Efficacy of non-pharmacological interventions on depressive symptoms in patients with Parkinson’s disease: a study protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Depression is the most dominant non-motor symptom of Parkinson’s disease (PD), with a prevalence of up to 50%, and can lead to a range of psychiatric and psychological problems that can affect quality of life and overall functioning. While several randomised controlled trials (RCTs) have tested the effect of certain non-pharmacological interventions on the outcome of PD depression symptoms, the comparative benefits and harms of these remain unclear. We will conduct a systematic review and network meta-analysis to compare the efficacy and safety of different non-pharmacological interventions for patients with PD depression.

Methods and analysis We will search PubMed, Web of Science, Cochrane, Embase, Google Scholar, the Chinese National Knowledge Infrastructure, the Chinese Biomedical Literature Database, WanFang Data and the Chongqing VIP Database from their inception date to June 2022. The studies will be limited to results published in English or Chinese. The primary outcomes will be the changes in the depressive symptoms, while secondary outcomes will include adverse effects and the quality of life. Two researchers will screen those documents that meet the inclusion criteria, extracting data according to the preset table and evaluating the methodological quality of the included studies using the Cochrane Risk of Bias 2.0 Tool. The STA and ADDIS statistical software will be used to conduct a systematic review and network meta-analysis. A traditional pairwise meta-analysis and a network meta-analysis will be performed to compare the efficacy and safety of different non-pharmacological interventions, ensuring the robustness of the findings. The Grading of Recommendations Assessment, Development and Evaluation system will be used to assess the overall quality of the body of evidence associated with the main results. The publication bias assessment will be conducted using comparison-adjusted funnel plots.

Ethics and dissemination All the data for this study will be extracted from published RCTs. As a literature-based systematic review, this study does not require ethical approval. The results will be disseminated through peer-reviewed journals and national/international conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study intends to compare the efficacy of all available non-pharmacological interventions in improving depression symptoms in patients with Parkinson’s disease through a network meta-analysis.

⇒ The study will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for incorporating network meta-analysis.

⇒ We will only retrieve data from Chinese and English databases, which could result in language bias.

⇒ The quality of the evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach.

⇒ The Cochrane Risk of Bias Tool will be used to assess the methodological quality of individual randomised controlled trials by two reviewers independently.

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INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disease, characterised by the inexorable progression of motor symptoms and non-motor symptoms.1–3 PD affects 1–2 per 1000 people at any time and 1% of people over the age of 60 years.4 The clinical hallmark of PD is a motor syndrome characterised by bradykinesia, rest tremor and rigidity, in addition to changes in posture and gait. PD is associated with a variety of non-motor symptoms, including hyposmia, constipation, urinary dysfunction, memory loss, depression, pain and sleep disturbances, severely affecting the patient’s overall functioning.5 Depression is one of the most common non-motor symptoms of PD, with depressive symptoms potentially occurring at any stage of the disease.6 The prevalence of
Depression has increased significantly in recent years, with up to 50% of people with PD presenting with this condition. Depression is usually accompanied by anxiety and is characterised by sadness, loss of interest, guilt, increased fatigue, helplessness, reduced drive, depressed mood, irritability and pessimism about the future. Moreover, some of the clinical features of PD and its motor and non-motor symptoms appear to be influenced by the patient’s depression, owing to their psychomotor retardation, reduced imitation and apathy. These factors lead in turn to increased motor impairment, cognitive decline and a reduced quality of life, with serious consequences for the patient’s physical and mental health. Depres-

sion is the most prevalent psychiatric problem in patients with PD and has a wide range of implications for PD management. Nevertheless, the attention it has received, to date, has been insufficient.

The pathophysiology of PD-associated depression may include: the degeneration of neurotransmitter systems, immunological impairment and gut dysbiosis. It may, additionally, be influenced by genetic, environmental and other risk factors. Depression in PD is related mainly to the degeneration of dopamine-producing neurons in the substantia nigra pars compacta region of the midbrain. It is also associated with imbalances and changes in neurotransmitter systems (dopamine, serotonin and noradrenergic hormones), the degeneration and depletion of NE and 5-HT levels, as well as disturbances in their transporters and autoreceptors. All of these factors may contribute to the emergence of depressive symptoms in patients with PD. Disturbances in monoaminergic transmission and the hypothalamic–pituitary–adrenal axis, increased neuroinflammatory events and impaired trophic support are thought to contribute to neuronal atrophy and death in PD. By means of diffusion tensor imaging techniques, microstructural abnormalities of the brain—such as impaired network integrity for the temporal and frontal cortices—have also been identified in patients with PD depression.

