



# BMJ Open Comparative efficacy of different acupuncture therapies on cancer-related insomnia: protocol for a systematic review and network meta-analysis

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## ABSTRACT

**Introduction** Cancer-related insomnia (CRI), as a common complication in cancer survivors, may further lead to depression, anxiety and other symptoms. Acupuncture therapy is a promising therapeutic strategy for CRI. The effectiveness of acupuncture therapy on CRI has been validated by several relevant meta-analyses. Questions remain, however, including which acupuncture regimen is optimal. We aim to conduct the first network meta-analysis to compare different acupuncture therapies, rank their effectiveness and assess which approach could be optimal for treatment of CRI.

**Methods and analysis** A comprehensive search of PubMed, Cochrane Library, Web of Science, Embase, China National Knowledge Infrastructure, Wanfang Database, VIP Database (China Science and Technology Journal Database), and China Biology Medicine (from inception until 1 March 2022) will be carried out to identify randomised controlled trials (RCTs) of acupuncture therapy for insomnia in cancer survivors, reported in English or Chinese. Reviews, animal studies, non-RCT studies, editorials and other secondary insomnia studies will be excluded. The primary outcome measure will be the Pittsburgh Sleep Quality Index. Pairwise meta-analysis will be performed in Stata and network meta-analysis by OpenBUGS, R and Stata. Network plots and funnel plots will be used to show the scale of studies and participants for each intervention and the potential publication bias, respectively. Both heterogeneity and consistency will be evaluated by R. ORs with 95% CIs and mean differences with 95% CI will be calculated in OpenBUGS and transformed into league figure and surface under the cumulative ranking by Stata to visualise the results.

**Ethics and dissemination** Ethical committee approval for this review is unnecessary since the data used will be extracted from pre-existing literature. The results will be submitted for publication in a peer-reviewed journal and presented at international academic conferences.

## INTRODUCTION

Cancer-related insomnia (CRI), which belongs to secondary insomnia, is a common complication of cancer. With a high incidence of 14%–80% in cancer survivors, CRI is particularly prevalent in lung, breast, and

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Strengths of this study include a broad search strategy which allows for more studies to be included.
- ⇒ We investigate the therapeutic effect of acupuncture therapies for patients diagnosed with cancer-related insomnia rather than for sleep quality, to avoid including cancer survivors without insomnia.
- ⇒ The inclusion of studies with different types of cancer and the data extraction based on descriptive information may cause potential heterogeneity.
- ⇒ We will only search Chinese and English databases, which may result in language bias.

head and neck cancers.<sup>1–3</sup> While the pathogenesis remains unclear, cancer diagnosis and treatment side effect are likely to be the initiating factors in the development of CRI, which includes but are not limited to pain, fatigue, hot flashes, nausea, anxiety, depression, ward environment and caregivers' sentiment.<sup>4–7</sup> CRI often degrades the quality of life of cancer survivors, further contributing to anxiety, depression, fatigue, and even cognitive impairment.<sup>6 8 9</sup> Worse still, those symptoms may in turn exacerbate insomnia. Unfortunately, despite the great prevalence and clinical significance of CRI in cancer survivors, it has been mentioned that the symptoms of CRI are seldom identified or treated properly in cancer clinical practice. Moreover, cancer survivors may even falsely judge CRI as a natural and transient reaction to the cancer diagnosis or treatment.<sup>6 10 11</sup> To improve the quality of sleep and life of cancer survivors, it is of great importance to have an effective and safe treatment for CRI.

