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Effectiveness of Non-Pharmacological Interventions for Pain Management in Cancer Patients: A protocol for Systematic Review and Network Meta-Analysis

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Effectiveness of Non-Pharmacological Interventions for Pain Management in Cancer Patients: A protocol for Systematic Review and Network Meta-Analysis

ABSTRACT

Introduction

Pain management in cancer patients is a critical aspect of oncological care, yet remains challenging with current pharmacological therapies. Non-pharmacological interventions, offering potential benefits without the adverse effects of drugs, have gained attention. However, the effectiveness of these diverse non-pharmacological interventions is not well understood, creating a gap in clinical practice. This study aims to conduct a systematic review and network meta-analysis to evaluate the efficacy of various non-pharmacological interventions for pain management in cancer patients, providing evidence-based guidance for clinicians and patients.

Methods and analysis

A systematic review and Bayesian network meta-analysis will be conducted. Six electronic databases will be searched to identify randomized controlled trials assessing the efficacy of interventions for cancer pain. Literature screening should be independently performed by two reviewers. A network meta-analysis will evaluate the effectiveness of various non-pharmacological interventions for cancer pain. A second network meta-analysis will compare the efficacy of different non-pharmacological interventions in relieving pain interference in patients with cancer pain. Bayesian 95% credible intervals will be used to estimate the pooled mean effect size for each treatment, and the surface under the cumulative ranking area will be employed to rank the effectiveness of the treatments.

Ethics and dissemination

Ethical approval is not required for this systematic review of the published data. Findings will be disseminated via peer-reviewed publication.

PROSPERO registration number

PROSPERO registration number CRD42024483025.

Pain in cancer patients is a common symptom, characterized not only by its high prevalence but also by its significant impact on the patients (1-3). A systematic review found that the overall incidence of pain in cancer patients is 44.5%, with 30.6% of patients experiencing moderate to severe pain (1). Beyond its high prevalence, cancer pain causes considerable physical discomfort and affects psychological and social functions, leading to symptoms such as fatigue, anxiety, and depression (2-4). This, in turn, reduces the quality of life of patients and impacts their work efficiency (2). The causes of pain in cancer patients are diverse, including tumor growth, side effects of treatment, among others (5, 6). The pain experience also varies depending on the type of cancer, its stage, and individual factors (6). Therefore, it is essential to adopt personalized pain management approaches for patients.

Interventions for pain in cancer patients include both pharmacological and non-pharmacological methods. A substantial body of research has confirmed the effectiveness of opioid medications and non-steroidal anti-inflammatory drugs (NSAIDs) in the intervention of cancer pain, and these have become standard medications in clinical use (7, 8). However, pharmacological interventions have many side effects and limitations, such as causing gastrointestinal reactions and increasing cardiovascular risks (7, 8). As a result, non-pharmacological treatments are gaining increasing attention. These non-pharmacological interventions include psychological therapies (such as Cognitive Behavioral Therapy and mindfulness), physical interventions (like exercise and acupuncture), and assistive techniques (such as guided imagery and yoga) (9, 10). These non-pharmacological methods not only alleviate pain in cancer patients but also improve their overall quality of life (11). Therefore, it is essential to identify and select effective non-pharmacological interventions.

Network Meta-Analysis (NMA) offers a comprehensive approach that allows researchers to rank a range of non-pharmacological interventions in terms of their

relative effectiveness or ineffectiveness (12). NMA integrates both direct and indirect evidence from a set of studies and can encompass data from multiple treatment modalities, even if these treatments have not been directly compared in Randomized Controlled Trials (RCTs) (12). This method effectively overcomes the main limitation of traditional pairwise meta-analyses, which can only compare two treatment methods at a time (12). Such an analytical approach is crucial for guiding clinical decision-making, developing evidence-based guidelines, and meeting the needs of personalized pain management strategies. In light of this, the aim of our study is to determine the relative effectiveness of various common non-pharmacological interventions for managing pain in cancer patients through NMA.

METHODS AND ANALYSIS

This systematic review has been officially registered with PROSPERO (registration number CRD42024483025) and adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines (13). We commit to conducting the systematic review in alignment with the directives provided in the Cochrane Handbook for Systematic Reviews of Interventions (14). Should there be any necessary modifications to the protocol, these will be duly updated through PROSPERO.

Inclusion and Exclusion Criteria

Studies will be eligible for inclusion if they meet the following PICOS elements:

(1) P (Population):

The study will include adults aged 18 and over who have been diagnosed with cancer and suffer from pain caused by the cancer, with no restrictions on gender.

(2) I (Intervention):

The interventions are non-pharmacological and/or psychological. This means that the intervention measures must be non-invasive or have no chemical effects on the participants.

(3) C (Control):

Other active treatments or control group; Control group was defined as a control that did not receive any active treatment (e.g. treatment as usual, routine treatment, usual activities, waitlist, et al) or an active treatment control condition that provided brief information-based support (e.g. educational activities, communication exercise, et al) or other psychological treatment such as CBT and cognitive therapy (CT).

(4) O (Outcome):

The reduction of pain related to cancer is to be measured using the following validated methods: Visual Analogue Scale (VAS), etc. The relief of pain interference in cancer patients is to be measured using the following validated methods: Multidimensional Pain Inventory (MPI), etc.

(5) S (Study Design):

The study will focuse on Randomized Controlled Trials (RCTs) published in English.

Studies will be excluded from our systematic review if they meet the following criteria: (1) published in languages other than English; (2) not a RCT design; (3) use or apply medical or pharmacological interventions; (4) include patients awaiting biopsy/diagnosis or who have already overcome the disease; (5) solely include children or adolescents; (6) involve pain studies related to pathologies other than cancer or diseases other than cancer; (7) have excessively broad inclusion criteria, where participants do not meet the standards for this systematic review; (8) include participants without a basic level of education or cognitive abilities impaired by disease or any form of mental disability; (9) do not include any outcomes relevant to the purpose of this review.

Data Collection and Search Methodology

Two independent reviewers systematically searched electronic databases, including the Cochrane Library, Web of Science, PubMed, EMBASE, PsycINFO, and Cumulative Index of Nursing and Allied Health Literature (CINAHL) databases to identify relevant studies available until January 10, 2024. In addition, reference lists of selected articles

and related review articles will be manually examined to uncover any potential relevant publications. The comprehensive search strategy is detailed in Appendix A.

Screening and data extraction

We will use EndNote X9 software to manage the database search results. The first step is to remove duplicate studies using the software. Then, two independent reviewers will screen the titles and abstracts of the retrieved studies according to the predefined criteria and exclude those that do not meet the criteria. Next, the same reviewers will read the full texts of the remaining studies and further exclude those that do not meet the criteria, resulting in the final selection of studies. The reviewers will work independently and will discuss any disagreements. If no consensus is reached, a third reviewer will arbitrate the disputed outcome.

Assessment of risk of bias

The researchers will use the Cochrane risk of bias tool to assess the methodological quality of the included studies (15). Two reviewers will independently evaluate the included studies. Any discrepancies in the evaluation will be resolved through discussions or by consulting a third reviewer.

The Cochrane Assessment of Bias tool will be used to assess the methodological quality and to capture the risk of bias in RCTs (15). Each item will be assessed as having low, unclear, or high risk of bias. The Cochrane risk of bias tool evaluated the included studies in the following seven areas: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias.

Missing Data

In instances where data are presented as medians or using alternative measures of variability, these will be transformed into mean and standard deviation (SD) values using established mathematical formulae (16). For data depicted solely in graphical

format, without accompanying numerical details in the text, extraction will be performed utilizing ImageJ software (available at https://imagej.nih.gov/ij/) (17). This process involves measuring the pixel length of graph axes for calibration, followed by determining the pixel length corresponding to the data points of interest (17). In cases where direct data extraction proves unfeasible, attempts will be made to obtain the necessary information from the study authors. Any arising discrepancies during the data extraction process will be resolved through consultation with an appointed adjudicator.

Statistical analysis

Effect measurements

For continuous outcomes, if the outcome is measured using the same scale, the mean difference (MD) and the corresponding 95% CI will be used. If different scales are used to measure related outcomes, the standardized mean difference (SMD) will be calculated (14). Subsequently, we will conduct pairwise meta-analyses and use a random-effects model for each comparison, followed by the generation of network graphs and evaluation to determine the feasibility of the NMA. Afterwards, we will conduct NMA analysis using Bayesian methods.