Imaging studies found that PD-associated depression is linked with numerous anatomical changes occurring in the amygdala, thalamus, hippocampus and ventral striatum. However, the pathophysiological mechanism of PD depression is not yet fully clear; it may be related to brain structure changes, including those in the limbic system and amygdala, as well as pathological changes such as monoaminergic disturbances, hippocampal atrophy and neuroinflammation.

Currently, the most effective treatment approach for PD depression is considered to be a combination of anti-parkinsonism medications with antidepressants. Although the latter constitute the first-line intervention for the treatment of PD depression, they have not achieved satisfactory results with regard to efficacy, tolerability and patient acceptability. Pharmacological treatments, such as dopamine agonists and monoamine oxidase inhibitors, fail to provide either adequate symptom control or a high quality of life. Dopaminergic medications induce severe side effects such as serious dyskinesias. Depression could be secondary to long-term levodopa treatment in approximately 35% of patients with relevant complications. Until now, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have been considered the standard treatment for depression in patients with PD. Gastrointestinal events are more common with SSRIs but the TCAs—amitriptyline and imipramine—also impose a high burden of adverse effects in the treatment of PD depression, potentially including drowsiness, urinary retention, constipation, cognitive impairment, dementia, hypotension and cardiac conduction abnormalities. Due to the significance of the side effects, the use of TCAs and monoamine oxidase type B inhibitors in combination with serotonergic antidepressants should be limited. In view of the significant side effects of the antidepressants, there is an urgent need for effective non-pharmacological treatments for PD depression.

A range of non-pharmacological intervention options is available, including physical therapy, psychotherapy and exercise therapy. Clinical non-pharmacological interventions such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), electroconvulsive therapy (ECT) and bright light therapy (BLT) have been proven effective for the depressive symptoms of PD. However, some studies have found that treatments such as ECT, DBS and TMS may have associated side effects and poor patient acceptance, leading to a decline in quality of life. Second, some non-pharmacological interventions such as cognitive–behavioural therapy (CBT), psychotherapy, music therapy and mindfulness-based therapies (MBTs) may be effective, although there is little high-quality, evidence-based medical evidence to support music and positive-thinking therapy. Exercise interventions include aerobic exercise, resistance exercise, dance, yoga and tai chi. These are recommended for the prevention and treatment of PD but also have a positive impact on patients’ depressive symptoms.

Currently, there is no evidence-based evaluation in the field comparing the clinical efficacy of different non-pharmacological interventions for the treatment of PD depression. For the current study, therefore, non-pharmacological interventions commonly used in clinical practice will be selected and relevant clinical evidence will be integrated using traditional meta and network meta-analysis (NMA) methods to compare the clinical efficacy and safety of various non-pharmacological interventions and thus identify the most effective non-pharmacological intervention for clinical treatment.

**METHODS AND ANALYSES**

This protocol was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement guidelines. Our study was established and registered with the International Prospective Register of Systematic Reviews (PROSPERO).
database. Any amendments to the protocol will be made through PROSPERO.

Inclusion criteria
Types of studies
The study will only include randomised controlled trials (RCTs) presented in English or Chinese. Non-experimental studies such as cohort, case–control and pre/post-studies will be excluded.

Types of participants
We will search for RCTs where participants were enrolled as follows: (1) participants were diagnosed with PD with depressive symptoms (including subthreshold depression symptoms); (2) participants were evaluated by depression scales; and (3) no restrictions on age, sex, ethnicity, nationality or educational levels.

