al. Effectiveness of auricular acupuncture in the treatment of cancer pain: randomized clinical trial. *Rev Esc Enferm USP* 2018;52:e03402-e02.
23. Chaimani A, Higgins JPT, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. *PloS one* 2013;8: e76654.
24. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *PloS one* 2014;9: e99682.
25. 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.
26. 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.
27. Lu W, Du P, Yang C, et al. The effect of computed tomography-guided 125I radioactive particle implantation in treating cancer and its pain. *Cancer Biother Radiopharm* 2018;33:176-81.
28. Zhang J, Zhang H, Luo Y. Association Between Activation of the Programmed Cell Death-1 (PD-1)/Programmed Death-Ligand 1 (PD-L1) Pathway and Pain in Patients with Cancer. *Med Sci Monit* 2019;25:1275-82.
29. Lu W, Du P, Yang C, et al. The effect of computed tomography-guided 125I radioactive particle implantation in treating cancer and its pain. *Cancer Biother Radiopharm* 2018;33:176-81.
30. Ham O-K, Chee W, Im E-O. The influence of social structure on cancer pain and quality of life.*West J Nurs Res* 2017;39:1547-66.
31. Edirisinghe NP, Makuloluwa TR, Amarasekara TD, et al. Psychometric Properties of Sinhala Version of Short-Form McGill Pain Questionnaire-2 (SF MPQ-2-Sin) among Patients

For peer review only

with Cancer Pain in Sri Lanka. *Pain Res Manag* 2019;2019:5050979.
32. Reis-Pina P, Lawlor PG, Barbosa A. Adequacy of cancer-related pain management and predictors of undertreatment at referral to a pain clinic. *J Pain Res* 2017;10:2097-2107.
33. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* extract 2010;39:167-79.
34. Huang Z, Su X, Diao Y, et al. Clinical Consumption of Opioid Analgesics in China: A Analysis of the National and Regional Data 2006–2016. *J Pain Sympto Manage* Retrospective 2020;59:829-35.
35. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928.
36. Guyatt GH, Oxman AD, Schünemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011;64:380-2.
37. Cipriani A, Higgins JPT, Geddes JR, et al. Conceptual and Technical Challenges in Network Meta-analysis. *Ann Intern Med* 2013;159:130-7.
38. Portenoy RK, Ahmed E. Cancer pain syndromes. *Hematol Oncol Clin North Am* 2018; 32:371-86.
39. Kleef4 MvdB-vEJdRAKHSMv, Patijn1 J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437-49.
40. Caldwell DM, Ades A, Higgins J. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *Bmj* 2005;331:897-900.
41. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3:80-97.
42. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *Bmj* 2008; 336:1106-10.

Figure 1 PRISMA flow diagram of the study selection process.

For peer review only

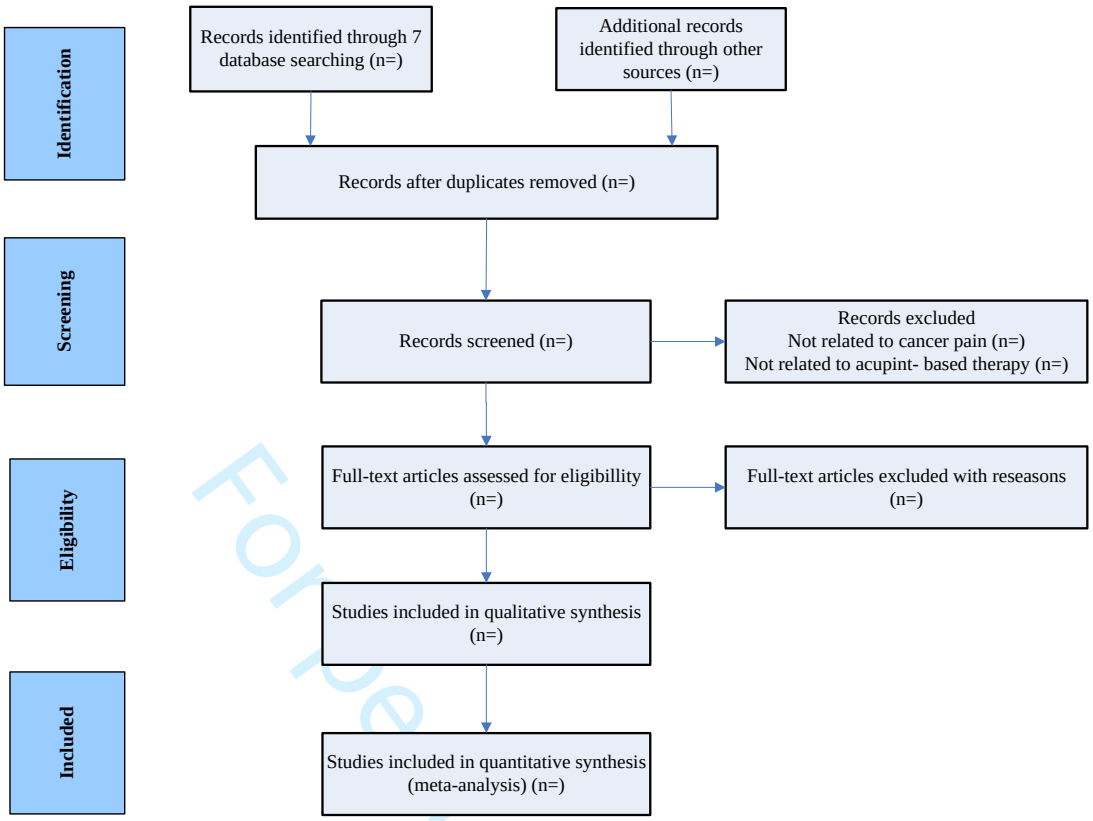

Figure 1 PRISMA flow diagram of the study selection process.

