

BMJ Open Effectiveness of acupuncture for cancer pain: protocol for an umbrella review and meta-analyses of controlled trials

Yihan He,^{1,2} Yihong Liu,^{1,2} Brian H May,¹ Anthony Lin Zhang,¹ Haibo Zhang,^{1,2} ChuanJian Lu,^{1,2} Lihong Yang,^{1,2} Xinfeng Guo,^{1,2} Charlie Changli Xue^{1,2}

To cite: He Y, Liu Y, May BH, *et al.* Effectiveness of acupuncture for cancer pain: protocol for an umbrella review and meta-analyses of controlled trials. *BMJ Open* 2017;7:e018494. doi:10.1136/bmjopen-2017-018494

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-018494>).

Received 11 July 2017

Revised 9 November 2017

Accepted 10 November 2017



CrossMark

¹China-Australia International Research Center for Chinese Medicine, RMIT University, Melbourne, Victoria, Australia

²Guangdong Provincial Academy of Chinese Medical Sciences, Guangdong Provincial Hospital of Chinese Medicine and The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China

Correspondence to

Professor Xinfeng Guo; drguoxinfeng@163.com and Dr Charlie Changli Xue; charlie.xue@rmit.edu.au

ABSTRACT

Introduction The National Comprehensive Cancer Network guidelines for adult cancer pain indicate that acupuncture and related therapies may be valuable additions to pharmacological interventions for pain management. Of the systematic reviews related to this topic, some concluded that acupuncture was promising for alleviating cancer pain, while others argued that the evidence was insufficient to support its effectiveness.

Methods and analysis This review will consist of three components: (1) synthesis of findings from existing systematic reviews; (2) updated meta-analyses of randomised clinical trials and (3) analyses of results of other types of clinical studies. We will search six English and four Chinese biomedical databases, dissertations and grey literature to identify systematic reviews and primary clinical studies. Two reviewers will screen results of the literature searches independently to identify included reviews and studies. Data from included articles will be abstracted for assessment, analysis and summary. Two assessors will appraise the quality of systematic reviews using Assessment of Multiple Systematic Reviews; assess the randomised controlled trials using the Cochrane Collaboration's risk of bias tool and other types of studies according to the Newcastle-Ottawa Scale. We will use 'summary of evidence' tables to present evidence from existing systematic reviews and meta-analyses. Using the primary clinical studies, we will conduct meta-analysis for each outcome, by grouping studies based on the type of acupuncture, the comparator and the specific type of pain. Sensitivity analyses are planned according to clinical factors, acupuncture method, methodological characteristics and presence of statistical heterogeneity as applicable. For the non-randomised studies, we will tabulate the characteristics, outcome measures and the reported results of each study. Consistencies and inconsistencies in evidence will be investigated and discussed. Finally, we will use the Grading of Recommendations Assessment, Development and Evaluation approach to evaluate the quality of the overall evidence.

Ethics and dissemination There are no ethical considerations associated with this review. The findings will be disseminated in peer-reviewed journals or conference presentations.

PROSPERO registration number CRD42017064113.

Strengths and limitations of this study

- The three components will provide comprehensive, clinically relevant assessments of the effectiveness and safety of acupuncture and related therapies for cancer pain.
- The umbrella review will provide a quality-appraised overview of existing systematic reviews.
- Meta-analyses will provide assessments of the randomised controlled trial evidence for specific acupuncture therapies and types of cancer pain.
- Analyses of non-randomised studies will identify consistencies and inconsistencies in evidence between study types.
- Anticipated limitations include study quality, diversity between studies and difficulties in synthesising and grading evidence from different types of clinical studies.

BACKGROUND

For people with cancer, pain is a distressing and intractable symptom with a prevalence rate of over 70%.¹ Two-thirds of patients in the advanced stage of cancer suffered from pain; more than half of patients undergoing anticancer treatment experienced pain and nearly 40% of patients after curative treatment still complained about pain. Among these patients, 40% graded their pain as moderate to severe (Numerical Rating Scale (NRS) Score ≥ 5).² As the possibility of early diagnosis and the improvement of curative technologies prolong survival time for patients affected by cancer,³ the requirement for alleviation of pain has been highlighted.⁴ Enormous advancements in knowledge of cancer pain and pain management have been achieved.^{5 6} Notably, the WHO analgesic ladder offers a systematic approach to pain relief.^{7 8} However, cancer pain control remains a critical challenge globally,^{9 10} including issues associated with inadequate pain relief, analgesic addiction and the side effects of pharmacological interventions.¹¹⁻¹⁴

