INPLASY PROTOCOL

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None declared.

A systematic review and meta-analysis protocol on how best to use non-pharmacologic therapies to manage chronic low back pain and depression in primary care

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Review question / Objective: **Primary aim - This meta-analysis will not only summarize a variety of non-pharmacologic therapies (NPTs) but also evaluate their efficacy in relieving depressive and pain symptoms in individuals living with chronic non-specific low back pain (CNSLBP) in the primary care setting. We will also perform subgroup analyses to identify possible confounders of the effects of NPTs including participant characteristics (e.g., gender, age, nationality, occupation, depression severity), CNSLBP characteristics (e.g., cause, duration, frequency, pain severity), and treatment characteristics (e.g., form, duration, and frequency). Review questions - We will endeavor to answer (1) whether to adopt NPTs when individuals living with CNSLBP have depressive symptoms; (2) which types and characteristics of NPTs can improve depressive and pain symptoms in individuals living with CNSLBP; (3) whether the effects of NPTs on depressive and pain symptoms vary according to participant, CNSLBP, and treatment characteristics, thereby providing evidence to support individual recommendations on prescribing specific and precise NPTs for different groups of individuals living with prolonged and persistent CNSLBP in primary care and daily nursing when they have poor psychological wellbeing.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 June 2022 and was last updated on 13 June 2022 (registration number INPLASY202260055).

INTRODUCTION

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low back pain (CNSLBP) in the primary care setting. We will also perform subgroup analyses to identify possible confounders of the effects of NPTs including participant characteristics (e.g., gender, age, nationality, occupation, depression severity), CNSLBP characteristics (e.g., cause, duration, frequency, pain severity), and treatment characteristics (e.g., form, duration, and frequency). Review questions - We will endeavor to answer (1) whether to adopt NPTs when individuals living with CNSLBP have depressive symptoms; (2) which types and characteristics of NPTs can improve depressive and pain symptoms in individuals living with CNSLBP; (3) whether the effects of NPTs on depressive and pain symptoms vary according to participant, CNSLBP, and treatment characteristics, thereby providing evidence to support individual recommendations on prescribing specific and precise NPTs for different groups of individuals living with prolonged and persistent CNSLBP in primary care and daily nursing when they have poor psychological wellbeing.

Rationale: Low back pain (LBP) is recognized by the World Health Organization as a global health problem, and it is one of the commonest reasons that patients seek healthcare and nursing services worldwide. Recent analyses of Global Burden of Disease (GBD) data in 204 countries and territories showed that LBP accounts for the highest burden of 150 musculoskeletal disorders, with approximately 568.4 million prevalent cases, 223.5 million incident cases, and 63.7 million years lived with disabilities globally. Moreover, GBD data show that the national economic burden from LBP was similar to that of high-cost diseases such as cardiovascular disease, cancer, and autoimmune disease. Chronic non-specific LBP (CNSLBP) is the most common type of chronic LBP, and it does not have a precise pathoanatomical cause. It is estimated that up to 90% of individuals experiencing chronic LBP have CNSLBP. Many patients with CNSLBP have ongoing and recurrent complaints, with the effects of CNSLBP extending beyond pain and resulting in significant mental health difficulties, including depression; indeed, people suffering from chronic LBP have a higher prevalence of depression than the general population. A retrospective cohort study found that those with chronic LBP and comorbid depression used more healthcare resources and had other comorbidities such as diabetes, hypertension, chronic obstructive pulmonary disease, and anxiety. A one-year prospective cohort study concluded that several psychological features are risk factors for persistent, severe LBP and disability, especially depression and catastrophization. In addition, converging evidence indicates that depressive symptoms may aggravate pain intensity, amplify disability, and worsen treatment outcomes in patients with chronic LBP, triggering a vicious cycle of LBP and depression. These studies highlight that therapeutic regimens that consider the patient's psychological profile may be more effective than those that focus on physical symptoms such as pain and disability alone when managing CNSLBP.