For peer review only

项目批准号	81590951
申请代码	H2707
归口管理部门	
依托单位代码	61113708A0136-0226

81590951 1015508

国家自然科学基金委员会

资助项目计划书

资助类别：重大项目

亚类说明：课题申请

附注说明：穴位的敏化研究

项目名称：穴位敏化现象和规律的临床研究

直接费用：330万元　　间接费用：64.284万元

项目资金：394.284万元　　执行年限：2016.01-2020.12

负 责 人：梁繁荣

通讯地址：成都市温江区柳台大道1166号

邮政编码：611137　　电　　话：028-61800006

电子邮件：lfr@cdutcm.edu.cn

依托单位：成都中医药大学

联 系 人：李炜弘　　电　　话：028-61800101

填表日期：2015年12月01日

国家自然科学基金委员会制

Version: 1.015.508

课题编号：2019YFC1709701 **密　级：公开**

国家重点研发计划
课题任务书

课题名称： “宣阳解郁，通络止痛”针法治疗偏头痛的循证评价及转化研究

所属项目： “宣阳解郁，通络止痛”法防治偏头痛的循证评价及机制研究

所属专项： 中医药现代化研究

项目牵头承担单位： 成都中医药大学

课题承担单位： 成都中医药大学

课题负责人： 赵凌

执行期限： 2019 年 12 月 至 2021 年 12 月

中华人民共和国科学技术部制

2019 年 12 月 21 日

0003YF 2019YFC1709701 2019-12-21 23:21:19

For peer review only

项目批准号	81973962
申请代码	H2718
归口管理部门	
依托单位代码	61113708A0136-0226

819739621007755

国家自然科学基金委员会

资助项目计划书

For peer review only

资助类别：面上项目

亚类说明：

附注说明：

项目名称：基于脑-肠轴的慢性偏头痛针刺疗效差异机制及适宜人群筛选的影像组学研究

直接费用：52万元　　执行年限：2020.01-2023.12

负 责 人：赵凌

通讯地址：成都市温江区柳台大道1166号

邮政编码：611137　　电　　话：13568801429

电子邮件：ling94@163.com

依托单位：成都中医药大学

联 系 人：张海　　电　　话：028-61800104

填表日期：2019年08月29日

国家自然科学基金委员会制

Version：1.007.755

附件

2020年第一批省级科技计划项目清单

单位：万元

序号	申报编号	项目名称	申报单位	推荐立项经费	2020年度立项经费	2021年度立项经费	推荐单位	备注
一、应用基础研究计划								
1	20YYJC0490	低应力全介质高反膜膜系技术研究	中国科学院光电技术研究所	10	10		中科院成都分院	
2	20YYJC0493	泥石流冲击柔性防护结构机理与荷载模型研究	中国科学院、水利部成都山地灾害与环境研究所	10	10		中科院成都分院	
3	20YYJC1857	凹槽表面的微尺度黏附接触力学行为研究	中国工程物理研究院总体工程研究所	10	10		中国工程物理研究院	
4	20YYJC3847	不同管道结构内高压储氢泄漏自燃机理研究	西南交通大学	10	10		四川省科学技术厅	
5	20YYJC4076	新型超结IGBT的研究	四川大学	10	10		四川省科学技术厅	
6	20YYJC4040	Grothendieck多项式的组合研究	四川大学	10	10		四川省科学技术厅	
7	20YYJC3482	高维回火型时间分数阶扩散-反应模型的数值模拟及应用研究	西南财经大学	10	10		四川省科学技术厅	
8	20YYJC3936	恶性黑色素瘤EZH2-HRK调控紊乱的机制及其功能研究	四川大学	10	10		四川省科学技术厅	
9	20YYJC4348	双效应氧化石墨烯/导电聚合物微囊用于电治疗骨修复研究	西南交通大学	10	10		四川省科学技术厅	
10	20YYJC3767	基于卫星影像点云的大范围城市场景三维重建	西南交通大学	10	10		四川省科学技术厅	
11	20YYJC3758	新型电缆贯通供电系统建模与优化方法研究	西南交通大学	10	10		四川省科学技术厅	
12	20YYJC4118	基于全域波形测量的配网设备智能诊断方法研究	四川大学	10	10		四川省科学技术厅	
13	20YYJC3384	薄弱外部电源条件下的川藏铁路牵引供电系统供电能力与可靠性分析方法研究	西南交通大学	10	10		四川省科学技术厅	
14	20YYJC3756	基于光载北斗折线阵列的“快准稳”高铁测姿研究	西南交通大学	10	10		四川省科学技术厅	
15	20YYJC4324	石墨烯表面等离子共振效应及其可调谐红外光电探测器的研究	电子科技大学	10	10		四川省科学技术厅	
16	20YYJC3770	基于激光超声合成孔径的钢轨疲劳裂纹成像及量化研究	西南交通大学	10	10		四川省科学技术厅	
17	20YYJC3709	非线性系统的鲁棒仿射投影滤波方法及在主动噪声控制中的应用	四川大学	9.5	9.5		四川省科学技术厅	
18	20YYJC3599	基于大脑影像生物信息和机器学习方法对精神分裂症患者个体化诊断预测及药物影响机制的多模态磁共振研究	四川大学	10	10		四川省科学技术厅	
19	20YYJC3715	基于蒙皮主动振动的临近空间飞行器翼型增升减阻机理及优化研究	四川大学	10	10		四川省科学技术厅	
20	20YYJC4262	基于线基的纳米电化学生物传感器微流控方法研究	电子科技大学	10	10		四川省科学技术厅	
21	20YYJC3928	基于AhR/ILC-3轴探讨肠道菌群调控类风湿关节炎发生机制的研究	四川大学	10	10		四川省科学技术厅	
22	20YYJC4543	基于pDCs探讨尿源干细胞对系统性硬化症皮肤纤维化的作用及作用机制	四川大学	10	10		四川省科学技术厅	
23	20YYJC3598	木质素寡聚物的结构对其自组装形成功能化木质素纳米颗粒的影响	四川大学	10	10		四川省科学技术厅	
24	20YYJC3326	具有钙化软骨界面力学传导与选择屏障性的新型骨软骨修复材料	四川大学	10	10		四川省科学技术厅	
25	20YYJC3730	SHP2-SOX9信号轴在青少年特发性脊柱侧凸中的作用及机制研究	四川大学	10	10		四川省科学技术厅	
26	20YYJC4207	基于数据解析的机场在线共乘模式运作优化研究	电子科技大学	10	10		四川省科学技术厅	
27	20YYJC3393	二维多态系统可靠性建模与优化	西南财经大学	10	10		四川省科学技术厅	
28	20YYJC4314	“医养结合”视阈下老年抑郁症的人工光干预系统研究—以机构养老空间白光干预为例	西南交通大学	10	10		四川省科学技术厅	
29	20YYJC3507	用于高效稳定钙钛矿太阳能电池的新型可自掺杂空穴传输材料	电子科技大学	10	10		四川省科学技术厅	
30	20YYJC3795	集成自适应代理模型和性能退化的结构可靠性分析方法研究	电子科技大学	10	10		四川省科学技术厅	
31	20YYJC4158	基于联动性能智能检测优化控制的曲面纹理加工质量提升方法研究	电子科技大学	10	10		四川省科学技术厅	
32	20YYJC4376	复杂服役环境下人工关节协同润滑及失效机理研究	西南交通大学	10	10		四川省科学技术厅	
33	20YYJC3633	梯形波胸外心脏按压改善脑微循环障碍而减轻心肺复苏后脑损伤的作用与机制研究	四川大学	10	10		四川省科学技术厅	
34	20YYJC4400	长波钢轨波磨形成和发展机理及防治措施研究	西南交通大学	10	10		四川省科学技术厅	
35	20YYJC4043	仿生六足机器人的多模式运动研究	西南交通大学	10	10		四川省科学技术厅	
36	20YYJC4266	弱监督下基于对抗样本增强的人体目标跟踪方法研究	电子科技大学	10	10		四川省科学技术厅	
37	20YYJC3841	面向多模态问答的机器推理方法研究	西南交通大学	10	10		四川省科学技术厅	
38	20YYJC4050	基于未确定视觉关系的零样本跨媒体检索技术研究	电子科技大学	10	10		四川省科学技术厅	
39	20YYJC3288	基于仿生三维超疏水改性的自清洁抗水损骨架空隙型水泥稳定碎石透水基层研究	西南交通大学	10	10		四川省科学技术厅	
40	20YYJC4111	基于金属离子自组装纳米药物的抗肿瘤活性评价及机制探究	四川大学	10	10		四川省科学技术厅	
41	20YYJC3609	基于等离激元的光子重复率可调量子光源的研究	电子科技大学	10	10		四川省科学技术厅	
42	20YYJC4349	科技金融视角下信用风险动态集成评估模型与方法及其应用研究	西南财经大学	10	10		四川省科学技术厅	
43	20YYJC3639	基于出行大数据的城市路网及其交通效率优化研究	四川大学	10	10		四川省科学技术厅	
44	20YYJC4370	仅依赖多目视觉的低成本无人飞行器集群自主协同控制	电子科技大学	10	10		四川省科学技术厅	
45	20YYJC4031	经TNF-α/Nf-κB调控髁突软骨干细胞参与颞下颌关节软骨发育与修复的机制研究	四川大学	10	10		四川省科学技术厅	
46	20YYJC3687			10	10			