Network meta-analysis

The execution of the NMA will utilize a Bayesian framework employing Markov chain Monte Carlo (MCMC) methods. This analysis will be implemented using the R Statistical Software, specifically through the Meta, and Gemtc package. Our approach involves running four parallel MCMC chains in the model, and conducting two distinct MCMC simulations to facilitate the comparison of convergence. The Bayesian model will be operationalized through an initial phase of 5,000 burn-in iterations, followed by a subsequent phase of 100,000 simulation iterations. The assessment of convergence will be conducted using the potential scale reduction factor, with an anticipated reduction target of below 1.05 (18, 19).

Heterogeneity, specifically pertaining to direct evidence, and model consistency (direct vs. indirect comparisons) will be evaluated using the node split function within the Gemtc package. This process will facilitate the exploration of sources of heterogeneity

across studies. The comparative analysis of each intervention will be conducted using standardized mean differences (SMD) along with 95% credible intervals, which are akin to the Bayesian equivalent of confidence intervals. Rank probabilities will be used to quantify the likelihood of each intervention's effectiveness. Additionally, the Surface Under the Cumulative Ranking (SUCRA) score will be employed to estimate the probability of an intervention being the most effective (18, 19).

Quality of evidence

The grading of evidence derived from the NMA will be executed in four distinct stages, utilizing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, facilitated by GRADE Pro software (20). The initial step involves presenting the effect sizes and confidence intervals (CIs) for both direct and indirect comparisons across interventions. Subsequently, the second step entails an independent assessment of the quality of evidence for each comparison. The third stage involves the presentation of the NMA results. In the final stage, the quality of evidence underpinning the NMA outcomes is evaluated. For direct comparisons, the grading approach mirrors that of traditional meta-analysis GRADE evidence grading. Indirect comparison evidence grading hinges on downgrading the quality of evidence in cases where direct comparisons are of lower quality. The overall quality of evidence for NMA results, which incorporates mixed (both direct and indirect) comparisons, will be adjudicated based on the higher quality of evidence present in either the direct or indirect comparisons, thus determining the final grade.

Additional analysis

Due to potential variations among the selected studies in terms of study populations, included interventions, and outcome measurements, we will conduct a series of subgroup analyses. We will investigate differences across populations residing in different continents (such as Europe, Asia, etc.), treatment durations (less than 12 weeks vs. more than 12 weeks), age groups (under 20 years, 20-40 years, 40-60 years, over 60 years), and follow-up periods (less than 4 weeks, 5-12 weeks, more than 12 weeks).

Additionally, we intend to conduct a sensitivity analysis to evaluate the potential impact of the quality of the included trials on the overall findings. This analysis will involve reassessing each outcome by specifically excluding those studies deemed to have a high risk of bias, thus gauging the robustness of our results in relation to the quality of the evidence.

Reporting bias evaluation

Assessment for reporting bias in the meta--analysis will be conducted when the included trials number at least ten (14). This threshold is based on statistical considerations, recognizing that with fewer than ten trials, the power to discern between random variations and genuine asymmetry is significantly compromised. To detect potential reporting bias, we will employ Begg's test for analyzing funnel plots (21). This method involves correlating the magnitude of effect sizes with their variance, where a notable correlation suggests the presence of reporting bias (21). Should asymmetry be observed in the funnel plots, we will consider alternative explanations beyond reporting bias, such as selective reporting of outcomes, inferior methodological quality in smaller studies, or the presence of heterogeneity.

Concluding report

This systematic review will be reported according to the extension of the PRISMA guidance for systematic reviews that include network meta-analysis (22).

We will employ the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as proposed by the GRADE working group, to assess the certainty of efficacy estimations derived from the NMA (20). This evaluation will encompass both direct and indirect comparisons across all outcomes of interest. The quality of these efficacy estimations from the NMA's treatment will be rigorously determined through a four-step evaluation process, ensuring a thorough and academically sound assessment:

Display both direct and indirect treatment estimates for each comparison within the evidence network. The direct effect estimate is derived from a head-to-head comparison,

such as trial A versus trial B. In contrast, the indirect estimate is obtained through the synthesis of two or more direct comparisons sharing a common reference point, for instance, deducing the effects of A versus B by analyzing the results from both trial A versus trial C and trial B versus trial C. This approach ensures a comprehensive and logically coherent assessment of the treatment effects within the network.

Assess the quality of each direct and indirect effect estimate, ensuring a thorough evaluation of their respective validity and reliability.

Provide the NMA estimate for each specific comparison within the evidence network, offering a detailed and comprehensive presentation of these findings.

Evaluate the quality of each effect estimate derived from the NMA, applying rigorous criteria to ascertain the robustness and credibility of these estimates.

A table will be constructed to encapsulate the 'network meta-analysis summary findings', in alignment with the guidelines set forth by the GRADE working group (20). This table will serve as a foundation for evaluating the certainty of evidence. For this evaluation, we will apply the following critical domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Upon completion of this analysis, the certainty of each piece of evidence will be categorized into one of four distinct levels: high, moderate, low, or very low. This structured approach ensures a comprehensive and academically sound assessment of the evidence within our study.

Patient and public involvement

This study will not include patient or public involvement in any stage, encompassing the planning or design phases. No invitation will be extended to patients to provide feedback on the study design, nor will they be consulted for the development of patient-relevant outcomes or in interpreting the results. Furthermore, patient contributions will not be sought for the writing or editing of this document, whether for enhancing readability or ensuring accuracy. This approach will be maintained throughout the research process.

ETHICS AND DISSEMINATION

Ethical committee approval is not necessitated for this protocol, given its nature as a

secondary analysis that aggregates data from primary studies. Dissemination of the findings will be conducted through publications in peer-reviewed journals, ensuring academic rigor and credibility in the presentation of the results.

Author contributions

LY and YHL are co-first authors, jointly responsible for the study design and manuscript writing. YHP, YHH, QCD, and YXH completed the Prospero registration information and contributed to the manuscript writing. DL reviewed and revised the manuscript. All authors made substantial contributions to the writing and editing of the manuscript and approved the final version prior to submission.

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Appendix A

#1 ("Neoplasms":ti,ab,kw OR neoplasm*:ti,ab,kw OR malignan*:ti,ab,kw OR

tumour*:ti,ab,kw OR tumor*:ti,ab,kw OR cancer*:ti,ab,kw OR carcinoma*:ti,ab,kw)

#2 ("Pain":ti,ab,kw OR pain*:ti,ab,kw OR nocicept*:ti,ab,kw OR neuropath*:ti,ab,kw)

#3 (#1 AND #2)

#4 ("Rehabilitation":ti,ab,kw OR "Cognitive Rehabilitation":ti,ab,kw OR "Neuropsychological Rehabilitation":ti,ab,kw OR "Neurorehabilitation":ti,ab,kw OR "Occupational Therapy":ti,ab,kw OR "Physical Therapy":ti,ab,kw OR "Psychosocial Rehabilitation":ti,ab,kw)

#5 ("Exercise":ti,ab,kw OR "Exercise Therapy":ti,ab,kw OR "Aerobic Exercise":ti,ab,kw OR Weightlifting":ti,ab,kw OR "Yoga":ti,ab,kw)

#6 (exercise therapy:ti,ab,kw OR stretching:ti,ab,kw OR "tai chi":ti,ab,kw OR yoga:ti,ab,kw) 4.("Psychotherapy":ti,ab,kw OR "Cognitive Behavior Therapy":ti,ab,kw OR "Behavior Therapy":ti,ab,kw OR "Psychotherapeutic Counseling":ti,ab,kw)

#7 (cognitive behavioral:ti,ab,kw OR relaxation:ti,ab,kw OR breathing:ti,ab,kw OR hypnosis:ti,ab,kw) 6.("Relaxation":ti,ab,kw OR "Relaxation Therapy":ti,ab,kw)

#8 ("Hypnosis":ti,ab,kw)

#9 (hydrotherapy:ti,ab,kw OR thermotherapy:ti,ab,kw OR heat:ti,ab,kw OR warm:ti,ab,kw OR cold:ti,ab,kw OR cool:ti,ab,kw)

#10 (Alternative Medicine:ti,ab,kw)

#11 ("Acupuncture":ti,ab,kw OR Aromatherapy:ti,ab,kw OR "Massage":ti,ab,kw OR "Herbal Medicine":ti,ab,kw OR "Meditation":ti,ab,kw OR "Osteopathic Medicine":ti,ab,kw) 11.(massage:ti,ab,kw OR chiropractic:ti,ab,kw OR manipulation:ti,ab,kw OR acupuncture:ti,ab,kw OR acupressure:ti,ab,kw OR osteopath*:ti,ab,kw OR homeopath*:ti,ab,kw OR naturopath*:ti,ab,kw OR aromathera*:ti,ab,kw OR art:ti,ab,kw OR music:ti,ab,kw OR alternative:ti,ab,kw OR complementary:ti,ab,kw OR CAM:ti,ab,kw)

