INPLASY PROTOCOL

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Conflicts of interest:
None.

Non-pharmacological interventions for depressive disorder in patients after traumatic brain injury (TBI): a protocol for a systematic review and network meta-analysis

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Review question / Objective: **We posed the following questions: (1) Are non-pharmacological interventions effective and safe for depressive disorder after TBI? (2) If so, among these non-pharmacological interventions, which is the most comparatively effective, safe, and acceptable intervention to manage depressive symptoms or treat depressive disorder after TBI? To answer these questions, we will perform a systematic review and Bayesian network meta-analysis (NMA) together with traditional pairwise meta-analysis to examine the relative efficacy, effectiveness, safety, tolerability and acceptability of non-pharmacological interventions, and then to identify the most effective non-pharmacological intervention for depressive disorder after TBI.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 August 2020 and was last updated on 07 August 2020 (registration number INPLASY202080022).

INTRODUCTION

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pairwise meta-analysis to examine the relative efficacy, effectiveness, safety, tolerability and acceptability of non-pharmacological interventions, and then to identify the most effective non-pharmacological intervention for depressive disorder after TBI.

Condition being studied: Due to the chronicity of depressive symptoms and intolerability to pharmacological treatments, patients with TBI are inclined to choose non-pharmacological interventions as an alternative option or as an add-on treatment. Plenty of randomized controlled trials have been conducted to confirm the effect of non-pharmacological interventions such as psychological interventions, physical interventions, complementary and alternative medicine (CAM) interventions on depressive disorder.Recently, non-pharmacological interventions have drawn the attention of investigators. Despite there are a few systematic reviews showed the effectiveness of non-pharmacological and their potential for a lesser tolerability burden in this vulnerable TBI population, unfortunately the reliability of the evidence might be influenced by between-study heterogeneity and other risks of bias.

METHODS

Search strategy: To ensure a broad search, titles, abstracts and keywords will be searched using a combination of Medical Subject Headings (MeSH) words and free-text terms incorporating database-specific controlled vocabularies and text words related to randomized controlled trials, non-pharmacological intervention, depressive disorder or depression, TBI or traumatic brain injury, etc.

Participant or population: We will include studies that enrolled patients who had a disease history of TBI as well as were confirmedly primary diagnosed with depressive disorder, or had clinically significant depressive symptoms, based on at least one of the standardized international or domestic authorized diagnostic criteria or guidelines for clinical research such as Feighner criteria, Research Diagnostic Criteria, Diagnostic and Statistical Manual of Mental Disorders 3rd edition (DSM-III), 3rd revised edition (DSM-III-R), 4th edition (DSM-IV), 5th edition (DSM-5), and International Classification of Diseases10th revision (ICD-10), etc. We will not apply restrictions with regard to any information about age, gender, race, education status, nationality, economic status, severity and duration of disease, etc. A concurrent secondary diagnosis of another psychiatric disorder after TBI will not be considered as an exclusion criterion, but studies in which all patients have a concurrent primary diagnosis of another Axis I or II disorder will be excluded. In addition, the participants with TBI suffering from bipolar disorder, treatment resistant depressive disorder, subthreshold depressive disorder, seasonal affective disorders, peripartum depressive disorder, depressive disorder in dementia or psychotic depression will be also excluded.

Intervention: We plan to include any form of non-pharmacological intervention can be used as monotherapy or combined treatments to reduce depressive symptoms or resolve the presence of a diagnosable depressive disorder after TBI. The non-pharmacological interventions might have been psychological, medical, physical or CAM interventions, such as cognitive behavioural therapy (CBT), meditation, acceptance, and commitment therapy (ACT), electro-convulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), homeopathy, music therapy, traditional Chinese medicine non-pharmacological intervention (for example acupuncture, moxibustion, traditional Chinese exercise Qigong, Tuina, cupping)and so forth. Trials comparing the same type of non-pharmacological intervention, but at different numbers of therapeutic sessions, and different treatment conditions (with or without nurses' involvement) will be considered as the same node in the network meta-analysis.

Comparator: To assess the efficacy, effectiveness, safety, tolerability and acceptability of non-pharmacological interventions, we plan to compare them with each other, and conventional pharmacological interventions, as well as placebo control, including placebo drugs, sham interventions, no intervention, waiting list membership, etc.

Study designs to be included: Only randomized controlled trials using non-pharmacological interventions for patients with depressive disorder after TBI will be considered.

Eligibility criteria: The eligibility criteria of the studies were established in terms of participant, intervention, comparison, outcome and study design type (PICOS) approach.