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

		放射敏感性的分子机制研究						
737	20ZDYF2868	EWI-2作为前列腺癌转移检测蛋白分子标志物的作用研究	四川大学	20	20		四川省科学技术厅	
738	20ZDYF3198	基于脱细胞技术的肿瘤细胞三维培养模型构建与应用	四川大学	20	20		四川省科学技术厅	
739	20ZDYF2709	神经活动调控α-突触核蛋白脑内扩散的环路机制研究	四川大学	20	20		四川省科学技术厅	
740	20ZDYF3300	药食用菌松茸资源评价与基于药效成分的多样性研究	四川省自然资源科学研究院（四川省生产力促进中心）	20	20		四川省科学技术厅	
741	20ZDYF3147	特色资源赶黄草降糖产品的关键技术研究	四川大学	20	20		四川省科学技术厅	
742	20ZDYF3297	青藏高原珍稀濒危藏药材毛瓣绿绒蒿保肝药效物质基础研究	西南民族大学	20	20		四川省科学技术厅	
743	20ZDYF3389	脑卒中后肢体痉挛的太极拳场景交互式康复训练关键技术研究	电子科技大学	20	20		四川省科学技术厅	
744	20ZDYF2696	基于精神疾病脑非对称性与“气机升降”理论的抑郁症“气机”辨识系统研究与应用	四川大学	20	20		四川省科学技术厅	
745	20ZDYF3264	濒危植物峨眉拟单性木兰回归种群生态监测	四川省自然资源科学研究院（四川省生产力促进中心）	20	20		四川省科学技术厅	
746	20ZDYF2716	高海拔地区岩土渣场生态修复材料开发与应用	四川大学	20	20		四川省科学技术厅	
747	20ZDYF2723	典型制革场地土壤铬形态转化机制及风险防控	四川大学	20	20		四川省科学技术厅	
748	20ZDYF3432	基于餐厨垃圾三相分离中固相废渣的干式连续厌氧消化技术研究与装备研发	农业部沼气科学研究所	20	20		四川省科学技术厅	
749	20ZDYF3221	食品中幽门螺杆菌污染情况及其耐受能力研究初探	四川大学	10	10		四川省科学技术厅	
750	20ZDYF2674	川西高原公路隧道火灾烟气特性及人员安全疏散技术研究	西南交通大学	20	20		四川省科学技术厅	
751	20ZDYF3358	高层建筑疏散人员–设施协同管控方法研究	西南交通大学	20	20		四川省科学技术厅	
752	20ZDYF3331	基于多源影像的堰塞湖导流辅助信息提取技术	应急管理部四川消防研究所	10	10		四川省科学技术厅	
753	20ZDYF3272	基于知识图谱库的经济犯罪研判技术研究（涉烟）	中国烟草总公司四川省公司	20	20		四川省科学技术厅	
754	20ZDYF3369	川藏铁路穿越蠕滑断层隧道抗错断技术研究	西南交通大学	20	20		四川省科学技术厅	
755	20ZDYF2914	地震灾后创面生态修复成套技术研发	四川大学	20	20		四川省科学技术厅	
756	20ZDYF2835	高寒高烈度山区Sackung型高边坡破裂-失稳-灾变机理	中国地质调查局成都地质调查中心	20	20		四川省科学技术厅	
757	20ZDYF3299	白水江流域地质灾害早期识别与风险评估	西南交通大学	20	20		四川省科学技术厅	
758	20ZDYF3107	基于人工智能的疑难伤口5G远程诊疗模式的构建及应用研究	四川大学	20	20		四川省科学技术厅	
759	20ZDYF3396	地方旅游资源与文化遗产的数字化保护—以安岳石刻华严洞为范本	电子科技大学	10	10		四川省科学技术厅	
760	20ZDYF2903	基于交通-生态安全的县级全域旅游大数据平台构建关键技术及国土空间开发应用示范研究	西南交通大学	20	20		四川省科学技术厅	
761	20ZDYF2382	补虚通络法有效验方抗肝纤维化的临床疗效评价及作用机制研究	成都中医药大学	100	100		四川省教育厅	
762	20ZDYF2407	六字诀干预原发性高血压血管病变的“治未病”思想研究	成都中医药大学	100	100		四川省教育厅	
763	20ZDYF1881	中药材及相关制剂外源性污染物快速检测技术研究	成都中医药大学	100	100		四川省教育厅	
764	20ZDYF1199	针灸干预结直肠癌患者术后胃肠功能紊乱的多中心临床循证评价	成都中医药大学	50	50		四川省教育厅	
765	20ZDYF1214	低温等离子体协同催化处理大风量低浓度有机废气关键技术研发与应用示范	西南石油大学	100	100		四川省教育厅	
766	20ZDYF2300	典型河流和湖库总氮污染来源解析与治理关键技术集成示范	西南科技大学	100	100		四川省教育厅	
767	20ZDYF2371	新一代视频图像增强技术研究应用	西南科技大学	100	100		四川省教育厅	
768	20ZDYF2255	川西北高原村镇聚落绿色宜居性能提升技术研究	成都理工大学	100	100		四川省教育厅	
769	20ZDYF2366	基于避灾视角下川南地区绿色宜居村镇聚落适宜性规划研究与示范	西华大学	100	100		四川省教育厅	
770	20ZDYF2379	FoxM1/ABCG2调控的P201/DOX联合用药对肝癌细胞的协同杀伤作用及抗耐药分子机制	西华大学	20	20		四川省教育厅	
771	20ZDYF2387	EZH2靶点抗肿瘤新药SKLB1039合成工艺关键技术研究	成都师范学院	20	20		四川省教育厅	
772	20ZDYF1190	成都PM2.5高暴露人群鼻腔菌群-肠道菌群-宿主交互作用及感毒清的调控机制：一项随机、双盲、安慰剂对照临床研究	成都中医药大学	20	20		四川省教育厅	
773	20ZDYF1231	中性粒细胞高效介导甲氨蝶呤靶向治疗类风湿性关节炎研究	西南医科大学	20	20		四川省教育厅	
774	20ZDYF2312	流式荧光法检测多种肠道病毒的方法学研究与试剂盒研发	成都医学院	20	20		四川省教育厅	
775	20ZDYF1698	基于人机交互的脑瘫患儿智能踝足矫形器的研发改进与临床应用	四川护理职业学院	20	20		四川省教育厅	
776	20ZDYF1160	基于深度学习的计算机辅助CT图像肝脏肿瘤诊断技术研究	西南科技大学	20	20		四川省教育厅	
777	20ZDYF2400	基于慢性疾病轨迹多学科团队参与的脑卒中自我管理模式构建与应用研究	成都医学院	20	20		四川省教育厅	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			1
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	
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
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
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	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3-4
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	4-5
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	6
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	6-7