Condition being studied: The current cornerstone of low back pain (LBP) management is relieving pain, restoring function, and improving prognosis to improve health-related quality of life (HRQoL). The latest American College of Physicians Clinical Practice Guidelines strongly recommend non-pharmacologic therapies (NPTs) as first-line options for patients with chronic LBP, with moderate-quality evidence for exercise, multidisciplinary rehabilitation, acupuncture, and mindfulness-based stress reduction. The clinical practice guideline also calls for prioritizing NPTs when treating and managing chronic non-specific LBP (CNSLBP), because NPTs have fewer associated harms but equivalent efficacy to pharmacologic options. However, the treatment of CNSLBP remains challenging because: 1) implementing these guidelines in clinical practice is limited by each clinician's expertise and experience; 2) the clinical efficacy of some guideline-endorsed NPTs for CNSLBP remain controversial; and 3) a

lack of individualized treatment may adversely affect outcomes in special patient populations with high-risk, poor prognostic factors such as psychiatric comorbidity. Considering these problems, the effects of non-guideline-recommended NPTs on CNSLBP have been investigated, such as extracorporeal shockwave therapy, myofascial release, Kinesio taping, and mechanical diagnosis and therapy. There have also been meta-analyses comparing the efficacy and safety of different NPTs in patients with CNSLBP, which have aimed to comprehensively and objectively guide clinician decision-making with respect to efficacy, harm reduction, and cost efficiency based on patient preference. Nevertheless, most existing studies have focused on evaluating the effects of various NPTs on pain, physical function, and HRQoL without considering the heterogeneity in patient characteristics with respect to the treatment and management of CNSLBP, reducing the applicability of the results in practice. This may be one reason why conclusions about the efficacy of some NPTs for CNSLBP differ. A recent systematic review and meta-analysis reported high-quality prognostic factors for LBP, highlighting that depressive symptoms are associated with disability and worse recovery. However, it is still uncertain how best to treat LBP patients with different degrees of severity of depression in the primary care setting. Given the high incidence and poor prognosis of depressive symptoms in chronic LBP, especially in the context of the COVID-19 pandemic, a systematic review is needed to assess all existing NPTs for the management of LBP in patients with varying degrees of depression managed in primary care. This would help to establish patient-centered management and recovery.

METHODS

Search strategy: To obtain more comprehensive evidence, three main subject heading domains will be combined with the AND operator: one to designate the clinical condition (low back pain), the second to designate the outcome condition (depressive symptoms), and the third to designate the study type (randomized controlled trial). To retrieve all potentially relevant studies, a combination of medical subject headings (MeSH) and free-text words related to low back pain, depressive symptoms, and randomized controlled trials will be used. Keywords and subject terms will be customized for each database and any necessary adjustments made prior to running the search. The retrieval will be conducted with no restrictions regarding the year but limited to English. If discrepancies occur, a consensus will be reached through consultation.

Participant or population: The study participants of interest will be adult patients (aged ≥18 years) with a diagnosis suggesting chronic non-specific low back pain (CNSLBP) based on at least one current or past definition or guideline. CNSLBP is usually defined as a primary area of pain, stiffness, or muscle tension located typically below the costal margin and above the inferior gluteal folds lasting 12 weeks or more, with or without sciatica (pain radiating from the buttock and downward along the course of the sciatic nerve). "Non-specific" indicates that the diagnosis of CNSLBP required exclusion of definite pathoanatomical causes of low back pain (LBP) such as radicular syndrome, cauda equina syndrome, structural deformities, spinal infection, spinal cord infarction, malignancy, fracture, osteoporosis, herniation, ankylosing spondylitis, rheumatoid arthritis, and rheumatic pain or other inflammatory conditions. In addition, participants with chronic LBP associated with specific conditions such as pregnancy, childbirth, chronic fatigue, and fibromyalgia will be excluded, as will studies focusing exclusively on acute exacerbations of CNSLBP. Studies including participants with a mixture of non-specific and specific chronic LBP will only be eligible if data on those two participants groups are presented separately. If a trial involves a mix of CNSLBP and other chronic pain patients, we will include the study only if outcomes are reported separately for our study population of interest or if at least

90% of trial participants are ≥18 years of age with predominant CNSLBP. We will not apply restrictions regarding gender, ethnicity, education, nationality, occupation, and economic status and cause, duration, intensity, frequency, and severity of CNSLBP.