Nowadays, cancer survivors with CRI are mainly treated with pharmacotherapy. Dimsdale *et al*<sup>12</sup> confirmed that eszopiclone can improve self-reported sleep quality and increase sleep duration. Palmer *et al*<sup>13</sup> verified that melatonin can regulate sleep rhythms and

improve the quality of sleep. However, pharmacotherapy has substantial side effects, including dependence, tolerance, residual daytime sedation and headache.<sup>14 15</sup> Hence, more and more cancer survivors are turning to complementary and alternative medicine (CAM). CAM for CRI includes Chinese herbal medicine, cognitive behavioural therapy (CBT), hygiene practices and music therapy, and so on. However, these interventions suffer from limitations in terms of undesired effects, clinical efficacy, popularity and professional deficiency.<sup>16</sup> Acupuncture therapy, on the contrary, is a potential CAM and has been used to manage and mitigate CRI in some studies.<sup>17-19</sup> Acupuncture therapy is an intervention in which the acupoints are pierced with fine needles for therapeutic purposes. Besides traditional needle acupuncture, there are other stimulations such as electroacupuncture, acupressure, auricular therapy, acupoint application, transcutaneous electrical acupoint stimulation (TEAS), and so on.<sup>20</sup> Several meta-analyses have indicated that acupuncture, electroacupuncture, auriculotherapy and moxibustion could lengthen sleep duration, shorten sleep latency and enhance sleep efficiency.<sup>21-24</sup> However, instead of comparisons among the various acupuncture regimens, only comparisons between acupuncture therapy and other therapies or placebo have been made in the aforementioned studies; thus, it is not clear which one is the optimal acupuncture regime for CRI. In summary, this study will compare and rank the efficacy of various acupuncture therapies to evaluate the most appropriate regimen for CRI. The results will provide clinicians with more information about evidence-based components to alleviate CRI.

## Methods and analysis

### Design

We plan to do a systematic review and network meta-analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) reporting guidelines<sup>25</sup> were followed in the preparation of this protocol. The review will be conducted in accordance with guidance from the *Cochrane Handbook*<sup>26</sup> and we will use PRISMA 2020 guidance<sup>27</sup> for reporting the results of the review.

### Criteria for study selection

#### Participants

Cancer survivors diagnosed with CRI ( $\geq 18$  years) were included, regardless of sex, nationality and the type or stage of neoplasm.

#### Interventions

All types of acupuncture regimens will be included, such as acupuncture, moxibustion, electroacupuncture, acupressure, TEAS, acupoint application and auriculotherapy. Definitions and general operation procedures of the different acupuncture therapies are presented in online supplemental file 1.

### Comparators

The following intervention regimes will be included to be compared with acupuncture therapies: (1) Sham acupuncture or usual care. (2) Pharmacotherapy. (3) Other interventions such as CBT.

### Outcome measures

The primary outcome is Pittsburgh Sleep Quality Index (PSQI). As a valid clinical insomnia-related scale when compared with other insomnia-related scales, PSQI has demonstrated strong reliability and validity, as well as moderate structural validity, and is the most commonly applied in numerous large-scale randomised controlled trials (RCTs) of insomnia.<sup>28-30</sup> Previous meta-analyses for CRI and our preliminary search results also indicated that PSQI is frequently used. Therefore, we select PSQI as the primary outcome.<sup>23 31</sup> The secondary outcomes include other sleep-related questionnaires such as Athens Insomnia Scale, Insomnia Severity Index and some questionnaires relevant to pain, fatigue, negative emotions and quality of life, such as Brief Fatigue Inventory, Hamilton Depression Rating Scale and Self-Rating Anxiety Scale.

### Types of studies

Inclusion will be limited to peer-reviewed RCTs, aiming to indicate the comparison of various interventions. As for language, only articles in English or Chinese will be included. Study designs that are non-RCTs, animal studies, qualitative studies, narrative reviews, editorials, case reports, uncontrolled studies and other secondary insomnia studies will be excluded.

