INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest:
None.

Thinking after COVID-19 outbreak: combined treatments versus TCM non-pharmacological intervention, pharmacotherapy for depression: protocol for a systematic review and network meta-analysis

Xu, MM[1]; Guo, Y[2]; Wang, L[3]; Wei, YL[4]; Chen, Y[5]; Yan, J[6].

Review question / Objective: **We posed the following questions: (1) Are combined treatments of Traditional Chinese Medicine non-pharmacological intervention and pharmacotherapy more effective, acceptable, and safer than either intervention alone in the improvement or treatment of depression? (2) If so, among these combined treatments, which is the most comparatively effective and acceptable combined treatment to manage depressive symptoms or treat depression? To answer above questions, we will perform a protocol for network meta-analysis together with pairwise meta-analysis to offer a retrospective investigation of current direct and indirect evidence regarding the efficacy, effectiveness, acceptability, and safety of the practice of Traditional Chinese Medicine non-pharmacological intervention combined with pharmacotherapy to improve or treat depression, and to identify cost-effective and optimal therapeutic approaches in depression to guide clinical treatment. First, using the pairwise meta-analysis, we will obtain estimates of efficacy, effectiveness, acceptability, and safety of combined treatments, in comparison with either intervention alone. Second, using Bayesian network meta-analysis, to examine the relative efficacy, effectiveness, safety, tolerability and acceptability of combined treatments, and then to identify the most effective combined treatment for depression. The results of this review should be timely useful for generating best practice guidelines for treating depression specifically directed to clinician, psychiatrist, or psychologist who work in this area during the COVID-19 pandemic.**

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 INPLASY202080023).

INTRODUCTION

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intervention alone in the improvement or treatment of depression? (2) If so, among these combined treatments, which is the most comparatively effective and acceptable combined treatment to manage depressive symptoms or treat depression? To answer above questions, we will perform a protocol for network meta-analysis together with pairwise meta-analysis to offer a retrospective investigation of current direct and indirect evidence regarding the efficacy, effectiveness, acceptability, and safety of the practice of Traditional Chinese Medicine non-pharmacological intervention combined with pharmacotherapy to improve or treat depression, and to identify cost-effective and optimal therapeutic approaches in depression to guide clinical treatment. First, using the pairwise meta-analysis, we will obtain estimates of efficacy, effectiveness, acceptability, and safety of combined treatments, in comparison with either intervention alone. Second, using Bayesian network meta-analysis, to examine the relative efficacy, effectiveness, safety, tolerability and acceptability of combined treatments, and then to identify the most effective combined treatment for depression. The results of this review should be timely useful for generating best practice guidelines for treating depression specifically directed to clinician, psychiatrist, or psychologist who work in this area during the COVID-19 pandemic.

Condition being studied: Nowadays, depression patients are increasingly intending to choose Traditional Chinese Medicine non-pharmacological interventions as an alternative option or as an add-on treatment. Recently, several randomized controlled trials or system reviews have been conducted to confirm superior effect of Traditional Chinese Medicine non-pharmacological interventions on improving depressive symptom compared to control conditions, often without having any side effects or adverse reactions. Additionally, combined with pharmacotherapy for depression, Traditional Chinese Medicine non-pharmacological interventions can also play a role in increasing effectiveness and alleviating toxic and side effects of antidepressants. Despite there is growing evidence from trials that combined treatments of Traditional Chinese Medicine non-pharmacological intervention and pharmacotherapy is superior to either intervention alone, unfortunately the reliability of the evidence might be influenced by between-study heterogeneity and other risks of bias. To the best of our knowledge, no published meta-analysis has authenticated the efficacy, effectiveness and acceptability of Traditional Chinese Medicine non-pharmacological intervention combined with pharmacotherapy to compare with each other, and either intervention alone, the effectiveness of Traditional Chinese Medicine non-pharmacological intervention combined with pharmacotherapy is still controversial.

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, Traditional Chinese Medicine non-pharmacological intervention, antidepressant or pharmacotherapy, depression or depressive disorder, etc.

Participant or population: We will include randomized controlled trials that enrolled participants, with confirmedly primary diagnosis of depression, to any degree, adopting any standard diagnostic guidelines to define participants suffering from depression, 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) or any diagnostic tool used for diagnosis or screening for depression. We will not apply restrictions with regard to age, gender, race, education status,

nationality, economic status, severity and duration of disease, etc. We will include a concurrent secondary diagnosis of another psychiatric disorder as long as the participants met the diagnostic criteria of depression, but studies in which all participants have a concurrent primary diagnosis of another Axis I or II disorder will be excluded. We will also exclude randomized controlled trials with a primary focus on participants with a concomitant medical illness. Participants suffering from bipolar depression, treatment resistant depression, subthreshold depression, seasonal affective depression, peripartum depression, depression in dementia, psychotic depression or depressive patients with a serious concomitant medical illness will be excluded.

Intervention: Any form of combined treatments of Traditional Chinese Medicine non-pharmacological intervention and pharmacotherapy can be used as monotherapy. The Traditional Chinese Medicine non-pharmacological interventions including various of acupuncture therapy, moxibustion therapy, Tuina (massage) therapy, Tai Chi, Qigong or acupressure, and so forth. The following active antidepressants approved by the regulatory agencies in the USA, Europe, or Japan or listed in the WHO Model List of Essential Medicines but only if administered within the therapeutic dose range were included, such as agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, levomilnacipran, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine, vilazodone and vortioxetine, amitriptyline and clomipramine, trazodone and nefazodone, etc. Trials comparing the same type of combined treatments of TCM non-pharmacological intervention and pharmacotherapy will be viewed as the same node in the NMA regardless of different therapeutic drug dosage (fixed or flexible dose), different protocols of intervention procedure, different delivery format (group, individual), different treatment medium (face-to-face, internet-based, telephone-based or other) and different intervention conditions (with or without nurses' involvement and family involvement).