#12 (transcutaneous electrical stimulation:ti,ab,kw)

#13 ("Electrical Stimulation":ti,ab,kw OR "Electrical Brain Stimulation":ti,ab,kw OR "Electroconvulsive Therapy":ti,ab,kw)

#14 ("Transcranial Magnetic Stimulation":ti,ab,kw)

#15 (transcranial magnetic stimulation:ti,ab,kw)

#16 (dorsal column stimulation:ti,ab,kw)

#17 (spinal cord stimulation:ti,ab,kw)

#18 (peripheral field stimulation:ti,ab,kw)

#19 (dorsal root entry zone lesion*:ti,ab,kw)

#20 (DREZ:ti,ab,kw)

#21 ("Osteopathic Medicine":ti,ab,kw)

#22 (orthotics:ti,ab,kw OR orthosis:ti,ab,kw OR brace*:ti,ab,kw)

#23 (nonpharmaco*:ti,ab,kw OR non - pharmaco*:ti,ab,kw)

#24 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#25 randomized controlled trial [pt]

#26 controlled clinical trial [pt]

#27 randomized [tiab]

#28 placebo [tiab]

#29 clinical trials as topic [mesh: noexp]

#30 randomly [tiab]

#31 trial [ti]

#32 #25 #26 or #27 or #28 or #29 or #30 or #31

#33 humans [mh]

#34 #32 and #33

#35 #3 and #24 and #34

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Title Page

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ABSTRACT

Introduction

Pain management in cancer patients is a critical aspect of oncological care, yet remains challenging with current pharmacological therapies. Non-pharmacological interventions, offering potential benefits without the adverse effects of drugs, have gained attention. However, the effectiveness of these diverse non-pharmacological interventions is not well understood, creating a gap in clinical practice. This study aims to conduct a systematic review and network meta-analysis to evaluate the efficacy of various non-pharmacological interventions for pain management in cancer patients, providing evidence-based guidance for clinicians and patients.

Methods and analysis

A systematic review and Bayesian network meta-analysis will be performed. To assess the efficacy of interventions for cancer pain, we will search six electronic databases: Cochrane Library, Web of Science, PubMed, EMBASE, PsycINFO, and the Cumulative Index to Nursing and Allied Health Literature, focusing on identifying randomized controlled trials. Literature screening should be independently performed by two reviewers. A network meta-analysis will evaluate the efficacy of various non-pharmacological interventions for cancer pain. A second network meta-analysis will compare the efficacy of different non-pharmacological interventions in relieving pain interference in patients with cancer pain. Bayesian 95% credible intervals will be used to estimate the pooled mean effect size for each treatment, and the surface under the cumulative ranking area will be employed to rank the effectiveness of the treatments.

Ethics and dissemination

Ethical approval is not required for this systematic review of the published data. Findings will be disseminated via peer-reviewed publication.

PROSPERO registration number CRD42024483025.

Key Words: Oncology; Pain; Exercise; Mental health; Network meta-analysis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

*Strength: The study employs a Bayesian network meta-analysis approach, allowing for a comprehensive comparison of multiple non-pharmacological interventions simultaneously, which enhances the depth and applicability of the findings.

*Strength: Utilizing six major electronic databases ensures a wide coverage of the literature, increasing the likelihood of capturing relevant randomized controlled trials and enhancing the robustness of the systematic review.

*Strength: The employment of the surface under the cumulative ranking (SUCRA) area to rank the interventions offers a clear, hierarchical understanding of treatment effectiveness, facilitating straightforward clinical decision-making.

*Limitation: Due to the nature of network meta-analysis (NMA), this study focuses solely on randomized controlled trials, which may exclude relevant studies with different designs that could offer additional insights into the efficacy of the interventions.

*Limitation: The reliance on published studies in English might overlook significant research conducted in other languages, potentially introducing language bias into the findings.

Introduction

Pain in cancer patients is a common symptom, characterized not only by its high prevalence but also by its significant impact on the patients (1-3). A systematic review has indicated varying prevalence rates of pain among cancer patients. The prevalence of pain is reported to be 66.4% in patients with advanced, metastatic, or terminal stages of cancer, and 50.7% across all stages of the disease. Furthermore, approximately 38% of patients experience moderate to severe pain (1). Beyond its high prevalence, cancer pain causes considerable physical discomfort and affects psychological and social functions, leading to symptoms such as fatigue, anxiety, and depression (2-4). This, in turn, reduces the quality of life of patients and impacts their work efficiency (2). The causes of pain in cancer patients are diverse, including tumor growth, side effects of treatment, among others (5, 6). The pain experience also varies depending on the type of cancer, its stage, and individual factors (6). Therefore, it is essential to adopt personalized pain management approaches for patients.

Clinical interventions for alleviating pain in cancer patients include both pharmacological and non-pharmacological methods. In terms of pharmacological interventions, the efficacy of opioid medications and non-steroidal anti-inflammatory drugs (NSAIDs) has been widely validated, making them standard treatments in clinical practice (7, 8). Building on this, the World Health Organization's analgesic ladder provides comprehensive guidelines for a rational use of these medications, recommending a stepwise approach to cancer pain management (9). This strategy starts with non-opioid analgesics, such as NSAIDs and acetaminophen, for mild pain, then moves to weak opioids for persistent discomfort, and finally employs strong opioids, like morphine, for severe pain (9). However, pharmacological interventions have many side effects and limitations, such as causing gastrointestinal reactions and increasing cardiovascular risks (7, 8). As a result, non-pharmacological treatments are gaining increasing attention. These non-pharmacological interventions include psychological therapies (such as Cognitive Behavioral Therapy and mindfulness), physical

interventions (like exercise and acupuncture), and assistive techniques (such as guided imagery and yoga) (10-12). These non-pharmacological methods not only alleviate pain in cancer patients but also improve their overall quality of life (13). Therefore, it is essential to identify and select effective non-pharmacological interventions.

Network Meta-Analysis (NMA) offers a comprehensive approach that allows researchers to rank a range of non-pharmacological interventions in terms of their relative efficacy (14). NMA integrates both direct and indirect evidence from a set of studies and can encompass data from multiple treatment modalities, even if these treatments have not been directly compared in Randomized Controlled Trials (RCTs) (14). This method effectively overcomes the main limitation of traditional pairwise meta-analyses, which can only compare two treatment methods at a time (14). Such an analytical approach is crucial for guiding clinical decision-making, developing evidence-based guidelines, and meeting the needs of personalized pain management strategies. In light of this, the aim of our study is to determine the relative effectiveness of various common non-pharmacological interventions for managing pain in cancer patients through NMA.

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Studies will be eligible for inclusion if they meet the following PICOS elements:

(1) P (Population):

The study will include adults aged 18 and over who have been diagnosed with cancer and suffer from pain caused by the cancer, with no restrictions on gender.

(2) I (Intervention):

To systematically assess the impact of various non-pharmacological interventions on pain management among cancer patients, we included psychological interventions such as Cognitive Behavioral Therapy (CBT), relaxation training, and mindfulness meditation, which are designed to help manage and alleviate pain through psychological regulation. Additionally, we incorporated physical therapies like thermotherapy, cryotherapy, and massage therapy that alleviate pain through physical contact and temperature variations. Complementary therapies included in our study were music therapy, aromatherapy, and acupressure, which stimulate the senses and promote relaxation to reduce pain. All interventions selected for this study are non-invasive and function independently of pharmacological effects.

(3) C (Control):

Given the comprehensive nature of NMA, this study imposes no restrictions on the choice of comparison groups. This approach allows the inclusion of a wide range of control interventions, from standard treatments and placebos to active therapies, thereby facilitating a broad evaluation of the relative therapeutic effects of various interventions.

(4) O (Outcome):

The reduction of pain related to cancer is to be measured using the following validated methods: Visual Analogue Scale, Brief Pain Inventory, The Numeric Rating Scale, Multidimensional Pain Inventory, The Numeric Rating Scale. The relief of pain interference in cancer patients is to be measured using the following validated methods: Multidimensional Pain Inventory, Brief Pain Inventory, The Psychological Inflexibility in Pain Scale, The Pain Interference Index, Multidimensional Pain Inventory, 10-cm Visual Analogue Scales.

(5) S (Study Design):

The study will focus on Randomized Controlled Trials (RCTs) published in English.