### Data sources and search strategy

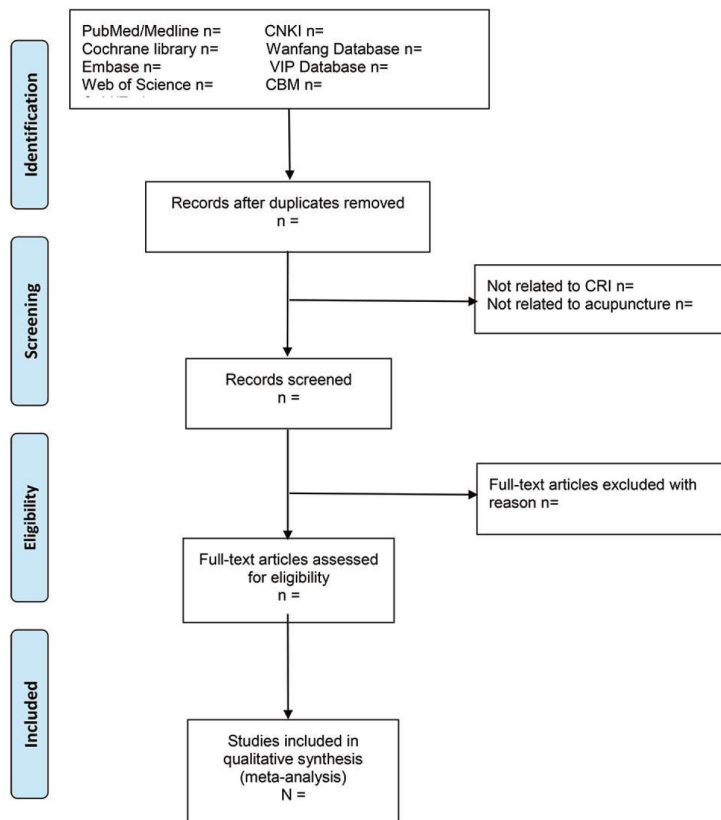
We will search eight electronic databases from inception until 1 March 2022, including PubMed, Cochrane Library, Web of Science, Embase, China National Knowledge Infrastructure, Wanfang Database, VIP Database (China Science and Technology Journal Database) and China Biology Medicine. We will search the relevant literature by combining subject terms with free terms. Full search strategies for all databases are listed in online supplemental file 2.

### Screening and selection

All electronic database records will be input into EndNote X9. After initial screening by examining titles and abstracts, a full-side review and evaluation will be conducted with the full texts of all relevant trials. Two investigators will scan each record respectively, and if a consensus cannot be reached, a third investigator will participate in the debate and draw a conclusion. Only the most informative and unabridged record of any duplicate articles will be included. Excluded studies will be documented and explained. The process of screening will be shown by a PRISMA flow chart as [figure 1](#).

### Assessment of risk of bias

The risk of bias will be appraised according to the Cochrane risk-of-bias tool (ROB) V.2.0, and the risk of



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process. CRI, cancer-related insomnia. CNKI, China National Knowledge Infrastructure. VIP, China Science and Technology Journal Database. CBM, China Biology Medicine disc.

bias will be classified into ‘low risk’, ‘high risk’ or ‘some concern’ according to the level of bias represented by the tool. Using ROB V.2.0, two investigators will assess all included studies. If necessary, the third investigator will request adjudications.

### Data extraction

Two investigators will independently extract relevant data from included studies into a database within Excel 2019. The third investigator will be the judge in case of doubts or non-conformity, and any disagreements will be resolved by discussion. And if data are demonstrated as figures, it can be retrieved by GetData Graph Digitizer. The following information will be extracted from each included research:

1. Studies information: title, first author, publication year, first author’s country, trial region or country, and registration of clinical trial registry.
2. Patient information: sample size, sex, the type and stage of neoplasm, acupuncture therapy plan, time, acupoints, and types of comparison.
3. Outcomes information: sample size, outcomes and measurement.

### Data synthesis and statistical analyses

#### Pairwise meta-analysis

Prior to the network meta-analysis, a pairwise meta-analysis for each comparison will be conducted to

explore heterogeneity via Stata. Weighted mean differences (WMDs) with 95% CIs will be adopted for continuous outcomes and ORs with 95% CIs for dichotomous outcomes. Heterogeneity will be estimated using the  $I^2$  statistic. A random-effects model will be adopted if  $I^2 > 50\%$ , or else, a fixed-effects model.