Clinical studies have shown benefits of acupuncture and related therapies for supportive and palliative care in cancer, by diminishing side effects of conventional therapies, relieving cancer-related concomitant symptoms and improving overall quality of life.^{14–17} Acupuncture and acupressure are listed in the National Comprehensive Cancer Network oncology guidelines as integrative interventions for adult cancer pain.¹⁸ A detailed guideline has been developed for acupuncture application in the management of pain and non-pain indications in patients with cancer.¹⁹

Traditionally, acupuncture involves the manual insertion of fine needles into specific loci on the body and its associated techniques include the application of pressure without needles (acupressure) and the application of heat (moxibustion). More modern techniques include electrical stimulation of needles (electroacupuncture) and skin areas (transcutaneous electrical nerve stimulation (TENS)), and the application of light lasers instead of needles (laser acupuncture).²⁰

An increasing number of randomised controlled trials (RCTs) of acupuncture for cancer pain have been conducted over the years. From the perspective of research design for clinical trials, acupuncture presents a range of challenges. Acupuncture included a variety of methods and techniques which may not be directly comparable.^{20,21} It is difficult to blind personnel and participants in RCTs. Sham/placebo acupuncture devices have been developed, but there is some controversy about whether these and other control methods used in acupuncture studies are truly inert.^{21–23} Another issue is whether the manipulation technique(s) used by the acupuncturist and the number of needles inserted impact on analgesia in a manner similar to medication dosage.^{21,24} Further, in traditional acupuncture, the intervention is not standardised and can be adjusted according to the syndrome (Zheng) of the individual patient.^{25,26} One approach to addressing the need to assess acupuncture in realistic settings has been the adoption of pragmatic trial designs.^{27,28} Furthermore, in studies of cancer pain, there can be considerable variation in the type of cancer and likely causes of the pain.²⁹ All these factors present issues when assessing the effects of acupuncture and related therapies in cancer pain and may limit the extent to which meta-analysis approaches are appropriate.

The need for this work

One review concluded the accumulated evidence suggested that acupuncture could be beneficial for pain and other symptoms in patients with cancer,³⁰ but a Cochrane systematic review concluded that evidence was insufficient to determine whether acupuncture was effective for the management of adult cancer pain. The conclusions were limited by small sample sizes and heterogeneity in methodology, cancer populations and acupuncture techniques.²¹

There are a number of systematic reviews related to acupuncture for cancer pain.^{21,31–38} One included

acupuncture for pain relief along with other outcomes,³⁵ while others discussed acupuncture and other Chinese medicine therapies for cancer care.^{36,37} Of the systematic reviews that explicitly evaluated the effectiveness of acupuncture for cancer pain management, some included RCTs for all types of cancer,^{33,34} while some specifically focused on acupuncture for particular conditions.^{31,32,38} Some reviews included Chinese databases^{32–37} but others limited searches to English language databases.^{21,31,38}

All these systematic reviews limited their inclusion criteria to RCTs. However, other types of clinical studies have been published^{39,40} and additional RCTs have been published in recent years.^{41–44} Given the variety of acupuncture and related therapies in current use in integrative cancer therapy and the diversity of cancer populations in which acupuncture has been applied, there is value in conducting a review that aims at integrating multiple levels of evidence. Systematic reviews generally focus on RCTs, but when the RCT evidence is not sufficient to address clinical questions, the inclusion of non-randomised studies can provide supporting evidence, may improve the generalisability of the conclusions, and can inform decision-makers of the totality of the available clinical evidence.⁴⁵

This study takes an umbrella review approach⁴⁶ to summarise the results of published reviews of acupuncture and related therapies for cancer pain. In addition, data from all types of clinical trials will be synthesised and analysed to arrive at a comprehensive evaluation of the effectiveness of each of the acupuncture and related interventions for specific categories of cancer pain.

OBJECTIVES

Umbrella reviews aim to provide synthesised and appraised evidence on a broad topic area for decision-makers in healthcare, including patients, physicians and policy-makers.⁴⁶ The present study: (1) conducts an umbrella review that aims to synthesise the findings of existing systematic reviews and meta-analyses⁴⁶; (2) conducts a systematic review and meta-analyses of randomised clinical trials and (3) summarises results of other types of clinical studies in order to assess the broad body of clinical evidence, inform clinical practice and identify directions for future clinical trials and other research. The following questions will be addressed: (1) Are acupuncture and related therapies effective for relieving pain associated with cancer? (2) Do acupuncture therapies enable reduction in analgesic consumption? (3) Are the effects (if any) related to the specific type or stage of cancer, the cancer therapies, degree of pain, the type of intervention or other variables?