Studies will be excluded from our systematic review if they meet the following criteria: (1) published in languages other than English; (2) not a RCT design; (3) use or apply medical or pharmacological interventions; (4) include patients awaiting biopsy/diagnosis or who have already overcome the disease; (5) solely include children or adolescents; (6) involve pain studies related to pathologies other than cancer or diseases other than cancer; (7) have excessively broad inclusion criteria, where participants do not meet the standards for this systematic review; (8) include participants without a basic level of education or cognitive abilities impaired by disease or any form of mental disability; (9) do not include any outcomes relevant to the purpose of this review.

Data Collection and Search Methodology

This study, which commenced in January 2024 and is expected to conclude in September 2024, will involve a systematic search of electronic databases by two independent reviewers. The literature retrieval will span from the establishment of the databases up to July 2024. Relevant studies will be identified from major databases including the Cochrane Library, Web of Science, PubMed, EMBASE, PsycINFO, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). In addition, reference lists of selected articles and related review articles will be manually examined to uncover any potential relevant publications. The comprehensive search strategy is detailed in Appendix A.

Screening and data extraction

We will use EndNote X9 software to manage the database search results. The first step is to remove duplicate studies using the software. Then, two independent reviewers will screen the titles and abstracts of the retrieved studies according to the predefined criteria

and exclude those that do not meet the criteria. Next, the same reviewers will read the full texts of the remaining studies and further exclude those that do not meet the criteria, resulting in the final selection of studies. The reviewers will work independently and will discuss any disagreements. If no consensus is reached, a third reviewer will arbitrate the disputed outcome.

Assessment of risk of bias

The researchers will use the Cochrane risk of bias tool to assess the methodological quality of the included studies (17). Two reviewers will independently evaluate the included studies. Any discrepancies in the evaluation will be resolved through discussions or by consulting a third reviewer. Each item will be assessed as having low, unclear, or high risk of bias. The Cochrane risk of bias tool will evaluate the included studies in the following seven areas: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias.

Missing Data

In instances where data are presented as medians or using alternative measures of variability, these will be transformed into mean and standard deviation (SD) values using established mathematical formulae (18). For data depicted solely in graphical format, without accompanying numerical details in the text, extraction will be performed utilizing ImageJ software (available at https://imagej.nih.gov/ij/) (19). This process involves measuring the pixel length of graph axes for calibration, followed by determining the pixel length corresponding to the data points of interest (19). In cases where direct data extraction proves unfeasible, attempts will be made to obtain the necessary information from the study authors. Any arising discrepancies during the data extraction process will be resolved through consultation with an appointed adjudicator.

Statistical analysis

Effect measurements

For continuous outcomes, if the outcome is measured using the same scale, the mean difference (MD) and the corresponding 95% CI will be used. If different scales are used to measure related outcomes, the standardized mean difference (SMD) will be calculated (16). Subsequently, we will conduct pairwise meta-analyses and use a random-effects model for each comparison, followed by the generation of network graphs and evaluation to determine the feasibility of the NMA. Afterwards, we will conduct NMA analysis using Bayesian methods.

Network meta-analysis

The execution of the NMA will utilize a Bayesian framework employing Markov chain Monte Carlo (MCMC) methods. This analysis will be implemented using the R Statistical Software, specifically through the Meta, and Gemtc package. Our approach involves running four parallel MCMC chains in the model, and conducting two distinct MCMC simulations to facilitate the comparison of convergence. The Bayesian model will be operationalized through an initial phase of 5,000 burn-in iterations, followed by a subsequent phase of 100,000 simulation iterations. The assessment of convergence will be conducted using the potential scale reduction factor, with an anticipated reduction target of below 1.05 (20, 21).

Heterogeneity, specifically pertaining to direct evidence, and model consistency (direct vs. indirect comparisons) will be evaluated using the node split function within the Gemtc package. This process will facilitate the exploration of sources of heterogeneity across studies. The comparative analysis of each intervention will be conducted using standardized mean differences (SMD) along with 95% credible intervals, which are akin to the Bayesian equivalent of confidence intervals. Rank probabilities will be used to quantify the likelihood of each intervention's effectiveness. Additionally, the Surface Under the Cumulative Ranking (SUCRA) score will be employed to estimate the probability of an intervention being the most effective (20, 21).

Quality of evidence

The grading of evidence derived from the NMA will be executed in four distinct stages, utilizing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, facilitated by GRADE Pro software (22). The initial step involves presenting the effect sizes and confidence intervals (CIs) for both direct and indirect comparisons across interventions. Subsequently, the second step entails an independent assessment of the quality of evidence for each comparison. The third stage involves the presentation of the NMA results. In the final stage, the quality of evidence underpinning the NMA outcomes is evaluated. For direct comparisons, we apply the same grading approach as the traditional meta-analysis using the GRADE system for evidence grading. When it comes to indirect comparisons, the quality of evidence is downgraded if the direct comparisons are of lower quality. The overall quality of evidence for NMA results, which includes both direct and indirect comparisons, is determined based on the highest quality of evidence found in either comparison type. This method ensures that the final grading reflects the most reliable evidence available.

Additional analysis

Given the potential differences in study populations, interventions, and outcome measurements among the included studies, we will conduct a series of subgroup analyses if data allows. We will investigate differences across populations residing in different continents (such as Europe, Asia, etc.), treatment durations (less than 12 weeks vs. more than 12 weeks), age groups (under 20 years, 20-40 years, 40-60 years, over 60 years), and follow-up periods (less than 4 weeks, 5-12 weeks, more than 12 weeks). Additionally, we intend to conduct a sensitivity analysis to evaluate the potential impact of the quality of the included trials on the overall findings. This analysis will involve reassessing each outcome by specifically excluding those studies deemed to have a high risk of bias, thus gauging the robustness of our results in relation to the quality of the evidence.

Reporting bias evaluation

Assessment for reporting bias in the NMA will be conducted when the included trials number at least ten (16). This threshold is based on statistical considerations, recognizing that with fewer than ten trials, the power to discern between random variations and genuine asymmetry is significantly compromised. To detect potential reporting bias, we will employ Begg's test for analyzing funnel plots (23). This method involves correlating the magnitude of effect sizes with their variance, where a notable correlation suggests the presence of reporting bias (23). Should asymmetry be observed in the funnel plots, we will consider alternative explanations beyond reporting bias, such as selective reporting of outcomes, inferior methodological quality in smaller studies, or the presence of heterogeneity.

Discussion

This systematic review and NMA explores a crucial area in cancer treatment—the use of non-pharmacological interventions for pain management in cancer patients. Pain management remains a key challenge in cancer treatment, significantly affecting patients' quality of life and treatment compliance (7, 8). While pharmacological treatments are mainstream, their adverse reactions can greatly diminish patients' well-being and adherence to treatment (7, 8). Therefore, exploring effective non-pharmacological treatment options is not only necessary but also urgent in enhancing comprehensive cancer therapy.

Previous studies have shown that non-pharmacological interventions such as CBT, relaxation training, and physical therapy vary in their efficacy in managing cancer-related pain (10-12). However, these studies often lack comparative analysis and are unable to rank the effectiveness of these interventions. By employing NMA, this study systematically compares and ranks these interventions, providing a broader perspective on their relative benefits and making a unique contribution to the existing literature. The findings of this study are expected to have a significant impact on clinical practice.

By providing evidence-based rankings of non-pharmacological interventions, clinicians can make the most appropriate decisions based on individual patient needs, thereby improving pain management in cancer care. Furthermore, the results of this study may encourage the adoption of a more holistic approach in cancer treatment, integrating non-pharmacological methods into standard treatment protocols to enhance overall patient care and satisfaction. By focusing on non-pharmacological interventions that do not involve pharmacology, this research addresses significant patient-centered concerns such as the desire to reduce medication side effects and the need for interventions that can be used concurrently with drug treatments without interactions. Additionally, the study's methodology—using Bayesian network meta-analysis—adds a robust statistical layer to the evaluation of treatment effects, enhancing the reliability of the conclusions. This not only aids clinical decision-making but also sets a precedent for future research methodologies in the field.

Overall, this systematic review and NMA not only fills a significant gap in the literature but also provides a comprehensive evidence-based ranking of non-pharmacological interventions for pain management in cancer patients. The results of this study are expected to impact clinical practice and future research directions, making a significant contribution to the field of oncological pain management.

Patient and public involvement

This study will not include patient or public involvement in any stage, encompassing the planning or design phases. No invitation will be extended to patients to provide feedback on the study design, nor will they be consulted for the development of patient-relevant outcomes or in interpreting the results. Furthermore, patient contributions will not be sought for the writing or editing of this document, whether for enhancing readability or ensuring accuracy. This approach will be maintained throughout the research process.