Comparator: Eligible comparison interventions will be a clinical antidepressant drug (with or without placebo) as indicated above, and a Traditional Chinese Medicine non-pharmacological intervention as indicated above, and other combined treatments of Traditional Chinese Medicine non-pharmacological intervention and clinical antidepressant drug.

Study designs to be included: We will only include high-quality randomized controlled trials, no date of dissemination and language restrictions will be applied.

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: A comprehensive electronically search will be undertaken mainly in the following databases: PubMed, MEDLINE, Cochrane Library, Web of Science database, EMBASE, China National Knowledge Infrastructure (CNKI), and Wanfang Data Chinese database. We will also search the other potentially eligible studies through the clinical trial registries, dissertations, informal publication, and grey literature from inception to the search date. The reference lists of previously published reviews and included RCTs will be tracked, and all relevant authors of chosen randomized controlled trials will be contacted by emails if it is necessary. On the other hand, we will try our best to contact the experts in the field and review the conference proceedings to obtain up-to-date information related to this topic. And a list of medical journals will be hand searched in the university library. Any relevant ongoing or unpublished randomized controlled trials will be identified 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. All relevant authors and principal researchers will be contacted to supplement any incomplete reports of the original papers or to provide data for unpublished studies.

Main outcome(s): 1. Overall efficacy (as continuous outcome), it refers to mean improvement in depressive symptoms, as measured by overall mean change scores on continuous observer-rated depressive symptom scale (self-rated or assessor-rated) from baseline to the end of the study duration. 2. 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.

Additional outcome(s): 1. Treatment response (as dichotomous outcome), defined as total number of participants who had a reduction of 50% or more on the total score in depressive symptomatology from baseline to study end point according to study's primary observer-rated depressive symptom scale. 2. Remission rate (as dichotomous outcome), it refers to by the total number of participants who achieved the criteria of remission, defined as participants with a score for depressive symptoms below a diagnostic threshold or other threshold on a validated depression assessment tool in different across trials. 3. Overall tolerability (as dichotomous outcome), defined as the proportion of participants who discontinued treatment and left the trial early due to any adverse events (including specific adverse events and withdrawal symptoms) during the delivery of intervention. 4. Social functioning/ health-related quality of life (as continuous outcome), as measured by overall change scores on any validated functioning improvement scales or quality of life scales. 5. Occurrence of specific adverse events (as dichotomous outcome), as reported in the include original studies. 6. Suicidality (as dichotomous or continuous outcome).

Quality assessment / Risk of bias analysis: Methodological quality and specifically risk of bias, of included studies, will be assessed independently by two reviewers according to the risk of bias (ROB) tool as described in the Cochrane Hand book. The risk of bias domains as following: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (for example conflicts of interest, follow-up, different characteristics and representativeness of participants, non-intention-to-treat or per-protocol analysis, etc.). After assessing all the domains, the methodological quality of each study will be classified as low risk of bias, high risk of bias or unclear risk of bias, where information is not sufficient to make a judgement. In addition, a detailed description will be provided in support of the judgment. The inter-rater reliability of assessing the risk of bias will also be rated using intraclass correlation coefficients. The authors from the original articles will be contacted to obtain missing information, if necessary. Any discrepancy in the risk of bias assessment between the two reviewers will be arbitration by team meeting. If the disagreement persists, a third reviewer will be consulted to reach consensus.

Strategy of data synthesis: The study characteristics, patient characteristics, intervention and outcome measures, and our assessment of the risk of bias will be summarized descriptively. 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. As we aim to answer above two clinical questions in this review, when quantitative analysis is plausible, we will

conduct two main analysis. To answer first clinical question, we will perform series of pairwise meta-analysis to compare combined treatments of Traditional Chinese Medicine non-pharmacological intervention and pharmacotherapy with either intervention alone to investigate the efficacy, effectiveness, safety, tolerability and acceptability of improving or treating depression. The first clinical question relates to whether combined treatments in the treatment of depression is more beneficial and/or safer than Traditional Chinese Medicine non-pharmacological intervention alone or pharmacotherapy alone. The second clinical question is about how the various combined treatments of Traditional Chinese Medicine non-pharmacological intervention and pharmacotherapy compare with each other, when the treatment of depression is taken into account. Therefore, we will then perform Bayesian network meta-analysis to compare with different combined treatments to answer which is the most effective and acceptable combined treatments for depression.

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 mean age, sex ratio, the whole study period, the severity, status, duration of depression at baseline, research and clinical setting, the source of outcome information (self-rated vs other-rated), type of Traditional Chinese Medicine non-pharmacological intervention, category or dosage of clinical antidepressant drug, frequency, durations of combined treatment, delivery format or treatment medium, treatment conditions, quality of evidence, sample size, and study year.

Sensibility analysis: To verify the robustness of our analysis conclusions, sensitivity analysis of outcomes will be executed according to different levels of methodological quality, study quality, sample size, effect of missing data as well as the analysis methods.

Language: English.

Country(ies) involved: China.

Keywords: Combined treatments of TCM non-pharmacological intervention and pharmacotherapy; depression; thinking after COVID-19 outbreak; pairwise meta-analysis; network meta-analysis.

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