Intervention: Any non-pharmacologic therapy (NPT) commonly used to manage and/or treat chronic non-specific low back pain (CNSLBP) in clinical primary care will be eligible for review. Surgical and interventional pain management (e.g., spinal injections, radiofrequency denervation, deep brain and spinal cord stimulation) will be excluded, as these are invasive procedures only recommended for low back pain as next-line treatment in secondary or tertiary care settings for severe or refractory CNSLBP where conservative primary care treatments have failed; they are not recommended in any clinical practice guideline when LBP is chronic and non-specific.

Comparator: Control interventions will be no treatment, waiting lists, or pharmacological therapies. The following comparisons will be considered: (1) non-pharmacologic therapy (NPT) alone versus no treatment or waiting lists; (2) NPT alone versus pharmacological therapy alone; (3) NPT plus pharmacological therapy versus non-pharmacologic therapy alone; and (4) NPT plus pharmacological therapy versus pharmacological therapy alone. We will exclude trials comparing only different types of NPT or different treatment doses with the same intervention.

Study designs to be included: Only full text articles of peer-reviewed and published randomized controlled trials (RCTs), including all relevant parallel-group RCTs including the first phase of crossover trials and cluster-randomized trials, will be considered eligible for this review. Where several publications report findings for the same population, the most comprehensive report including the largest sample size, longest follow-up, complete methods section, and comprehensive reporting of results report will be chosen.

Eligibility criteria: Eligibility criteria will be established according to the review objectives and the participants, intervention, comparison, outcome, and study design (PICOS) approach.

Information sources: Studies will be identified through a literature search from inception to search date in the following English electronic databases: 1) PubMed; 2) Embase; 3) Cochrane Library; and 4) Web of Science. In addition, the reference lists of previously published relevant reviews and included randomized controlled trials will be manually searched to identify any other eligible publications missed by electronic searching. We will not include grey literature due to the high risk of bias from a lack of peer review. The search will be repeated prior to the publication of the review in an aim to include any potentially eligible study that might have been published after the initial search.

Main outcome(s): The primary outcome will be a reduction in the severity of depressive symptoms at the end of the treatment period measured as a continuous variable according to the Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI), Self-Rating Depression Scale (SDS), Montgomery-Åsberg Depression Rating Scale (MADRS), Patient Health Questionnaire-9 (PHQ-9), or any other depressive symptoms rating scale with evidence of adequate validity and reliability.

Additional outcome(s): The secondary outcomes will include: (1) Total effective rate (as a dichotomous outcome): defined as the proportion of participants with a clinically relevant improvement according to a predefined change in validated depressive symptoms rating scales at the end of the treatment period. (2) Pain intensity: measured as a continuous variable on any validated scales, such as a Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), McGill Pain Questionnaire (MPQ), or other rating scale with evidence of adequate validity and reliability at the end of the treatment period. (3) HRQoL: measured as a

continuous variable on any validated HRQoL scale such as the Medical Outcomes Study 36/12-Item Short-Form Health Survey (SF-36/12), Brief Form of the World Health Organization's Quality of Life Questionnaire (WHOQOL-BREF), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Nottingham Health Profile (NHP), or other well-recognized HRQoL scales with evidence of adequate validity and reliability at the end of the treatment period. (4) Acceptability (dichotomous outcome): defined as the proportion of participants who drop out of the study for any reason during treatment delivery. (5) Tolerability (dichotomous outcome): defined as the proportion of participants who discontinued treatment due to any adverse events during treatment delivery. (6) Safety (dichotomous outcome): defined as the proportion of participants who experienced at least one adverse effect during treatment delivery.