ETHICS AND DISSEMINATION

Ethical committee approval is not necessitated for this protocol, given its nature as a secondary analysis that aggregates data from primary studies. Dissemination of the findings will be conducted through publications in peer-reviewed journals, ensuring academic rigor and credibility in the presentation of the results.

Funding Statements

None

Competing Interests

No competing interest

Author contributions

LY and YHL are co-first authors, jointly responsible for the study design and manuscript writing. YHP, YHH, QCD, and YXH completed the Prospero registration information and contributed to the manuscript writing. DL reviewed and revised the manuscript, and acted as guarantor. All authors made substantial contributions to the writing and editing of the manuscript and approved the final version prior to submission.

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Cochrane Library

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#26 controlled clinical trial [pt]

#27 randomized [tiab]

#28 placebo [tiab]

#29 clinical trials as topic [mesh: noexp]

#30 randomly [tiab]

#31 trial [ti]

#32 #25 #26 or #27 or #28 or #29 or #30 or #31

#33 humans [mh]

#34 #32 and #33

#35 #3 and #24 and #34

Web of Science

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TS=("Pain" OR pain* OR nocicept* OR neuropath*)

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TS=(dorsal root entry zone lesion*)

TS=(DREZ)

TS=("Osteopathic Medicine")

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#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

PUBMED

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("Hypnosis"[MeSH Terms])

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EMBASE

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23.(nonpharmaco*:ti,ab,kw OR non-pharmaco*:ti,ab,kw) 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23

PsycINFO, and Cumulative Index of Nursing and Allied Health Literature

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2.(AB "pain*" OR AB "nocicept*" OR AB "neuropath*")

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20.(AB "DREZ")

21.(AB "Osteopathic Medicine")

22.(AB "orthotics" OR AB "orthosis" OR AB "brace*")

23.(AB "nonpharmaco*" OR AB "non - pharmaco*")

1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23

RCT：

(TI "randomized controlled trial" OR AB "randomized controlled trial" OR TI "randomised controlled trial" OR AB "randomised controlled trial" OR TI "RCT" OR AB "RCT" OR TI "randomized clinical trial" OR AB "randomized clinical trial" OR TI "random allocation" OR AB "random allocation" OR TI "double-blind method" OR AB "double-blind method" OR TI "single-blind method" OR AB "single-blind method"

BMJ Open

Effectiveness of Non-Pharmacological Interventions for Pain Management in Cancer Patients: A protocol for Systematic Review and Network Meta-Analysis

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Title Page

Title:

Effectiveness of Non-Pharmacological Interventions for Pain Management in Cancer Patients: A protocol for Systematic Review and Network Meta-Analysis

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ABSTRACT

Introduction

Pain management in cancer patients is a critical aspect of oncological care, yet remains challenging with current pharmacological therapies. Non-pharmacological interventions, offering potential benefits without the adverse effects of drugs, have gained attention. However, the effectiveness of these diverse non-pharmacological interventions is not well understood, creating a gap in clinical practice. This study aims to conduct a systematic review and network meta-analysis to evaluate the efficacy of various non-pharmacological interventions for pain management in cancer patients, providing evidence-based guidance for clinicians and patients.

Methods and analysis

A systematic review and Bayesian network meta-analysis will be performed. To assess the efficacy of interventions for cancer pain, we will search six electronic databases: Cochrane Library, Web of Science, PubMed, EMBASE, PsycINFO, and the Cumulative Index to Nursing and Allied Health Literature, focusing on identifying randomized controlled trials. Literature screening should be independently performed by two reviewers. A network meta-analysis will evaluate the efficacy of various non-pharmacological interventions for cancer pain. A second network meta-analysis will compare the efficacy of different non-pharmacological interventions in relieving pain interference in patients with cancer pain. Bayesian 95% credible intervals will be used to estimate the pooled mean effect size for each treatment, and the surface under the cumulative ranking area will be employed to rank the effectiveness of the treatments.

Ethics and dissemination

Ethical approval is not required for this systematic review of the published data. Findings will be disseminated via peer-reviewed publication.

PROSPERO registration number CRD42024483025.

Key Words: Oncology; Pain; Exercise; Mental health; Network meta-analysis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

*Strength: The study employs a Bayesian network meta-analysis approach, allowing for a comprehensive comparison of multiple non-pharmacological interventions simultaneously, which enhances the depth and applicability of the findings.

*Strength: Utilizing six major electronic databases ensures a wide coverage of the literature, increasing the likelihood of capturing relevant randomized controlled trials and enhancing the robustness of the systematic review.

*Strength: The employment of the surface under the cumulative ranking (SUCRA) area to rank the interventions offers a clear, hierarchical understanding of treatment effectiveness, facilitating straightforward clinical decision-making.

*Limitation: Due to the nature of network meta-analysis, this study focuses solely on randomized controlled trials, which may exclude relevant studies with different designs that could offer additional insights into the efficacy of the interventions.

*Limitation: The reliance on published studies in English might overlook significant research conducted in other languages, potentially introducing language bias into the findings.

Introduction

Pain in cancer patients is a common symptom, characterized not only by its high prevalence but also by its significant impact on the patients.[1-3] A systematic review has indicated varying prevalence rates of pain among cancer patients.[1] The prevalence of pain is reported to be 66.4% in patients with advanced, metastatic, or terminal stages of cancer, and 50.7% across all stages of the disease.[1] Furthermore, approximately 38% of patients experience moderate to severe pain.[1] Beyond its high prevalence, cancer pain causes considerable physical discomfort and affects psychological and social functions, leading to symptoms such as fatigue, anxiety, and depression.[2-4] This, in turn, reduces the quality of life of patients and impacts their work efficiency.[2] The causes of pain in cancer patients are diverse, including tumor growth, side effects of treatment, among others.[5 6] The pain experience also varies depending on the type of cancer, its stage, and individual factors.[6] Therefore, it is essential to adopt personalized pain management approaches for patients.

Clinical interventions for alleviating pain in cancer patients include both pharmacological and non-pharmacological methods. In terms of pharmacological interventions, the efficacy of opioid medications and non-steroidal anti-inflammatory drugs (NSAIDs) has been widely validated, making them standard treatments in clinical practice.[7 8] Building on this, the World Health Organization's analgesic ladder provides comprehensive guidelines for a rational use of these medications, recommending a stepwise approach to cancer pain management.[9] This strategy starts with non-opioid analgesics, such as NSAIDs and acetaminophen, for mild pain, then moves to weak opioids for persistent discomfort, and finally employs strong opioids, like morphine, for severe pain.[9] However, pharmacological interventions have many side effects and limitations, such as causing gastrointestinal reactions and increasing cardiovascular risks.[7 8] As a result, non-pharmacological treatments are gaining increasing attention. These non-pharmacological interventions include psychological therapies (such as Cognitive Behavioral Therapy and mindfulness), physical interventions (like exercise and acupuncture), and assistive techniques (such as guided imagery and yoga).[10-12]

Research indicates that certain non-pharmacological methods may contribute to pain relief in cancer patients and potentially enhance their overall quality of life.[13] Therefore, it is essential to identify and select effective non-pharmacological interventions.

Network meta-analysis (NMA) can synthesize both direct and indirect evidence from various studies regarding treatment methods, including those not directly compared in randomized controlled trials (RCTs).[14] This enables researchers to rank the relative efficacy of a range of non-pharmacological interventions.[14] This approach addresses a major limitation of traditional meta-analysis, which can only compare two treatments at a time, thus enabling a more comprehensive assessment of the effectiveness of various non-pharmacological methods for alleviating cancer pain. Consequently, compared to the studies by Ruano et al. and Cuthbert et al.,[11 12] this research is expected to reveal specific differences in effectiveness among these methods and provide a ranked assessment of their efficacy, offering more comprehensive evidence to support clinical decision-making. Furthermore, the literature search for these two traditional meta-analyses focusing on non-pharmacological interventions for cancer pain concluded in 2020. Following the recommendations of Cochrane, it is prudent to update systematic reviews when they surpass a certain age, considering their academic value and practical utility.[15 16]

METHODS AND ANALYSIS

This systematic review has been officially registered with PROSPERO (registration number CRD42024483025) and its protocol reporting has been following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) items.[17] We commit to conducting the systematic review in alignment with the directives provided in the Cochrane Handbook for Systematic Reviews of Interventions.[18] Should there be any necessary modifications to the protocol, these will be duly updated through PROSPERO.

Inclusion and Exclusion Criteria

Studies will be eligible for inclusion if they meet the following PICOS elements:

(1) P (Population):

The study will include adults aged 18 and over who have been diagnosed with cancer and suffer from pain caused by the cancer, with no restrictions on gender.