Types of interventions
Based on our previous literature search, the non-pharmacological interventions may consist of: (1) exercise programmes (aerobic exercise, resistance exercise, dance, yoga and tai chi); (2) psychotherapy: emotion focused or cognition focused; (3) CBT: talk that focuses on current behaviours and problems; (4) MBT: focusing in a particular purposeful, present, non-judgemental way; (5) music therapy: the use of sounds and music; (6) rTMS: a non-invasive neuromodulation technique based on electromagnetic induction; (7) DBS: electrical stimulation of specific brain areas, such as the subthalamic nucleus and globus pallidus pars inferens; (8) ECT: the application of current to the head; and (9) BLT: specific light exposure. Studies that used either single or multiple non-pharmacological intervention(s) will be considered.

Types of control groups
Treatments in the comparison groups can be standard treatment (antidepressants or usual care), placebo or sham interventions.

Types of outcome measures
The primary outcome measures will be the efficacy outcomes for PD depression, including: the Beck Depression Inventory, Hamilton Depression Scale, Hospital Anxiety and Depression Scale, Self-Rating Depression Scale, Geriatric Depression Scale and Montgomery-Asberg Depression Rating Scale.

The secondary outcomes will include measures of quality of life such as the Parkinson’s Disease Questionnaire-39, and of adverse events, whereby the safety of the non-pharmacological interventions is tested by the incidence of adverse events.

Exclusion criteria
We will also apply the exclusion criteria as follows: (1) inconsistent research types (non-RCTs): cohort studies, case–control studies, case reports, literature reviews; (2) literature where the full text is absent, despite all efforts to obtain it; (3) the absence of any relevant reported outcomes or duplicate studies. Studies that meet any of the criteria above will be excluded.

Data sources and search strategy
The literature will be comprehensively retrieved from the following databases: PubMed, Web of Science, Cochrane, Embase, Google Scholar, the Chinese National Knowledge Infrastructure, the Chinese Biomedical Literature Database, WanFang Data and the Chongqing VIP Database. The search period will range from the date of establishment of the database to June 2022. The studies will be limited to results published in English or Chinese. Based on the principle of combining subject words with free words, the search will be conducted using search terms such as “non-pharmacological intervention”, “Parkinson”, “RCT”, “depressive”, “repetitive transcranial magnetic stimulation”, “deep brain stimulation” and “electroconvulsive therapy”. According to the search modes of different databases, the search may be adjusted as appropriate to generate a comprehensive search. Furthermore, to identify any further relevant publications of relevance, the authors will manually check the bibliographies of every trial retrieved, and of any existing systematic reviews and meta-analyses. With regard to studies that are identified but unavailable, attempts will be made to contact the authors by email. Publications returned by the search but which do not include the study data will be excluded. A specific search strategy is presented in the online supplemental materials using PubMed as an example.

Study selection
According to the above-mentioned eligibility criteria, two researchers (XJ and HS) will independently search literature in English and Chinese published in English and Chinese electronic databases, and use EndNote V.X9 software to conduct the search strategy and remove duplicates. The two researchers will independently undertake an initial screening of the studies by reading the titles and abstracts according to the inclusion criteria. Then, the second screening will be conducted using a full-text reading and recording the reasons for exclusion. In the event of inconsistent results from the two researchers, and where the disagreement cannot be resolved by discussion, the third researcher (HL) will be consulted. The selection procedure is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses-compliant flow chart diagram (see figure 1).

Data extraction
We (HS and JJ) will independently extract the relevant data from the included articles. The extracted data will be as follows: (1) basic information (study type, first author, year of publication and country); (2) participants (mean age and range, gender, sample size, diagnostic criteria and course of the disease); (3) interventions (including intervention type and details of the intervention, including the session, duration or dosage of the intervention); (4)
controls (for example, control type, and details of the control session, duration or dosage); (5) outcomes of interest (data for each measurement outcome, adverse events and duration of follow-up). The information will then be compiled and imported into a predesigned Excel form. We will contact the corresponding authors for any necessary further information or data, where possible. Disagreements with regard to any of the extracted data will prompt recheck of the original document to address the error.