/bmjopen-2020-039687 on 7 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

For peer review only

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
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)	7-8
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	7-8
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	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-10
	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 I^2, Kendall's τ)	9-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9-10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

For peer review only

/bmjopen-2020-039087 on 7 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

BMJ Open

Acupuncture for chronic cancer-related pain: a systematic review and network meta-analysis protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039087.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Jun-2020
Complete List of Authors:	Yang, Jiao; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School guixing, xu; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School zihan, yin; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School ying, cheng; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School Sun, Sheng; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School qianhua, zheng; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School Chen, Jiao; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School Liang, Fan-rong; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School Zhao, Ling; Chengdu University of Traditional Chinese Medicine, Acupuncture and Tuina School
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Anaesthesia, Oncology
Keywords:	Anaesthesia in oncology < ANAESTHETICS, COMPLEMENTARY MEDICINE, Pain management < ANAESTHETICS

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2020-039087 on 7 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

Acupuncture for chronic cancer-related pain: a systematic review and network meta-analysis protocol

Jiao Yang[a1], Guixing Xu[a1], Zihan Yin[a1], Ying Cheng[a], Mingsheng Sun[a], Qianhua Zheng[a], Jiao Chen[a], Fan-rong Liang[a*], Ling Zhao[a*]

[a] Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, 610075, CN

[1]Jiao Yang , Guixing Xu and Zihan Yin contributed equally to this work.

[*]Fan-rong Liang and Ling Zhao are correspondence authors.

Correspondence author at: Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, CN

E-mail addresses: acuresearch@126.com (FRL), zhaoling@cdutcm.edu.cn (LZ).

For peer review only

ABSTRACT

Introduction Chronic cancer-related pain is one of the most commonly excruciating symptoms which can be caused by the cancer itself (by the primary tumor or by metastases) or by its treatment (surgery, chemotherapy, and radiotherapy). Although multiple clinical trials and systematic reviews have suggested that acupuncture could be effective in treating chronic cancer-related pain, the comparative efficacy and safety of these acupuncture methods remains unclear. We, therefore, perform this study to evaluate and rank the efficacy and safety of different acupuncture methods for chronic cancer-related pain.

Methods and analysis Seven databases will be searched, including Cochrane Library, MEDLINE, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP) and Chinese Biomedical Literature Database (CBM) from their inception to March 2020. The primary outcome is the change of pain intensity. Bayesian network meta-analysis will be conducted using software R3.5.1. Finally, we will use the Grading of Recommendations Assessment, Development and Evaluation System (GRADE) to assess the quality of evidence.

Ethics and dissemination Ethical approval is not required for literature-based studies. The results will be disseminated through peer-reviewed publication.

PROSPERO registration number CRD42020165747

Strengths and limitations of this study

► This study will be the first of its kind to compare the efficacy and safety of various acupuncture methods in the treatment of chronic cancer-related pain using Bayesian network meta-analysis.

► The quality of evidence will be assessed by the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE).

► The study will be strictly carried out according to the recommendation of Cochrane handbook for systematic reviews of interventions.

► We will only retrieve data from Chinese and English databases which could limit

For peer review only

available data or result in language bias.