(2) I (Intervention):

To systematically assess the impact of various non-pharmacological interventions on pain management among cancer patients, we will include psychological interventions such as Cognitive Behavioral Therapy (CBT), relaxation training, and mindfulness meditation, designed to help manage and alleviate pain through psychological regulation. Additionally, we will incorporate physical therapies like thermotherapy, cryotherapy, and massage therapy that alleviate pain through physical contact and temperature variations. Complementary therapies to be included in our study are music therapy, aromatherapy, and acupressure, which stimulate the senses and promote relaxation to reduce pain. All interventions selected for this study will be non-invasive and function independently of pharmacological effects.

(3) C (Control):

Given the comprehensive nature of NMA, this study will impose no restrictions on the choice of comparison groups. This approach will allow the inclusion of a wide range of control interventions, from standard treatments and placebos to active therapies, thereby facilitating a broad evaluation of the relative therapeutic effects of various interventions.

(4) O (Outcome):

The reduction of pain related to cancer is to be measured using the following validated methods: Visual Analogue Scale, Brief Pain Inventory, The Numeric Rating Scale, Multidimensional Pain Inventory, The Numeric Rating Scale. The relief of pain interference in cancer patients is to be measured using the following validated methods: Multidimensional Pain Inventory, Brief Pain Inventory, The Psychological Inflexibility in Pain Scale, The Pain Interference Index, Multidimensional Pain Inventory, 10-cm

Visual Analogue Scales.

(5) S (Study Design):

The study will focus on RCTs published in English. Our literature search will be confined to publications in English, primarily due to the limitations of our team's resources and language proficiency. Given that English is the predominant language in our field of research and covers the vast majority of innovative and comprehensive studies, this approach will help ensure manageability and high quality of data, thereby maintaining rigorous analytical standards. This practice is consistent with similar language restrictions adopted within our field.

Studies will be excluded from our systematic review if they meet the following criteria: (1) published in languages other than English; (2) not a RCT design; (3) use or apply medical or pharmacological interventions; (4) include patients awaiting biopsy/diagnosis or who have already overcome the disease; (5) solely include children or adolescents; (6) involve pain studies related to pathologies other than cancer or diseases other than cancer; (7) have excessively broad inclusion criteria, where participants do not meet the standards for this systematic review; (8) include participants without a basic level of education or cognitive abilities impaired by disease or any form of mental disability; (9) do not include any outcomes relevant to the purpose of this review.

Data Collection and Search Methodology

This systematic review is scheduled to be conducted over a period of approximately nine months, aiming for completion by September 2024. It will entail a comprehensive search of electronic databases, conducted by two independent reviewers. The literature retrieval will cover the period from the inception of the databases until July 2024. Relevant studies will be identified from major databases including the Cochrane Library, Web of Science, PubMed, EMBASE, PsycINFO, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). In addition, reference lists of selected

articles and related review articles will be manually examined to uncover any potential relevant publications. The comprehensive search strategy is detailed in Appendix A.

Screening and data extraction

We will use EndNote X9 software to manage the database search results. The first step is to remove duplicate studies using the software. Then, two independent reviewers will screen the titles and abstracts of the retrieved studies according to the predefined criteria and exclude those that do not meet the criteria. Next, the same reviewers will read the full texts of the remaining studies and further exclude those that do not meet the criteria, resulting in the final selection of studies. The reviewers will work independently and will discuss any disagreements. If no consensus is reached, a third reviewer will arbitrate the disputed outcome.

Assessment of risk of bias

The researchers will use the Cochrane risk of bias tool to assess the methodological quality of the included studies.[19] Two reviewers will independently evaluate the included studies. Any discrepancies in the evaluation will be resolved through discussions or by consulting a third reviewer. Each item will be assessed as having low, unclear, or high risk of bias. The Cochrane risk of bias tool will evaluate the included studies in the following seven areas: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias.

Missing Data

In instances where data are presented as medians or using alternative measures of variability, these will be transformed into mean and standard deviation (SD) values using established mathematical formulae.[20] For data depicted solely in graphical format, without accompanying numerical details in the text, extraction will be performed

utilizing ImageJ software (available at https://imagej.nih.gov/ij/).[21] This process involves measuring the pixel length of graph axes for calibration, followed by determining the pixel length corresponding to the data points of interest.[21] In cases where direct data extraction proves unfeasible, attempts will be made to obtain the necessary information from the study authors. Any arising discrepancies during the data extraction process will be resolved through consultation with an appointed adjudicator.

Statistical analysis

Effect measurements

For continuous outcomes, if the outcome is measured using the same scale, the mean difference (MD) and the corresponding 95% CI will be used. If different scales are used to measure related outcomes, the standardized mean difference (SMD) will be calculated.[18] Subsequently, we will conduct pairwise meta-analyses and use a random-effects model for each comparison, followed by the generation of network graphs and evaluation to determine the feasibility of the NMA. Afterwards, we will conduct NMA analysis using Bayesian methods.

Network meta-analysis

The execution of the NMA will utilize a Bayesian framework employing Markov chain Monte Carlo (MCMC) methods. This analysis will be implemented using the R Statistical Software, specifically through the Meta, and Gemtc package. Our approach involves running four parallel MCMC chains in the model, and conducting two distinct MCMC simulations to facilitate the comparison of convergence. The Bayesian model will be operationalized through an initial phase of 5,000 burn-in iterations, followed by a subsequent phase of 100,000 simulation iterations. The assessment of convergence will be conducted using the potential scale reduction factor, with an anticipated reduction target of below 1.05.[22 23]

Heterogeneity, specifically pertaining to direct evidence, and model consistency (direct vs. indirect comparisons) will be evaluated using the node split function within the Gemtc package. This process will facilitate the exploration of sources of heterogeneity

across studies. The comparative analysis of each intervention will be conducted using standardized mean differences (SMD) along with 95% credible intervals, which are akin to the Bayesian equivalent of confidence intervals. Rank probabilities will be used to quantify the likelihood of each intervention's effectiveness. Additionally, the Surface Under the Cumulative Ranking (SUCRA) score will be employed to estimate the probability of an intervention being the most effective.[22 23]

Quality of evidence

The grading of evidence derived from the NMA will be executed in four distinct stages, utilizing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, facilitated by GRADE Pro software.[24] The initial step involves presenting the effect sizes and confidence intervals (CIs) for both direct and indirect comparisons across interventions. Subsequently, the second step entails an independent assessment of the quality of evidence for each comparison. The third stage involves the presentation of the NMA results. In the final stage, the quality of evidence underpinning the NMA outcomes is evaluated. For direct comparisons, we apply the same grading approach as the traditional meta-analysis using the GRADE system for evidence grading. When it comes to indirect comparisons, the quality of evidence is downgraded if the direct comparisons are of lower quality. The overall quality of evidence for NMA results, which includes both direct and indirect comparisons, is determined based on the highest quality of evidence found in either comparison type. This method ensures that the final grading reflects the most reliable evidence available.

Additional analysis

Given the potential differences in study populations, interventions, and outcome measurements among the included studies, we will conduct a series of subgroup analyses if data allows. We will investigate differences across populations residing in different continents (such as Europe, Asia, etc.), treatment durations (less than 12 weeks vs. more than 12 weeks), age groups (under 20 years, 20-40 years, 40-60 years, over 60

years), and follow-up periods (less than 4 weeks, 5-12 weeks, more than 12 weeks). Additionally, we intend to conduct a sensitivity analysis to evaluate the potential impact of the quality of the included trials on the overall findings. This analysis will involve reassessing each outcome by specifically excluding those studies deemed to have a high risk of bias, thus gauging the robustness of our results in relation to the quality of the evidence.

Reporting bias evaluation

Assessment for reporting bias in the NMA will be conducted when the included trials number at least ten.[18] This threshold is based on statistical considerations, recognizing that with fewer than ten trials, the power to discern between random variations and genuine asymmetry is significantly compromised. To detect potential reporting bias, we will employ Begg's test for analyzing funnel plots.[25] This method involves correlating the magnitude of effect sizes with their variance, where a notable correlation suggests the presence of reporting bias.[25] Should asymmetry be observed in the funnel plots, we will consider alternative explanations beyond reporting bias, such as selective reporting of outcomes, inferior methodological quality in smaller studies, or the presence of heterogeneity.

Discussion

The objective of this systematic review is to explore a significant area in cancer treatment—the use of non-pharmacological interventions for pain management in cancer patients. Pain management remains a key challenge in cancer treatment, significantly affecting patients' quality of life and treatment compliance.[7 8] While pharmacological treatments are mainstream, their adverse reactions can greatly diminish patients' well-being and adherence to treatment.[7 8] Therefore, exploring effective non-pharmacological treatment options is not only necessary but also urgent in enhancing comprehensive cancer therapy.