Data management: According to the inclusion criteria, a standardized electronic data extraction form will be prepared prior to data extraction. We will also conduct calibration exercises before starting data extraction and management to ensure high consistency and accuracy of extractions between reviewers. For studies fulfilling the inclusion criteria, four reviewers will independently extract data from the included randomized controlled trials (RCTs), including study details (article title, first author, publication year, publication source, publication language, country, setting), study design (eligibility criteria, recruitment method, randomization method, allocation concealment method, blinding method, time points, follow-up period), notes (financial source, competing interests), participant characteristics (number of arms, sample size, gender proportion, mean age, diagnostic criteria, baseline chronic non-specific low back pain condition, baseline depressive severity), intervention and comparison characteristics (type, frequency, number of sessions, session duration, total period in the intervention, type of comparison, details of comparison), outcome data (methods of outcome assessment, primary outcomes, secondary outcomes, the improved Jadad scale score, the Cochrane Collaboration's Risk of Bias), and conclusions (key findings of the study).

Quality assessment / Risk of bias analysis: The methodological quality of each eligible study will be assessed by two or more independent reviewers according to the Revised Cochrane Collaboration's Risk of Bias (RoB) v2.0 tool. This version is structured into five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each domain includes several signaling questions that elicit information relevant to an assessment of risk of bias. Based on the answers to all signaling questions in one domain, we will rate the domain as a low risk of bias, some concerns, or a high risk of bias. Finally, we will obtain an overall risk of bias judged as low risk of bias, some concerns, or a high risk of bias considering the risk of bias judgement in five domains. While the Cochrane RoB assessment tool represents a qualitative tool, the improved Jadad scale will be used as a quantitative method to assess the methodological quality of the included studies. The improved Jadad scale rates studies according to (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel or outcome assessment, and (4) reporting of the number of dropouts and reasons for withdrawal. Each trial will be scored on a scale from 0 to 7, with 0–3 indicating low quality, 4–5 moderate quality, and 6–7 high quality. The inter-rater reliability of two reviewers assessing the risk of bias will be calculated. Any discrepancy in the RoB assessment between the two reviewers will be resolved through arbitration by discussion. If the disagreement persists, a third reviewer will be consulted to reach consensus.

Strategy of data synthesis: Eligible randomized controlled trials (RCTs) and results will be qualitatively summarized. If more than three studies evaluate similar

treatments and outcomes, a meta-analysis will be performed using RevMan v5.4 software (Cochrane, London, UK) to estimate the treatment effect. For meta-analyses, we will include studies that score equal to or greater than 4 on the improved Jadad scale (range 0-7), since these studies can be regarded as having sufficient similarity in clinical characteristics and high methodological quality. We will adopt the Mantel-Haenszel random-effects model for all meta-analyses due to the broad spectrum of non-pharmacologic intervention components in the included studies. The pooled estimates of the standard mean difference (SMD) with 95% confidence intervals (CIs) will be calculated for continuous outcomes, while for dichotomous outcomes, data will be analyzed using the risk ratio (RR) with 95% CIs. Throughout the analyses, two-sided tests will be used and a P-value 0.1 and I2 index values <50% will be regarded as having no statistical heterogeneity. When the P-value is ≤0.1 and I2 index is ≥50%, the study will be considered to have substantial heterogeneity.

Subgroup analysis: Where sufficient data are available in the included randomized controlled trials (RCTs), we will carry out subgroup analyses and multiple meta-regressions for relevant outcomes to investigate possible sources of heterogeneity including in the following characteristics: publication year; publication language; setting; sample size; gender; age; nationality; ethnicity; occupation; degree of depressive symptoms; diagnostic criteria; cause, severity, frequencies, and duration of chronic non-specific low back pain; format, frequency, and number of sessions; session duration; total period of intervention, type of comparison; time-point of outcomes; duration of follow-up; and the methodological quality of the selected RCTs.

Sensitivity analysis: Sensitivity analyses will be performed for relevant outcomes to explore the robustness and reliability of the review conclusions where feasible. Meta-analysis will be repeated by excluding each related study with a small sample size, a high risk of bias, and incomplete results one at a time and re-evaluating the effect size. If the results are inconsistent, they will be discussed, and caution will be taken when drawing conclusions.

Language: English.

Country(ies) involved: China; USA; Singapore.

Keywords: Non-pharmacologic therapies, efficacy, chronic low back pain, meta-analysis, nursing, randomized controlled trial, safety, systematic review, protocol.

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