►The quality of the pooled effects will be affected by original trials

INTRODUCTION

Chronic cancer-related pain is one of the most common symptoms in cancer patients,[1] which includes chronic cancer pain and chronic post-cancer treatment pain.[2] Studies showed that the incidence of chronic cancer-related pain is established to be 33% for patients after curative treatment, 59% for patients undergoing anticancer treatment and 64% for patients with metastatic, advanced or terminal disease.[3 4] Particularly, pain is highly prevalent at early stages in certain cancer types such as pancreatic cancer (44%) and head and neck cancer (40%).[5] It could lead to mood disturbance, dyspepsia and poor quality of life.[6 7] In terms of treatment approach, the WHO analgesic ladder recommends opioid therapy on the basis of pain intensity.[8] However, over half of all cancer patients still suffering intolerable pain.[9] The inadequate management of chronic cancer-related pain have a significant harmful impact on quality of life for patients[10] and may lead to increased healthcare costs.[11]Moreover, many patients develop adverse effects from analgesic regimen, such as constipation, nausea, drowsiness, confusion, and hallucinations.[12 13] Each adverse effect requires a careful assessment and treatment strategy, and increase the financial burden of patients.[14] Therefore, it is necessary to explore other forms of alternative therapies which are both safe and effective in relieving chronic cancer-related pain.

The United States and Europe have developed guidelines on complementary and alternative medicine (CAM) for chronic cancer-related pain,[15] most patients use CAM as an adjunct therapy along with the conventional treatments.[16] As one of CAM treatments, acupuncture plays an important role in the treatment of pain.[17-19] In recent years, various acupuncture methods has been widely used in treating chronic cancer-related pain and adverse effects related to the cancer treatments.[20-25] Most National Cancer Institute-designated comprehensive cancer centers have begun offering acupuncture. In addition, systematic reviews showed that acupuncture and/or acupressure is significantly associated with reducing chronic cancer-related pain and

For peer review only

decrease the use of analgesics.[21 22] Another Cochrane systematic review showed that all studies reported benefits of acupuncture in managing pancreatic cancer pain.[23] The comparison between acupuncture plus drug therapy and drug therapy alone demonstrated a significant favour in the acupuncture plus drug therapy.[24] A randomized control trial indicates the efficacy of auricular acupuncture for patients receiving chemotherapy.[25] However, due to the diversity of acupuncture approach, its relative effectiveness have not yet been studied or explained. Clinicians are confused about how to choose the optimal acupuncture method for chronic cancer-related pain.

Studies showed that the rankings of different treatments can be provided using the network meta-analysis (NMA) to analyze the direct and indirect randomized data.[26 27] Therefore, we will perform this network meta-analysis to comprehensively evaluate the effectiveness of various acupuncture therapies for chronic cancer-related pain.

Objective

The purpose of this study is to compare the efficacy and safety of existing acupuncture methods for the treatment of chronic cancer-related pain through NMA and systematic review.

METHODS

This protocol will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement and the Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis.[28 29] The research has been registered on PROSPERO (supplementary file 1 for PRISMA-P checklist).

Criteria for including studies in this review

Types of studies

The review will include randomised controlled trials (RCTs) that were reported in English or Chinese without any regional restrictions. The first period of randomised cross-over trials will be included. Non-RCTs reviews, case report, animal experimental studies, expert experience, conference article and duplicated publications will be excluded.

For peer review only

Types of participants

We will include patients with chronic cancer-related pain which includes chronic cancer pain and chronic post-cancer treatment pain, regardless of the cancer type. We will define chronic cancer-related pain as pain directly linked to the development of cancer confirmed by pathology or radiology. Trials that studied chronic cancer-related pain mixed with other types of pain and trials studied chronic post-cancer surgery pain will be excluded.

Types of interventions

We will define acupuncture in this review as acupoint-based therapy, regardless of needling techniques and stimulation method, including manual acupuncture, electro-acupuncture, auricular (ear) acupuncture, acupressure, acupoint application, moxibustion, catgut embedding, transcutaneous electrical acupoint stimulation, acupoint injection, et.al. We will rule out interventions without stimulating the acupoint.

Types of control groups

Treatments in the comparison groups can be sham-acupuncture, placebo, pharmacotherapy or no additional intervention to usual care. Studies compared different types of acupoint-based therapy will be included.

Types of outcome measures

Studies reporting one or more of the following outcomes will be included.

Primary outcomes

The change of pain intensity will be measured by a visual analogue scale (VAS),[30-32] McGill Pain Questionnaire (MPQ),[33 34] Brief Pain Inventory (BPI)[35] or other validated outcome measures.

Secondary outcomes

(1) Quality of life measured by validated scales including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQC30), the General Version of the Functional Assessment of Cancer Therapy (FACT-G), the Edmonton Symptom Assessment System (ESAS) or other validated scales.[36]

(2) Consumption of analgesics including opioids and non-opioids.[37]

(3) Frequency of breakthrough pain and rescue medication use or dosage.

(4) Side effects of analgesic regimen, such as nausea and vomiting, constipation, and cognitive deficits.

(5) Safety of the acupoint-based therapies, including adverse events and withdrawals for any reasons.

Search methods for identification of studies

The following databases will be searched from their inception to March 2020: Cochrane Library, MEDLINE, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), Chinese Biomedical Literature Database (CBM), World Health Organization Clinical Trials Registry, Chinese clinical registry, ClinicalTrials.gov, and reference lists of articles to identify additional studies.

The following medical search headings (MeSH) will be used: “cancer”, ” tumor” , ”carcinoma” , “neoplasms”, “pain”, “analgesia”, “acupuncture”, “electro acupuncture”, “auriculotherapy”, “acupoint”, “needle” , “acupoint catgut embedding”, “wrist-ankle acupuncture”, “moxibustion”, “scalp acupuncture”, “transcutaneous electrical acupoint stimulation”,” acupoint injection”, “randomized controlled trial”,” randomised controlled”, “randomised, controlled”, “clinical trial”. Chinese translations of these search terms will be used for the Chinese databases. The search strategy for MEDLINE is shown in table 1.

Table 1 Search strategy in MEDLINE (Ovid SP).