Previous studies have shown that non-pharmacological interventions such as CBT, relaxation training, and physical therapy vary in their efficacy in managing cancer-related pain.[10-12] However, these studies often lack comparative analysis and are unable to rank the effectiveness of these interventions. By employing NMA, this study will systematically compares and ranks these interventions, providing a broader perspective on their relative benefits and making a unique contribution to the existing literature. The findings of this study are expected to have a significant impact on clinical practice. By providing evidence-based rankings of non-pharmacological interventions, clinicians will be able to make the most appropriate decisions based on individual patient needs, thereby enhancing pain management in cancer care. Furthermore, the results of this study may encourage the adoption of a more holistic approach in cancer treatment, integrating non-pharmacological methods into standard treatment protocols to enhance overall patient care and satisfaction. By focusing on non-pharmacological interventions that do not involve pharmacology, this research addresses significant patient-centered concerns such as the desire to reduce medication side effects and the need for interventions that can be used concurrently with drug treatments without interactions. Additionally, the study's methodology—using Bayesian network meta-analysis—adds a robust statistical layer to the evaluation of treatment effects, enhancing the reliability of the conclusions. This not only aids clinical decision-making but also sets a precedent for future research methodologies in the field.

Patient and public involvement

This study will not include patient or public involvement in any stage, encompassing the planning or design phases. No invitation will be extended to patients to provide feedback on the study design, nor will they be consulted for the development of patient-relevant outcomes or in interpreting the results. Furthermore, patient contributions will not be sought for the writing or editing of this document, whether for enhancing readability or ensuring accuracy. This approach will be maintained throughout the research process.

ETHICS AND DISSEMINATION

Ethical committee approval is not necessitated for this protocol, given its nature as a secondary analysis that aggregates data from primary studies. Dissemination of the findings will be conducted through publications in peer-reviewed journals, ensuring academic rigor and credibility in the presentation of the results.

Funding Statements

None

Competing Interests

No competing interest

Author contributions

LY and YHL are co-first authors, jointly responsible for the study design and manuscript writing. YHP, YHH, QCD, and YXH completed the Prospero registration information and contributed to the manuscript writing. DL reviewed and revised the manuscript, and acted as guarantor. All authors made substantial contributions to the writing and editing of the manuscript and approved the final version prior to submission.

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Cochrane Library

#1 ("Neoplasms":ti,ab,kw OR neoplasm*:ti,ab,kw OR malignan*:ti,ab,kw OR tumour*:ti,ab,kw OR tumor*:ti,ab,kw OR cancer*:ti,ab,kw OR carcinoma*:ti,ab,kw)

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#3 (#1 AND #2)

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#5 ("Exercise":ti,ab,kw OR "Exercise Therapy":ti,ab,kw OR "Aerobic Exercise":ti,ab,kw OR Weightlifting":ti,ab,kw OR "Yoga":ti,ab,kw)

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#12 (transcutaneous electrical stimulation:ti,ab,kw)

#13 ("Electrical Stimulation":ti,ab,kw OR "Electrical Brain Stimulation":ti,ab,kw OR "Electroconvulsive Therapy":ti,ab,kw)

#14 ("Transcranial Magnetic Stimulation":ti,ab,kw)

#15 (transcranial magnetic stimulation:ti,ab,kw)

#16 (dorsal column stimulation:ti,ab,kw)

#17 (spinal cord stimulation:ti,ab,kw)

#18 (peripheral field stimulation:ti,ab,kw)

#19 (dorsal root entry zone lesion*:ti,ab,kw)

#20 (DREZ:ti,ab,kw)

#21 ("Osteopathic Medicine":ti,ab,kw)

#22 (orthotics:ti,ab,kw OR orthosis:ti,ab,kw OR brace*:ti,ab,kw)

#23 (nonpharmaco*:ti,ab,kw OR non - pharmaco*:ti,ab,kw)

#24 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

#25 randomized controlled trial [pt]

#26 controlled clinical trial [pt]

#27 randomized [tiab]

#28 placebo [tiab]

#29 clinical trials as topic [mesh: noexp]

#30 randomly [tiab]

#31 trial [ti]

#32 #25 #26 or #27 or #28 or #29 or #30 or #31

#33 humans [mh]

#34 #32 and #33

#35 #3 and #24 and #34

Web of Science

TS=("Neoplasms" OR neoplasm* OR malignan* OR tumour* OR tumor* OR cancer* OR carcinoma*)

TS=("Pain" OR pain* OR nocicept* OR neuropath*)

#1 AND #2

TS=("Rehabilitation" OR "Cognitive Rehabilitation" OR "Neuropsychological Rehabilitation" OR "Neurorehabilitation" OR "Occupational Therapy" OR "Physical Therapy" OR "Psychosocial Rehabilitation")

TS=("Exercise" OR "Exercise Therapy" OR "Aerobic Exercise" OR "Weightlifting" OR "Yoga")

TS=(exercise therapy OR stretching OR "tai chi" OR yoga)

TS=("Psychotherapy" OR "Cognitive Behavior Therapy" OR "Behavior Therapy" OR "Psychotherapeutic Counseling")

TS=(cognitive behavioral OR relaxation OR breathing OR hypnosis)

TS=("Relaxation" OR "Relaxation Therapy")

TS=("Hypnosis")

TS=(hydrotherapy OR thermotherapy OR heat OR warm OR cold OR cool)

TS=("Alternative Medicine")

TS=("Acupuncture" OR Aromatherapy OR "Massage" OR "Herbal Medicine" OR "Meditation" OR "Osteopathic Medicine")

TS=(massage OR chiropractic OR manipulation OR acupuncture OR acupressure OR osteopath* OR homeopath* OR naturopath* OR aromathera* OR art OR music OR alternative OR complementary OR CAM)

TS=("transcutaneous electrical stimulation")

TS=("Electrical Stimulation" OR "Electrical Brain Stimulation" OR "Electroconvulsive Therapy")

TS=("Transcranial Magnetic Stimulation")

TS=(transcranial magnetic stimulation)

TS=(dorsal column stimulation)

TS=(spinal cord stimulation)

TS=(peripheral field stimulation)

TS=(dorsal root entry zone lesion*)

TS=(DREZ)

TS=("Osteopathic Medicine")

TS=(orthotics OR orthosis OR brace*)

TS=(nonpharmaco* OR non - pharmaco*)

#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

PUBMED

("Rehabilitation"[MeSH Terms] OR Cognitive Rehabilitation[Title/Abstract] OR Neuropsychological Rehabilitation[Title/Abstract] OR Neurorehabilitation[Title/Abstract] OR "Occupational Therapy"[MeSH Terms] OR Physical Therapy[Title/Abstract] OR Psychosocial Rehabilitation[Title/Abstract])

("Exercise"[MeSH Terms] OR "Exercise Therapy"[MeSH Terms] OR Aerobic Exercise[Title/Abstract] OR Weightlifting[Title/Abstract] OR "Yoga"[MeSH Terms])

(exercise therapy[Title/Abstract] OR stretching[Title/Abstract] OR "tai chi"[Title/Abstract] OR yoga[Title/Abstract])

("Psychotherapy"[MeSH Terms] OR Cognitive Behavior Therapy[Title/Abstract] OR "Behavior Therapy"[MeSH Terms] OR "Psychotherapeutic Counseling"[MeSH Terms])

(cognitive behavioral[Title/Abstract] OR relaxation[Title/Abstract] OR breathing[Title/Abstract] OR hypnosis[Title/Abstract])

("Relaxation"[MeSH Terms] OR "Relaxation Therapy"[MeSH Terms])

("Hypnosis"[MeSH Terms])

(hydrotherapy[Title/Abstract] OR thermotherapy[Title/Abstract] OR heat[Title/Abstract] OR warm[Title/Abstract] OR cold[Title/Abstract] OR cool[Title/Abstract])

(Alternative Medicine[Title/Abstract])

("Acupuncture"[MeSH Terms] OR Aromatherapy[MeSH Terms] OR "Massage"[MeSH Terms] OR "Herbal Medicine"[MeSH Terms] OR "Meditation"[MeSH Terms] OR "Osteopathic Medicine"[MeSH Terms])

(massage[Title/Abstract] OR chiropractic[Title/Abstract] OR manipulation[Title/Abstract] OR acupuncture[Title/Abstract] OR acupressure[Title/Abstract] OR osteopath*[Title/Abstract] OR homeopath*[Title/Abstract] OR naturopath*[Title/Abstract] OR aromathera*[Title/Abstract] OR art[Title/Abstract] OR music[Title/Abstract] OR alternative[Title/Abstract] OR complementary[Title/Abstract] OR CAM[Title/Abstract])