METHODS

This protocol was developed according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement (online supplementary file

1)^{47 48} and has been registered on PROSPERO (no. CRD42017064113). The anticipated start date of this study is 01/12/2017.

DESIGN

This study comprises three main components:

1. An umbrella review of systematic reviews and meta-analyses.
2. A systematic review of randomised controlled studies with meta-analyses of outcome data (if possible).
3. Summaries of the results of non-randomised clinical studies on acupuncture and related therapies for cancer pain.

We have performed a scoping literature review of all cancer pain-related publications in the Cochrane library. This preparatory step helped define the inclusion criteria, develop the literature search strategies and determine the data to be extracted from eligible reviews and clinical studies.

ELIGIBILITY CRITERIA

Types of studies

Articles published in English or Chinese including:

1. systematic reviews and/or meta-analyses of the effects of acupuncture and related therapies on pain relating to cancer;
2. RCTs (with or without blinding) including cross-over designs and pragmatic trials;
3. non-randomised studies, including case-control studies, case series studies, cohort studies, concurrently controlled studies, cross-sectional studies, historically controlled studies, time series studies and case studies.^{45 49}

Types of participants

Adult participants with cancer pain, including pain directly caused by the development of cancer and pain related to treatments for cancer.¹⁸

Types of intervention

We will consider acupuncture and related therapies regardless of needling techniques and stimulation method, including manual acupuncture, electroacupuncture, ear acupuncture, acupressure, moxibustion, TENS and combinations of these. Treatments in the comparison groups can be sham/placebo acupuncture, pharmacotherapy or no additional intervention to usual care.^{50 51}

Types of outcome measures

We will consider systematic reviews and clinical studies that report numerical data on one or more of the following outcomes:

1. Patient-reported pain intensity or pain relief measured using a Visual Analogue Scale, Verbal Rating Scale, NRS,⁵² the McGill Pain Questionnaire,⁵³ the Brief Pain Inventory⁵⁴ or other validated outcome measures.⁵⁵

2. Quality of life measured using validated scales, including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire,⁵⁶ the General Version of the Functional Assessment of Cancer Therapy,⁵⁷ the Edmonton Symptom Assessment System⁵⁸ or other validated scales.⁵⁹
3. Consumption of analgesics including opioids and non-opioids.¹⁸
4. Frequency of breakthrough pain⁶⁰ and rescue medication use or dosage.
5. Safety of the acupuncture intervention including adverse events and withdrawals for any reason.

SEARCH STRATEGY

To identify systematic reviews and/or meta-analyses of acupuncture and related therapies for cancer pain, we will search PubMed (1966 to present), Embase (1974 to present) and CINAHL (1982 to present), JBI Database of Systematic Reviews and Implementation Reports (2003 to present), the Cochrane Database of Systematic Reviews (1992 to present) and the PROSPERO register.⁴⁶ Considering that acupuncture is frequently used in China, we will search the following Chinese databases: Chinese Biomedical Literature Database (CBM, 1978 to present), VIP Database for Chinese Technical Periodicals (CQVIP, 1989 to present), China National Knowledge Infrastructure (CNKI, 1994 to present) and Wanfang Data (1998 to present). The search strategy for PubMed/MEDLINE database is shown in online supplementary file 2.

To identify clinical studies, we will search PubMed, Embase, CINAHL and the Chinese databases CBM, CQVIP, CNKI and Wangfang Data. Search terms will generally consist of three groups: (1) clinical condition (cancer, tumour, carcinoma, neoplasm, pain, analgesia, etc); (2) intervention (acupuncture, electroacupuncture, auriculotherapy, acupoint, needle, acupressure, etc) and (3) study type (random, controlled trial, cohort, case-control, comparative study, case series, etc), with adjustments for different databases.⁶¹

In addition, we will search clinical trial registries, dissertations and grey literature.⁶¹

Screening and selection

Following the comprehensive searches for systematic reviews and clinical studies, two reviewers (YHH and YHL) 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 will be consulted to resolve any disagreement by discussion and consensus.⁶²

DATA EXTRACTION

All data extraction will be undertaken by two independent reviewers (YHH and YHL) who will extract information using predesigned forms.

For systematic reviews, we will extract^{46 63}:

1. identification information (publication year, first author);
2. general information (objectives, type of review, target condition, comparator);
3. methodological characteristics (included study type, any restriction on included studies, databases searched and date ranges, methods of data extraction and assessment of study quality, meta-analysis method);
4. participants (inclusion/exclusion criteria, type of cancer, type of pain);
5. interventions (type of acupuncture and related therapy, type of control intervention);
6. included data (primary and secondary outcomes, number of studies, numbers and types of participants, country and setting of studies);
7. synthesis method, summary and conclusions.