Number	Search Items
1	exp Acupuncture Therapy
2	exp Medicine, East Asian Traditional
3	Acupuncture
4	(acupuncture or acupoint* or electroacupuncture or electro-acupuncture or meridian* or moxibustion* or "traditional chinese medicine" or "traditional oriental medicine" or auriculotherapy or needle or “acupoint

For peer review only

	catgut embedding" or "wrist-ankle acupuncture" or "scalp acupuncture" or "transcutaneous electrical acupoint stimulation" or " acupoint injection").mp.
5	Or 1-4
6	exp Neoplasms
7	(neoplasm* or cancer* or carcino* or malignan* or tumor* or tumour*).mp.
8	Or 6-7
9	exp Pain/
10	pain*.mp.
11	exp Analgesia
12	(analges* or nocicept* or neuropath*).mp.
13	Or 9-12
14	13 and 8 and 5
15	randomized controlled trial.pt.
16	controlled clinical trial.pt.
17	randomized.ab.
18	placebo.ab
19	drug therapy.fs
20	randomly.ab.
21	trial.ab.
22	groups.ab.
23	Or 15-22
24	exp animals/ not humans.sh.
25	23 not 24
26	25 and 14

Data collection and analysis

Selection of studies

For peer review only

Two reviewers (Jiao Yang and GuiXing Xu) will screen all hits independently based on the titles and abstracts. Full texts will be downloaded for further evaluation when necessary. By the next stage, the reviewers will examine the full text articles according to the inclusion criteria. A third reviewer (Qianhua Zheng) will be consulted to resolve any disagreement by discussion and consensus. The selection procedure will be shown in a PRISMA flow chart (Fig.1)

Data extraction and management

Two independent reviewers(ZiHan Yin and MingSheng Sun) will extract information using a pre-designed form including: (1) identification information (publication year, first author); (2) general information (country, study type, number of centres, sample size, study design); (3) participants (type and/or stage of cancer, age, sex, pain intensity before treatment); (4) interventions (type of acupuncture, acupuncture points selection, treatment frequency/session/duration); (5) comparator (if there is any, details of the treatment including name, dosage, frequency and course); (6) outcomes (data and time points for each measurement, safety).

We will try to contact corresponding authors for missing data or clarification for unclear information. Any disagreements will be arbitrated by a third reviewer (Ling Zhao). Cross-check of all data will be done by ZHY and MSS before transfer into RevMan software (V.5.3).

Quality assessment

Two or more independent reviews (Ying Cheng and Jiao Chen) will appraise the quality of the included trials using the risk of bias tool developed by the Cochrane Collaboration.[38] We will appraise each study in terms of selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), selective reporting bias and other bias. Trials will be evaluated and classified into three levels: low risk, high risk and unclear. Any disagreements will be arbitrated by a third reviewer (Ling Zhao).

The GRADE system will be used to grade the quality of the evidence for main outcomes.[39] Two reviewers will use the GRADE system to independently assess the

quality of evidence for each outcome. Evidence quality will be rated 'high', 'moderate', 'low' or 'very low' according to the GRADE rating standards. The quality of evidence of a specific study will be assessed according to the risk of bias, inconsistency, indirectness, imprecision and publication bias.

Assessment of similarity and consistency

An assessment of similarity and consistency will be performed to produce a credible and valid result. Since it is difficult to determine similarity using statistical analysis, the assessment will be based on clinical and methodological characteristics including study designs, participant characteristics, and interventions. We will conduct the Z test to check the consistency, and the *P*-value will be calculated to confirm whether there are inconsistencies among the comparison of direct and indirect. If the $P > 0.05$, there is no statistical significance, so the comparison of direct and indirect is consistency; on the contrary, inconsistency is considered.

Network meta-analysis

Efficacy data will be synthesized and statistically analyzed in R3.5.1 with the Bayesian method.[40] Dichotomous data will be investigated by using a risk ratio with 95% CIs. For continuous outcomes, data will be analyzed by using a standard mean difference with 95% CIs or a weighted mean difference. The weighted mean difference will be used for the same scale or the same assessment instrument; whereas standard mean difference will be used for different assessment tools.

The contribution of different designs to the final effect size of the network meta-analysis will be evaluated by net-heat plots. The acupoint-based therapies will be ranked by using P-score that measures the extent of certainty when treatment is better than control. A P-score equals 100% when a treatment is certain to be the best and 0% of a P-score indicates a treatment to be the worst. We will use the forest plots to present the results of network meta-analysis. Ranking of the different acupuncture methods will be displayed according to the surface under the cumulative ranking curve analysis (SUCRA). Network plot will be used to show the comparisons between interventions.

Assessment of heterogeneity

For peer review only

Clinical and methodological heterogeneity will be evaluated by closely checking the features of the participants, interventions and outcomes of the inclusive studies and comparing fit of the fixed effect model and random effect model. Statistical heterogeneity will be assessed by the I^2 index. Values of I^2<50% will indicate that heterogeneity is not salient for the cases that we explore, otherwise, substantial heterogeneity will be considered.[39] Meta-analysis will be performed after removal of studies where main or unacceptable sources of heterogeneity were derived. Furthermore, if the source of heterogeneity cannot be explored, a narrative review will be provided.

Meta-regression, subgroup analysis and sensitivity analysis

A network meta-regression will be performed to explore sources of heterogeneity using a random effects network meta-regression model. If sufficient evidence is available, we will conduct subgroup analyses based on cancer types and degree of pain. In order to obtain a stable conclusion, a sensitivity analysis will be conducted to remove effects of trials with small sample size and remove studies rated as high risk of bias based on accounting of methodological quality. These steps will be crucial to ensure the accuracy and depth of inferences from results.

Patients and public involvement

There were no patients nor public will be directly involved in this review. Only data already existent in the literature and the aforementioned sources will be used for this study.

DISCUSSION

Pain is often accompanied by cancer patients and represents a major challenge for both clinicians and patients.[41] More than one third of patients with cancer rate their pain as moderate to severe in nature.[42] In most National Cancer Institution, acupuncture has a decisive role in the treatment of chronic cancer-related pain, but acupuncture therapies for chronic cancer-related pain are diverse. Clinicians are confused to select the optimal way. However, exploring the most suitable acupuncture methods may not only increase financial burden but also waste medical resources.

NMA can be used to integrate direct and indirect comparisons across a set of

multiple variables, it can help to evaluate the comparative efficacy and safety of various acupuncture methods.[43 44] Bayesian methods involve a formal combination of a prior probability distribution with a (likelihood) distribution of the pooled effect based on the observed data to obtain a posterior probability distribution of the pooled effect.[45] Compared with frequency methods, Bayesian methods can naturally lead to a decision framework to support decision-making.[45-47] This overcomes the defect of the frequency method in parameter estimation which estimates the maximum likelihood through continuous iteration and causes instable results. Moreover, Bayesian meta-analysis is straightforward in making predictions and possible of incorporating different sources of uncertainty,[45 47] which was recommended for NMA. Therefore, efficacy data will be synthesized and analyzed with Bayesian method in our review. Based on the type of single study, we will conduct a rigorous analysis of multiple inclusion criteria and quality scores for results evaluated by GRADE.[48]

To the best of our knowledge, this study will be the first SR and NMA to investigate acupuncture therapies for chronic cancer-related pain. Based on evidence of comparative effectiveness and safety, the NMA is expected to provide a ranking of these methods for cancer patients suffering from pain. Moreover, the NMA may assist patients, physicians and clinical research investigators to choose the most appropriate acupuncture method. Finally, we sincerely hope that our results will offer credible evidence for the clinicians and encourage wider application of acupuncture for chronic cancer-related pain.