#### Network meta-analysis

Network meta-analyses will be carried out using OpenBUGS, Stata and R. ORs with 95% CIs will be calculated for dichotomous outcomes and WMDs with 95% CIs for continuous outcomes. The scale of studies and participants for each intervention are shown in network plots by Stata. Both consistency and heterogeneity will be analysed by R. ORs with 95% CIs and mean differences (MDs) with 95% CIs will be analysed by OpenBUGS. Then the results will be transformed into the surface under the cumulative ranking curves and league figures by Stata to visualise the comparisons and rank the effectiveness of all interventions. In addition, funnel plots will be applied to evaluate the potential bias of the publication.

#### Subgroup and sensitivity analyses

Subgroup analysis and sensitivity analysis will be performed if necessary.

### Quality of evidence

Grading of Recommendations Assessment, Development and Evaluation system will be applied to evaluate the quality of evidence, with three factors (residual confounding, dose-effect relation and large effect) enhancing the quality and five factors (study limitations, inconsistency, indirectness, publication bias and imprecision) lowering the quality, and the quality of each included research will be classified into four grades: very low, low, moderate and high.

### Patient and public involvement

None.

### Ethics and dissemination

Ethical committee approval for this review is unnecessary since the data used will be extracted from pre-existing literature. The results will be submitted for publication in a peer-reviewed journal and presented at international academic conferences.

## DISCUSSION

The incidence of cancer continues to rise, but the mortality rate decreases with the implementation of secondary prevention and treatment advances,<sup>32–34</sup> resulting in a substantial number of cancer survivors. In addition, the incidence of CRI among cancer survivors was elevated. Therefore, it is of great significance for clinical practice on how to effectively alleviate CRI and improve the quality of life of cancer survivors. Acupuncture therapy, as a traditional Chinese medicine treatment, has contributed to the alleviation of CRI, and has been proven to be effective and safe in the treatment of CRI in low to moderate evidence. Given the variety of acupuncture therapies, and the lack of studies comparing them, clinicians are unable to estimate the curative effect of the various regimen forms. While reviews comparing some of the acupuncture therapies have been provided earlier,<sup>22</sup> <sup>23</sup> several are in need of updating, and so far there is no network meta-analysis comparing the merits of all existing acupuncture therapies to narrow this knowledge gap. In light of these concerns, our study aims to generate a serviceable ranking of acupuncture therapies in the treatment of CRI via network meta-analyses. We recognise the potential limitations of this study. First, only English and Chinese articles will be included, so any related research in other languages could be missed. Second, as in other reviews and network meta-analyses, the conclusions are restricted by the number and quality of available studies, the level of detail of the PICO (population, interventions, comparisons, and outcomes) contents and the potential heterogeneity of interventions of included studies. To reduce the limitations, all eligible studies will be covered as far as possible with relatively stringent inclusion criteria, and if necessary, subgroup analysis will be carried out based on pairwise meta-analysis.

This systematic review will synthesise the available information to give updated and comprehensive evidence for the treatment of CRI with acupuncture therapy and rank the different acupuncture regimens for CRI treatment. The results of this network meta-analysis will share superior recommendations for clinicians regarding evidence-based components to alleviate CRI and provide reliable evidence for the subsequent related research.

**Contributors** The original idea was conceived by LC. LC, SX and ZJ drafted the manuscript for this protocol. SX, ZJ, YT, XS and LC participated in the design of the study and the setting of the inclusion and exclusion criteria. LC and SX designed the search strategy, and XL will be responsible for the modifications. YT and XS will perform the literature screening and data extraction. LC, SX and ZJ will be in charge of the software operation. LC and XL will review the overall work. All authors have read and approved the publication of the protocol.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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**Data availability statement** Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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