(transcutaneous electrical stimulation[Title/Abstract])

("Electrical Stimulation"[MeSH Terms] OR "Electrical Brain Stimulation"[Title/Abstract] OR "Electroconvulsive Therapy"[MeSH Terms])

("Transcranial Magnetic Stimulation"[MeSH Terms])

(transcranial magnetic stimulation[Title/Abstract])

(dorsal column stimulation[Title/Abstract])

(spinal cord stimulation[Title/Abstract])

(peripheral field stimulation[Title/Abstract])

(dorsal root entry zone lesion*[Title/Abstract])

(DREZ[Title/Abstract])

("Osteopathic Medicine"[MeSH Terms])

(orthotics[Title/Abstract] OR orthosis[Title/Abstract] OR brace*[Title/Abstract])

(nonpharmaco*[Title/Abstract] OR non‐pharmaco*[Title/Abstract])

24.(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23)

25.("Neoplasms"[Mesh] OR neoplasm*[Title/Abstract] OR malignan*[Title/Abstract] OR tumour*[Title/Abstract] OR tumor*[Title/Abstract] OR cancer*[Title/Abstract] OR carcinoma*[Title/Abstract])

26.("Pain"[Mesh] OR pain*[Title/Abstract] OR nocicept*[Title/Abstract] OR neuropath*[Title/Abstract])

27.(#25 AND #26)

28.("Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh:NoExp] OR randomized[Title/Abstract] OR placebo [Title/Abstract] OR randomly[Title/Abstract] OR trial[Title/Abstract]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

6.(#24 AND #27 AND #28)

EMBASE

1.('Neoplasms'/exp OR neoplasm*:ab,ti OR malignan*:ab,ti OR tumour*:ab,ti OR tumor*:ab,ti OR cancer*:ab,ti OR carcinoma*:ab,ti)

2.('Pain'/exp OR pain*:ab,ti OR nocicept*:ab,ti OR neuropath*:ab,ti)

3.(#1 AND #2)

1.('Rehabilitation':ti,ab,kw OR 'Cognitive Rehabilitation':ti,ab,kw OR 'Neuropsychological Rehabilitation':ti,ab,kw OR 'Neurorehabilitation':ti,ab,kw OR 'Occupational Therapy':ti,ab,kw OR 'Physical Therapy':ti,ab,kw OR 'Psychosocial Rehabilitation':ti,ab,kw)

2.('Exercise':ti,ab,kw OR 'Exercise Therapy':ti,ab,kw OR 'Aerobic Exercise':ti,ab,kw OR 'Weightlifting':ti,ab,kw OR 'Yoga':ti,ab,kw)

3.(exercise therapy:ti,ab,kw OR stretching:ti,ab,kw OR 'tai chi':ti,ab,kw OR yoga:ti,ab,kw)

4.('Psychotherapy':ti,ab,kw OR 'Cognitive Behavior Therapy':ti,ab,kw OR 'Behavior Therapy':ti,ab,kw OR 'Psychotherapeutic Counseling':ti,ab,kw)

5.(cognitive behavioral:ti,ab,kw OR relaxation:ti,ab,kw OR breathing:ti,ab,kw OR

hypnosis:ti,ab,kw) 6.('Relaxation':ti,ab,kw OR 'Relaxation Therapy':ti,ab,kw)

7.('Hypnosis':ti,ab,kw)

8.(hydrotherapy:ti,ab,kw OR thermotherapy:ti,ab,kw OR heat:ti,ab,kw OR warm:ti,ab,kw OR cold:ti,ab,kw OR cool:ti,ab,kw)

9.('Alternative Medicine':ti,ab,kw)

10.('Acupuncture':ti,ab,kw OR Aromatherapy:ti,ab,kw OR 'Massage':ti,ab,kw OR 'Herbal Medicine':ti,ab,kw OR 'Meditation':ti,ab,kw OR 'Osteopathic Medicine':ti,ab,kw)

11.(massage:ti,ab,kw OR chiropractic:ti,ab,kw OR manipulation:ti,ab,kw OR acupuncture:ti,ab,kw OR acupressure:ti,ab,kw OR osteopath*:ti,ab,kw OR homeopath*:ti,ab,kw OR naturopath*:ti,ab,kw OR aromathera*:ti,ab,kw OR art:ti,ab,kw OR music:ti,ab,kw OR alternative:ti,ab,kw OR complementary:ti,ab,kw OR CAM:ti,ab,kw)

12.(transcutaneous electrical stimulation:ti,ab,kw)

13.('Electrical Stimulation':ti,ab,kw OR 'Electrical Brain Stimulation':ti,ab,kw OR 'Electroconvulsive Therapy':ti,ab,kw)

14.('Transcranial Magnetic Stimulation':ti,ab,kw)

15.(transcranial magnetic stimulation:ti,ab,kw)

16.(dorsal column stimulation:ti,ab,kw)

17.(spinal cord stimulation:ti,ab,kw)

18.(peripheral field stimulation:ti,ab,kw)

19.(dorsal root entry zone lesion*:ti,ab,kw)

20.(DREZ:ti,ab,kw)

21.('Osteopathic Medicine':ti,ab,kw)

22.(orthotics:ti,ab,kw OR orthosis:ti,ab,kw OR brace*:ti,ab,kw)

23.(nonpharmaco*:ti,ab,kw OR non-pharmaco*:ti,ab,kw) 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23

PsycINFO, and Cumulative Index of Nursing and Allied Health Literature

1.(AB "neoplasm*" OR AB "malignan*" OR AB "tumour*" OR AB "tumor*" OR AB "cancer*" OR AB "carcinoma*")

2.(AB "pain*" OR AB "nocicept*" OR AB "neuropath*")

3.(1 AND 2)

1.(AB "Rehabilitation" OR AB "Cognitive Rehabilitation" OR AB "Neuropsychological Rehabilitation" OR AB "Neurorehabilitation" OR AB "Occupational Therapy" OR AB "Physical Therapy" OR AB "Psychosocial Rehabilitation")

2.(AB "Exercise" OR AB "Exercise Therapy" OR AB "Aerobic Exercise" OR AB "Weightlifting" OR AB "Yoga")

3.(AB "exercise therapy" OR AB "stretching" OR AB "tai chi" OR AB "yoga")

4.(AB "Psychotherapy" OR AB "Cognitive Behavior Therapy" OR AB "Behavior Therapy" OR AB "Psychotherapeutic Counseling")

5.(AB "cognitive behavioral" OR AB "relaxation" OR AB "breathing" OR AB "hypnosis")

6.(AB "Relaxation" OR AB "Relaxation Therapy")

7.(AB "Hypnosis")

8.(AB "hydrotherapy" OR AB "thermotherapy" OR AB "heat" OR AB "warm" OR AB "cold" OR AB "cool")

9.(AB "Alternative Medicine")

10.(AB "Acupuncture" OR AB "Aromatherapy" OR AB "Massage" OR AB "Herbal Medicine" OR AB "Meditation" OR AB "Osteopathic Medicine")

11.(AB "massage" OR AB "chiropractic" OR AB "manipulation" OR AB "acupuncture" OR AB "acupressure" OR AB "osteopath*" OR AB "homeopath*" OR AB "naturopath*" OR AB "aromathera*" OR AB "art" OR AB "music" OR AB "alternative" OR AB "complementary" OR AB "CAM")

12.(AB "transcutaneous electrical stimulation")

13.(AB "Electrical Stimulation" OR AB "Electrical Brain Stimulation" OR AB "Electroconvulsive Therapy")

14.(AB "Transcranial Magnetic Stimulation")

15.(AB "transcranial magnetic stimulation")

16.(AB "dorsal column stimulation")

17.(AB "spinal cord stimulation")

18.(AB "peripheral field stimulation")

19.(AB "dorsal root entry zone lesion*")

20.(AB "DREZ")

21.(AB "Osteopathic Medicine")

22.(AB "orthotics" OR AB "orthosis" OR AB "brace*")

23.(AB "nonpharmaco*" OR AB "non - pharmaco*")

1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23

RCT：

(TI "randomized controlled trial" OR AB "randomized controlled trial" OR TI "randomised controlled trial" OR AB "randomised controlled trial" OR TI "RCT" OR AB "RCT" OR TI "randomized clinical trial" OR AB "randomized clinical trial" OR TI "random allocation" OR AB "random allocation" OR TI "double-blind method" OR AB "double-blind method" OR TI "single-blind method" OR AB "single-blind method"