Ethics and dissemination

The results will be disseminated through peer-review journals or conference reports. There are no ethical considerations related to the agreement, since no private data will be included in the SR. We will not endanger the individual's privacy or compromise their rights.

Acknowledgements

None

Contributions

Jiao Yang, Zihan Yin and Ling Zhao conceived this study. Jiao Yang, Guixing Xu and Zihan Yin will develop the study protocol and will implement the systematic review under the supervision of Jiao Chen and Qianhua Zheng. Guixing Xu will provide the statistical analysis plan of the study and will conduct data analysis. Ying Cheng and Mingsheng Sun will perform the study search, screening, and extraction of data whereas Fanrong Liang will review the work. Jiao Yang, Zihan Yin and Guixing Xu wrote the first manuscript draft and all authors gave input to the final draft of the protocol.

Funding

This work was financially supported by the National Key Research and Development Program (No.2019YFC1709700), the National Natural Science Foundation of China (No. 81590951, 81722050, 81973961) and Sichuan Technology Centre (No. 20ZDYF1199，2019YFS0081).

Competing interests

None declared.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

References

1. Sanford NN, Sher DJ, Butler SS, et al. Prevalence of chronic pain among cancer survivors in the United States, 2010 - 2017. *Cancer* 2019;125:4310-18
2. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain 2019;160:19-27 doi: 10.1097/j.pain.0000000000001384 [published Online First: 27 December 2018
3. Brown MR, Ramirez JD, Farquhar-Smith P. Pain in cancer survivors. *Br J Pain* 2014;8: 139-53..
4. Van dB-vEM, de Rijke J, Kessels A, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437-49.
5. Burton AW, Fanciullo GJ, Beasley RD, et al. Chronic Pain in the Cancer Survivor: A New Frontier. *Pain Medicine* 2010;8:189-98.
6. Deng G, Cassileth B. Integrative oncology: complementary therapies for pain, anxiety, and mood

For peer review only

disturbance. *CA Cancer J Clin* 2005;55:109-16.

7. Hamood R, Hamood H, Merhasin I, et al. Chronic pain and other symptoms among breast cancer survivors: prevalence, predictors, and effects on quality of life. *Breast Cancer Res Treat* 2018;167:157-69.
8. Wiffen PJ, Wee B, Derry S, et al. Opioids for cancer pain-an overview of Cochrane reviews. *Cochrane database syst rev* 2017;7: 1465-1858.
9. Van dB-vEM, de Rijke J, Kessels A, et al. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437-49.
10. Giacalone A, Lleshi A, Zanet E, et al. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. *Cancer* 2012;118:1955-6.
11. Fortner BV, Theodore AO, Russell KP. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain* 2002;3:38-44.
12. Fallon M, Giusti R, Aielli F, et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2018;29 (Suppl 4):iv166-iv91.
13. Swarm RA, Abernethy AP, Anghelescu DL, et al. NCCN clinical practice guidelines in Oncology:Adult Cancer Pain(Version3.2019). *JNCCN* 2019;11:992-1034.
14. Ricardo Buenaventura M, Rajive Adlaka M, Nalini Sehgal M. Opioid complications and side effects. *Pain physician* 2008;11:S105-S20.
15. American College of Chest Physicians. New ACCP cancer care guidelines include CAM. *J Altern Complement Med* 2007;13:1049.
16. Richardson MA, Sanders T, Palmer JL, et al. Complementary/Alternative Medicine Use in a Comprehensive Cancer Center and the Implications for Oncology. *J Clin Oncol* 2000;18:2505-14.
17. MacPherson H, Vertosick E, Foster N, et al. The persistence of the effects of acupuncture after a course of treatment: a meta-analysis of patients with chronic pain. *Pain* 2017;158:784.
18. Zhao L, Chen J, Li Y, et al. The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial. *JAMA Intern Med* 2017;177:508-15.
19. Zhao L, Li D, Zheng H, et al. Acupuncture as adjunctive therapy for chronic stable angina: a randomized clinical trial. *JAMA Intern Med* 2019;179:1388-97.
20. Hershman DL, Unger JM, Greenlee H, et al. Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. *Jama* 2018;320:167-76 doi: 10.1001/jama.2018.8907 [published Online First: 13 July 2018]
21. He Y, Guo X, May BH, et al. Clinical Evidence for Association of Acupuncture and Acupressure With.
    Improved Cancer Pain: A Systematic Review and Meta-Analysis. *JAMA Oncol*Published Online First: 19 December 2019. doi: 10.1001/jamaoncol.2019.5233
22. Peng H, Peng HD, Xu L, et al. [Efficacy of acupuncture in treatment of cancer pain: a systematic review]. *Zhong xi yi jie he xue bao = Journal of Chinese integrative medicine* 2010;8(6):501-9. doi: 10.3736/jcim20100601 [published Online First: 2010/06/17]
23. Paley CA, Johnson MI, Tashani OA, et al. Acupuncture for cancer pain in adults. *The Cochrane database*
    of systematic reviews 2015;2015(10):Cd007753. doi: 10.1002/14651858.CD007753.pub3 [published Online First: 2015/10/16]