Information sources: The Information sources form following electronic databases including PubMed, Ovid Medline, Cochrane Library, Web of Science database, Embase Database, China National Knowledge Infrastructure(CNKI), and Wanfang Data Chinese database.The reference lists of previously published reviews and selected RCTs will be tracked, and corresponding authors of chosen RCTs will be contacted if it is necessary. A list of medical journals will be hand searched in the university library. Any relevant ongoing or unpublished experimental studies that are relevant to this topic will be gained from the WHO International Clinical Trials Registry Platform (http://www.who.int/trialsearch), meta-Register of Controlled Trials (http:// http://www.controlled-trials.com), United States (US) National Institutes of Health Ongoing Trials Register (http://www.clinicaltrials.gov), and the Chinese Clinical Trial Registry (http://www.chictr.org/cn/). Potential gray literature will be searched in OpenGrey.eu. website. No publication language, publication date and publication status restrictions will be applied.

Main outcome(s): Overall efficacy (as a continuous outcome), it refers to mean improvement in depressive symptoms, as measured by overall mean change scores on continuous observer-rated scale (self-rated or assessor-rated) for depressive disorder from baseline to the end of the study duration.

Additional outcome(s): 1. Treatment response (as dichotomous outcome), defined as 50% or greater reduction from baseline to study end point in the study's primary observer-rated depression scale. 2. Remission rate (as dichotomous outcome), it refers to by the total number of patients who achieved the criteria of remission, defined as being below the threshold in depressive disorder rating score in different across trials. 3. Overall acceptability (as dichotomous outcome), operationalized as the proportion of participants who terminated the study early owing to any cause up to the end of the study duration. 4. Tolerability of treatment (as dichotomous outcome), defined as the proportion of patients who discontinued treatment due to any adverse events during the delivery of the non-pharmacological interventions. 5. Social functioning (as continuous outcome), as measured by overall change scores on any validated global assessment of functioning scales such as Global Assessment of Functioning (GAF) scale or quality of life scales. 6. Occurrence of adverse events (as dichotomous outcome), as reported in the include studies. 7. Suicide-related outcome (as continuous outcome), estimated by the reported the number of patients who deliberately self-harmed, attempted or completed suicide from baseline to study end point.

Quality assessment / Risk of bias analysis: Two reviewers will independently evaluate the methodological quality of eligible studies by using the risk of bias (ROB) assessment tool described in the Cochrane Collaboration Handbook. The risk of bias domains including: selection bias (random sequence generation, allocation concealment), performance and detection bias (blinding of therapists and participants), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data assessment for each outcome, differential dropout),

reporting bias (authors of RCTs explained whether reported outcomes were selective or not), other sources of bias (for example conflicts of interest, follow-up, different characteristics and representativeness of participants, non-intention-to-treat or per-protocol analysis and so forth). After assessing all the domains, we will evaluate the methodological quality of each study as low, unclear and high risk of bias. The inter-rater reliability of the two reviewers assessing the risk of bias will also be calculated. Any discrepancies in judgements of bias will be resolved through discussion with a third reviewer.

Strategy of data synthesis: If the data are not available for quantitative analysis or information are insufficient, we will summarize the evidence and give a narratively reported regarding the findings of our study. Traditional pairwise meta-analyses will be performed using STATA. We will perform network meta-analysis in a Bayesian hierarchical framework using WinBUGS with GeMTC package of R software to compare the efficacy, effectiveness, safety, tolerability and acceptability across of selected non-pharmacological interventions for depressive disorder after TBI, and obtain a comprehensive ranking of selected non-pharmacological interventions. We will use the Markov Chain Monte Carlo simulation technique to generate samples. The Brooks-Gelman-Rubin plots method will be adopted to assess model convergence. Convergence will be found to be adequate after running 50000 samples for each chain. These samples will then be set as the "burn-in" period, and then posterior summaries will be produced based on a further 100 000 subsequent simulations. For primary and secondary outcomes, the ranking probability (best, second-best, third-best and so on) of each non-pharmacological intervention will be calculated and graphically ranked with rank gram plots, and a treatment hierarchy using the probability of being the best treatment can be obtained. The surface under the cumulative ranking curve (SUCRA) and probability values will be summarized and reported as SUCRA for each non-pharmacological intervention. SUCRA curves will be described with percentages, 100% for the best treatment while 0% for the worst. In this systematic review, both fixed-effect and random-effect models in the Bayesian network meta-analysis will be considered based on the results of the deviance information criterion.

Subgroup analysis: When there had been a sufficient studies available, in order to investigate possible the sources of heterogeneity or inconsistency among the results of studies, the subgroup analysis on primary and secondary outcomes will be performed as following characteristics: for example (1) age group, (2) sex ratio, (3) the severity of depressive disorder at baseline; (4) the non-pharmacological intervention duration, (5) injury severity of TBI disease history, (6) time post-injury (acute versus long-term), (7) comorbid general psychiatric disorders, (8) risk of bias, and (9) sample size. Meanwhile, the network meta-regression meta-analysis will be conducted to explore the possible sources of heterogeneity.

Sensibility analysis: To verify the robustness of study conclusions, we will perform the sensitivity analysis of outcomes according to methodological quality, study quality, sample size, effect of missing data as well as the analysis methods.

Language: English.

Country(ies) involved: China.

Keywords: Non-pharmacological intervention; depressive disorder after TBI; network meta-analysis.

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