Risk of bias assessment

Two reviewers (JJ and HS) will independently assess the risk of bias in the included studies, using the Cochrane Risk of Bias Tool for Randomised Trials 2.0 (RoB 2.0). RoB 2.0 evaluates the following domains: randomisation process, deviations from the intended interventions, missing outcome data, outcome measurement and reporting bias. Each domain will be assigned a category characterising the potential risk of bias as either ‘low risk’, ‘some concerns’ or ‘high risk’. Assessments will be produced in respect of each individual domain and in addition, the overall risk of bias rating, which will be presented by means of a traffic light plot and a risk of bias summary bar graph. If any disagreement exists, third-party experts will be invited to help discuss and explain the quality evaluation.

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group focus will be used to rate the certainty of the efficacy estimations,
based on the NMA for all of the comparisons (direct and indirect) and all of the results of interest. Two reviewers will use the GRADE system to independently evaluate the quality of the evidence for each outcome, which will be assessed according to the following five main criteria: risk of bias, imprecision, indirectness, heterogeneity, publication bias. The certainty of evidence will be rated according to four levels: high, moderate, low or very low. The GRADEprofiler software (GRADEpro, V.3.6.1) (available at www.Gradeworkinggroup.org) will be used to conduct the evaluation processes.

**Statistical analysis**

Where there are more than two studies existing on the same pair of interventions, we will use STATA Statistical Software V.15 (StataCorp, College Station, Texas, USA) for standard pairwise meta-analysis, and the results will be compared with those from the NMA. For continuous data, the mean difference with the corresponding 95% CIs of the change score will be reported as the measure of relative treatment effects. When trials use different measurement scales for a certain outcome, the standardised mean difference with 95% CIs will be calculated. For dichotomous outcomes, the relative risk with the corresponding 95% CIs of the adverse event data will be considered the measure of treatment safety.

We will perform NMA to simultaneously compare multiple interventions. For each outcome, a network plot of all included comparisons will be generated using Stata V.15, where interventions are represented by nodes and where the line between nodes represents a direct comparison between the two. The size of the nodes and lines are proportional to the number of studies included. In addition, Stata V.15 will also be performed with surface under the cumulative ranking curve, illustrating the ranked probabilities of different non-pharmacological interventions on various outcomes.

NMA will be performed as the primary method for data synthesis. Bayesian NMA will be performed for each outcome with a random-effects model in the ADDIS V.1.16.8 software (Gert van Valkenhoef, Groningen, The Netherlands), which adopts the Bayesian Markov Chain Monte Carlo (MCMC) algorithm. ADDIS software uses relevant instructions to call the data results of the random-effects model based on the Bayesian MCMC algorithm for prior evaluation and processing. To set the initial value, four Markov chains will be used, with the initial value of the model to be set to 0.5, the refinement iteration step set to 10 and the number of iterations to be 50000. Of these, the first 20000 iterations will be used for annealing to eliminate the influence of the initial value, with the final 30000 iterations used for sampling.

**Assessment of heterogeneity**

In each pairwise comparison, we will use the $X^2$ test and $I^2$ statistic to describe heterogeneity. Statistical heterogeneity ($p>0.1$, $I^2 \leq 50\%$) indicates that there is no significant heterogeneity among the studies, and a fixed-effects model will therefore be suitable for meta-analysis. Otherwise, heterogeneity ($p<0.1$, $I^2 >50\%$) indicates the existence of significant heterogeneity, and the random-effects model will therefore be appropriate for the meta-analysis. Should the elimination of a high degree of heterogeneity be impossible, the study will adopt the descriptive review method.

**Assessment of similarity and consistency**

Similarity and consistency will be evaluated to obtain valid and credible results. Owing to the challenges of clarifying similarity by means of statistical analysis, similarity will be assessed according to clinical characteristics and methodological characteristics. Study design, participant characteristics and interventions will be included in the assessment.

The Node-Split method will be used for inconsistency testing. Where no obvious difference is observed between the studies within the subgroup ($p>0.05$), the heterogeneity of the included study will be considered to be low. The analysis will thus be based on a consistency model. Otherwise, where $p<0.05$, this demonstrates statistical significance and indicates inconsistency, establishing that the heterogeneity of the included studies is high. Meanwhile, an inconsistency model will be used for the analysis. A consistency model or an inconsistency model will be chosen based on the results.