For all types of clinical studies, we will extract^{62 64 65}:

1. identification information (publication year, first author);
2. general information (country, study type, setting, number of centres, sample size, study duration);
3. participants (type and/or stage of cancer, age, sex, type of pain, pain intensity before treatment, Chinese medicine syndrome);
4. interventions (type of acupuncture and related therapy, acupuncture point selection, treatment frequency, number of sessions, duration of each session, point stimulation/manipulation method(s));
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, type and number of adverse events in each group).

For both systematic reviews and clinical studies, information related to syndrome/pattern of Chinese medicine will be extracted, including therapeutic principles, Chinese medicine syndrome/pattern and related outcomes.⁶⁶

We will try to contact corresponding authors for any missing data or clarification for unclear information.^{46 62}

QUALITY ASSESSMENT

Two reviewers (YHH and YHL) will appraise the quality of the included reviews independently according to the Assessment of Multiple Systematic Reviews (AMSTAR) tool.⁶⁷ A systematic review that reports one item in accordance with AMSTAR receives one point with a maximum score of 11 points. A score of 8–11 represents high quality, while 4–7 means medium quality, and a review with a score below 4 is judged as low quality.

The quality of the RCTs will be assessed using the risk of bias tool developed by the Cochrane Collaboration. 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) and attrition bias (incomplete outcome data).⁶⁸

We will carry out quality assessment for non-randomised controlled studies according to the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies in meta-analyses.^{69 70}

Evidence synthesis for systematic reviews

We will report a summary of the findings of the systematic reviews and meta-analyses. For each review, this will include: the type of acupuncture and related therapies; syndrome/pattern in Chinese medicine, the type of cancer pain included (related to neoplasm, related to cancer therapy); the number of included clinical studies; numbers of participants; the outcome measures assessed; any meta-analysis results for each outcome, heterogeneity and reviewers' conclusions. 'Summary of evidence' tables will be used to present syntheses of the overall evidence for each type of cancer pain, type of acupuncture intervention, type of control intervention and outcome measure.⁴⁶

Evidence synthesis for RCTs

We will use data extracted from published RCTs to perform meta-analyses, calculating effect size and 95% CI by the random-effects model. Heterogeneity among trials will be identified by the χ^2 test and reported as I^2 .⁷¹ We will assess publication bias using funnel plots and Egger's test for asymmetry when at least 10 trials are available.⁷²

When conducting meta-analysis, for each outcome studies will be grouped according to: (1) the type of acupuncture (eg, manual acupuncture, electroacupuncture, ear acupuncture, acupressure, moxibustion and TENS); (2) the comparator (eg, placebo/sham acupuncture, pharmaceutical therapy, usual care only) and (3) the specific type of pain such as breakthrough pain,⁷³ cancer-induced bone pain⁷⁴ or aromatase inhibitor-associated arthralgia.⁷⁵

Sensitivity analyses are planned based on clinical factors (cancer type, degree of pain, Chinese medicine syndrome/pattern), acupuncture method (stimulation method, dosage, specific acupuncture points), methodological characteristics (sample size, risk of bias), and presence of statistical heterogeneity as applicable.

Evidence synthesis for non-randomised studies

First, we will tabulate the characteristics of each of the non-randomised studies, the outcome measures and the reported results. Where possible, studies will be grouped according to study type, type of acupuncture intervention, type of control (if applicable), type of cancer pain and study quality.

We will compare the results of the meta-analyses of the RCTs with the reported results of non-randomised studies when the studies are similar in terms of acupuncture type and type of cancer pain. If the results for the effects of the RCTs and non-randomised studies are consistent and show the same trend, the evidence from

the non-randomised studies may provide support that an effect is likely to exist or not exist. On the other hand, if the findings from the non-randomised studies are inconsistent with the evidence from the RCTs, we should be more cautious in the interpretation of the RCT evidence. In balancing the two bodies of evidence, we will need to take a number of factors into consideration including the numbers of participants in the studies, the quality of the studies and the clinical relevance of the interventions. In synthesising the results of the different types of clinical studies, we will consider the non-randomised studies as complementary to the RCTs.⁴⁵

We will use the Grading of Recommendations Assessment, Development and Evaluation approach to evaluate the quality of the overall evidence.⁷⁶

CONCLUDING REMARKS

This review will build on previous assessments of the evidence for acupuncture and related therapies in the management of cancer pain, by synthesising the results of previous systematic reviews, conducting updated meta-analyses of the outcomes of RCTs, summarising evidence from non-randomised clinical studies and synthesising evidence from multiple sources.