For peer review only

24. Choi TY, Lee MS, Kim TH, et al. Acupuncture for the treatment of cancer pain: a systematic review of randomised clinical trials. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2012;20(6):1147-58. doi: 10.1007/s00520-012-1432-9 [published Online First: 2012/03/27]
25. Ruela LdO, Iunes DH, Nogueira DA, et al. Effectiveness of auricular acupuncture in the treatment of cancer pain: randomized clinical trial. *Rev Esc Enferm USP* 2018;52:e03402-e02.
26. Chaimani A, Higgins JPT, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. *PloS one* 2013;8: e76654
27. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *PloS one* 2014;9: e99682
28. 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.
29. 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.
30. Lu W, Du P, Yang C, et al. The effect of computed tomography-guided 125I radioactive particle implantation in treating cancer and its pain. *Cancer Biother Radiopharm* 2018;33:176-81.
31. Zhang J, Zhang H, Luo Y. Association Between Activation of the Programmed Cell Death-1 (PD-1)/Programmed Death-Ligand 1 (PD-L1) Pathway and Pain in Patients with Cancer. *Med Sci Monit* 2019;25:1275-82.
32. Lu W, Du P, Yang C, et al. The effect of computed tomography-guided 125I radioactive particle implantation in treating cancer and its pain. *Cancer Biother Radiopharm* 2018;33:176-81.
33. Ham O-K, Chee W, Im E-O. The influence of social structure on cancer pain and quality of life. *West J Nurs Res* 2017;39:1547-66.
34. Edirisinghe NP, Makuloluwa TR, Amarasekara TD, et al. Psychometric Properties of Sinhala Version of Short-Form McGill Pain Questionnaire-2 (SF MPQ-2-Sin) among Patients with Cancer Pain in Sri Lanka. *Pain Res Manag* 2019;2019:5050979.
35. Reis-Pina P, Lawlor PG, Barbosa A. Adequacy of cancer-related pain management and predictors of undertreatment at referral to a pain clinic. *J Pain Res* 2017;10:2097-2107.
36. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* extract 2010;39:167-79.
37. Huang Z, Su X, Diao Y, et al. Clinical Consumption of Opioid Analgesics in China: A Analysis of the National and Regional Data 2006–2016. *J Pain Sympto Manage* Retrospective 2020;59:829-35.
38. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011;343:d5928.
39. Guyatt GH, Oxman AD, Schünemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *J Clin Epidemiol* 2011;64:380-2.
40. Cipriani A, Higgins JPT, Geddes JR, et al. Conceptual and Technical Challenges in Network Meta-analysis. *Ann Intern Med* 2013;159:130-7.

For peer review only

41. Portenoy RK, Ahmed E. Cancer pain syndromes. *Hematol Oncol Clin North Am*2018;32:371-86.
42. Kleef4 MvdB-vEJdRAKHSMv, Patijn1 J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437-49.
43. Caldwell DM, Ades A, Higgins J. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *Bmj* 2005;331:897-900.
44. Salanti G. Indirect and mixed-treatment comparison, network, or multiple‐treatments meta analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3:80-97.
45. Haidich AB. Meta-analysis in medical research. *Hippokratian* 2010;14(Suppl1):P29-P37.
46. Luce BR, Claxton K. Redefining the analytical approach to pharmacoeconomics.*Health Econ* 1999;8:187–9.
47. Spiegelhalter DJ, Abrams KR, Myles JP, et al. Bayesian approaches to clinical trials and health-care evaluations. Vol. 13. *John Wiley & Sons* 2004;22: 80–5.
48. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *Bmj* 2008; 336:1106-10.

Figure 1 PRISMA flow diagram of the study selection process.

For peer review only

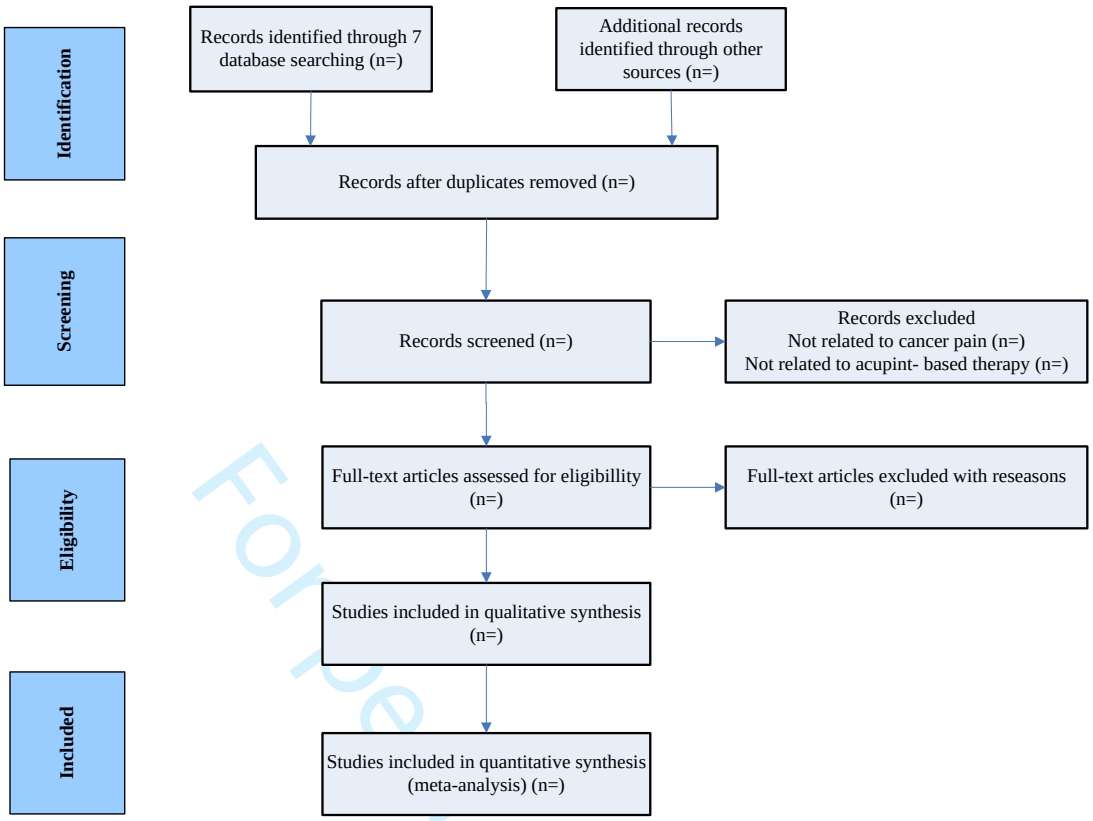

Figure 1 PRISMA flow diagram of the study selection process.

For peer review only

bmjopen-2020-039887 on 7 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			1
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	
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
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	1
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	
Support:			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3-4
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	4-5
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	6
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	6-7

For peer review only

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
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)	7-8
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	7-8
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	7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
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	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-10
	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 I^2, Kendall's τ)	8-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8-9

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

For peer review only

/bmjopen-2020-039087 on 7 October 2020. Downloaded from http://bmjopen.bmj.com/ on April 10, 2024 by guest. Protected by copyright.