ADDIS software mainly evaluates the final iterative effect of the interchain and intrachain variances through the convergence of the model, that is, the subsequent evaluation through the potential scale reduced factor (PSRF) parameters. The recommended use of this software is to limit the PSRF value, which is more reasonable to be between 1 and 1.05. If the PSRF value is not very close to 1, the expansion of the model can continue. Where research through software analysis calculations and data analysis establishes a PSRF that is close to or equal to 1, this indicates that good convergence performance has been achieved, and that the results obtained from the consistency model analysis are reliable.

**Subgroup analysis and sensitivity analysis**

If the evidence suggests significant statistical or clinical heterogeneity, this will be investigated by conducting further subgroup and sensitivity analyses, to explore the possible sources of heterogeneity and inconsistency. Subgroup analysis will be performed based on the average age of participants, sex, the course of the disease and the treatment time since these factors are particularly important for efficacy and safety. We will also conduct sensitivity analyses for outcomes by excluding trials with imputed data, trials with an overall sample size smaller than 20 and trials rated as having a high risk of bias. In addition, the sensitivity analysis will be performed by excluding one article at a time, with subsequent observations made as to the robustness of the results.
Assessment of publication bias
If, in respect of each treatment comparison, over 10 studies are included in the NMA, a comparison-adjusted funnel plot with Egger’s test will be used to investigate any potential publication bias.54,55

Patient and public involvement
There will be no direct patient or public involvement in any aspect of this study, including posing the research question, establishing the study design and methods, planning the data analysis or drafting this manuscript.

Ethics and dissemination
Ethics approval is not required for this protocol because we will only pool published data. The results will be disseminated through peer-reviewed journals and national/international conference presentations.

DISCUSSION
PD depression engenders inherent emotional distress in patients and may further negatively impact their quality of life, motor and cognitive deficits, functional disability and many other clinical aspects of the disease, exerting a negative influence and hindering PD management and treatment.56–58 The side effects of drug treatment for PD depression may aggravate the patient’s condition, in contrast to certain non-pharmacological treatments which have fewer side effects.57 Furthermore, evidence exists for the reduction of PD depression by a range of interventions, such as rTMS, DBS, ECT, BLT, CBT, psychotherapy, yoga, music therapy, MBTs, aerobic exercise, resistance exercise, dance and tai chi.59–63 To further clarify the efficacy of different non-pharmacological treatments, the NMA will be performed to produce direct and indirect comparisons of the various non-pharmacological interventions.

Traditional meta-analysis approaches are appropriate for exploring interventions but are incapable of determining the optimal intervention types for patients with PD depression. However, systematic reviews and NMA approach combine direct evidence with indirect evidence, achieving a comparison of non-pharmacological interventions which has not been evaluated directly.64 Furthermore, by virtue of its comparison of the effectiveness and safety of non-pharmacological treatments, it is anticipated that this NMA will produce a ranking of non-pharmacological treatments for PD depression.65 The study will involve a comprehensive and systematic search for literature in public databases, which will include RCT as the sole, eligible study type. It is undeniable, however, that this study will also have some limitations. First, non-pharmacological interventions for PD depression constitute a very broad area of research, yet this study concentrates on a number of potentially effective therapies—physical, psychological and exercise therapy, among others—which may limit its applications in clinical practice. Second, the interpretation based on evidence from the NMA for ranking the results is limited and will therefore need to be combined with clinical experience and involve consideration of the specific situations of individual patients with PD depression.

To the best of our knowledge, this study will be the first systematic review and NMA attempt to investigate the efficacy and safety of non-pharmacological interventions for the treatment of PD depression. The results of this study may assist patients and therapists in selecting the optimal treatment to improve PD depression and may also provide convincing evidence as a basis for treatment guidelines.

Contributors GW and HL conceived the idea and initiated this protocol. GW and XQ contributed to the development of the search strategy for this review protocol, which was revised by HL. The manuscript was prepared and written by XJ and LZ. HL, WS, CO, HS and JJ participated in the critical revision of the manuscript and arbitrated in cases of disagreement to ensure the absence of errors. All authors read and gave input to the final draft of the protocol.

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Competing interests None declared.

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