In assessing the results of non-randomised studies, a number of issues will need consideration, including the sources of bias in the selection of participants, confounding effects of variability in baseline characteristics, issues relating to potential bias in participant-reported outcomes and the effects of attrition bias.^{77–80}

In synthesising and comparing the results of non-randomised studies and RCTs, we will need to pay attention to issues relating to the external validity of the interventions, whether the reported results from these clinical studies may be generalised to clinical populations, and whether the interventions reflect current clinical practice.^{81–83} In cases where no RCT evidence is available for a particular intervention, type of cancer pain or outcome measure, we will need to base assessments on the available non-randomised studies while acknowledging the limitations of this level of evidence.⁴⁵ In such cases, the non-randomised studies may indicate future directions for RCTs, for example, the pilot study on acupuncture for cancer-induced bone pain³⁹ and the pragmatic pilot study on acupuncture for uncontrolled cancer pain,⁴⁰ both suggest that further RCTs are warranted.

Syndrome/pattern (Zheng) differentiation is an essential notion in the theory of Chinese medicine that informs the selection and application of therapeutic interventions.⁸⁴ RCTs and systematic reviews have examined the effects of syndrome differentiation in a number of disorders.^{85–86} Syndrome distribution among patients with advanced cancer with opioid-related constipation has been determined by a cross-sectional study⁸⁷ and treatment based on syndrome differentiation has been suggested.⁶⁶ Where possible, this review will examine effects related to the

application of syndrome/pattern differentiation in the include studies and determine any implications for future clinical studies.

A likely limitation with the overall quality of the evidence is inadequate methodological reporting in many articles published in Chinese. Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture have not been adopted by many Chinese language journals and information required for assessment of risk of bias may not be available in reports of RCTs.^{88–91} Poor quality of reporting in RCTs on acupuncture for cancer pain in Chinese journals makes it difficult to assess the validity of the results.⁹² These issues will be considered when conducting sensitivity analyses based on methodological quality and when interpreting results.⁹³

The proposed review has several strengths. The umbrella review component will provide an overview of the field and identify issues relating to meta-analysis in a condition as diverse as cancer pain and highlight considerations that will need to be taken into account in the systematic review component. A strength of the systematic review component is the inclusion of multiple Chinese and English language databases and grey literature which should ensure a comprehensive search of the literature. A further strength is any meta-analyses will be informed by rigorous methodology as detailed in the Cochrane Handbook for Systematic Reviews of Interventions.⁹⁴ The addition of the component on non-randomised studies will strengthen the overall project by providing an extended coverage of the clinical literature which may provide supporting evidence to complement the RCT literature and fill any clinically relevant gaps.

Anticipated limitations and challenges include issues relating the quality of the available evidence as outlined above, diversity between clinical studies precluding data pooling in meta-analyses, small sample sizes limiting confidence in outcomes, and difficulties in synthesising and grading evidence from different types of clinical studies. Heterogeneity between the included studies is likely to lead to bias in the results; therefore, we will exercise caution in the interpretation of the results and take a critical approach when assessing the overall evidence.^{95–97}

Despite of these anticipated limitations, evaluating the effectiveness of acupuncture for cancer pain is of great importance for clinical practice given the challenges of pain alleviation in patient care.^{1–3} We will consider the issues relating to the scope and overlap of systematic reviews included in the umbrella review,⁹⁸ whether their conclusions are affected by the results of the updated meta-analysis, and whether the results reported by the non-randomised studies are consistent or inconsistent with the results of the meta-analyses. By identifying the strengths, weaknesses and any gaps in the available clinical evidence with regard to particular types of acupuncture interventions or particular

outcomes that have been assessed in clinical studies, the results of this review can inform future clinical research. Furthermore, by conducting a comprehensive evaluation of multiple types of studies, we anticipate identifying promising acupuncture interventions for specific clinical applications in the management of cancer pain.

Contributors This protocol was first conceived by YH, with critical contributions from the other authors. XG and CCX obtained funding for this study. YH and YL wrote the first draft of the protocol and submitted the registration on PROSPERO. BHM, ALZ and HZ provided help to design and edited the manuscript. C-JL and LY revised the manuscript. All authors contributed constructive comments on the manuscript and approved the final paper. YH, XG and CCX are the guarantors for the publication and are fully responsible for the paper.

Funding Guangdong Provincial Academy of Chinese Medical Sciences, China, and RMIT University through the China-Australia International Research Centre for Chinese Medicine as well as PhD scholarship support to the first author provided by the School of Health and Biomedical Sciences, RMIT University.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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