INPLASY PROTOCOL

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None declared.

Can acupuncture plus antidepressants improve the therapeutic effectiveness and reduce adverse drug reactions in patients with depression? A systematic review and meta-analysis of RCTs

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Review question / Objective: **We will perform this systematic review and meta-analysis to not only provide an update of the latest evidence for improving the therapeutic effectiveness of acupuncture as an adjunct to antidepressants in treating depression, but also particularly evaluate the effect of acupuncture plus antidepressants compared with antidepressants alone on adverse drug reactions, giving the patients and physicians an insight into its application in this field.**
Information sources: **Studies will be identified through a computerized literature search of four English electronic databases (PubMed, Embase, Cochrane library, Web of Science) from their inception to search date. Only studies published in English with the full-reported available will be included. When several publications reported findings for the same participants, the most recent or most informative study will be chosen. Additionally, reference lists of included studies and previous published systematic reviews will be also searched to identify additional publications.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 May 2021 and was last updated on 02 May 2021 (registration number INPLASY202150008).

INTRODUCTION

Review question / Objective: **We will perform this systematic review and meta-analysis to not only provide an update of the latest evidence for improving the therapeutic effectiveness of acupuncture as an adjunct to antidepressants in treating depression, but also particularly evaluate the effect of acupuncture plus antidepressants compared with antidepressants alone on adverse drug reactions, giving the patients and**

physicians an insight into its application in this field.

Condition being studied: Depression is a common affective disorder characterized clinically by long lasting depressed mood, lack of interest and decline of cognition and behavior, with more than 264 million people affected and a lifetime prevalence of 19%. According to the global burden of disease study, depression has prevailed as the third leading cause of non-fatal health loss for nearly three decades and is a major contributor to disability. Antidepressants are recommended for the first-line treatment strategy of depressive disorders in different practice guidelines. The pharmacotherapy is effective for some depressive patients, but there are still a substantial proportion of patients who have a partial response or no response at all to the active treatment. Moreover, some depressive patients don't have full adherence and compliance to treatment strategy due to delayed onset of action and intolerable side-effects such as sexual dysfunction, weight gain, nausea, and headaches, thereby increasing the recurrence rate of depressive episode and compromising therapeutic efficacy. Therefore, it is essential to seek the better remedies including complementary and alternative medicine (CAM) combined with the antidepressants, which conduces to enhancing efficacy of antidepressants and minimizing the side-effects. Acupuncture treatment is an important CAM which originates from traditional Chinese medicine (TCM), has made great contribution to the Chinese healthcare system for thousands of years and now enjoys a high reputation in many other countries. In recent years, a growing number of clinical studies also have confirmed that acupuncture is efficacious for depressive disorders and is what most patients would prefer, in two main styles, manual acupuncture (MA) and electroacupuncture (EA) stimulated by hand and a small electric current, respectively. Several reviews and meta-analyses have examined the effectiveness and safety of acupuncture in the treatment of depression. However, these systematic reviews mainly focused on the effectiveness of acupuncture for the clinical treatment of depression, but did not specifically emphasized whether the acupuncture as an adjunct could reduce the antidepressant-induced side-effects, thereby improving tolerability and increasing the therapeutic compliance. Consequently, a systematic review and meta-analysis need to provide an update of the latest evidence for improving the therapeutic effectiveness and reducing adverse drug reactions of acupuncture as an adjunct to antidepressants in treating depression.

METHODS

Search strategy: The search strategy consisted of 3 components: clinical condition (depression/depressive disorder), intervention (manual acupuncture/electroacupuncture), and study type (RCT). In order to retrieve all the potentially relevant studies, a combination of Medical Subject Headings (MeSH) and free-text words incorporating each database-specific controlled vocabularies and text words related to depression, acupuncture/electroacupuncture, RCT will be used.

Participant or population: Study participants with a clinically primary diagnosis of depression, based on at least one of the standardized international or domestic authorized diagnostic criteria or guidelines for clinical research will be included in this study, regardless of age, gender, nationality, ethnicity, occupation or education, and the cause, severity, duration of depression.

Intervention: This study will focus on the depression therapy with use of manual acupuncture/electro-acupuncture (regardless of point selection, intensity, frequency or duration of intervention, and stimulation methods) combined with antidepressants.

Comparator: Studies of comparison will adopt antidepressants as the only treatment to minimize the interference of

confounding factors. Herbal medicine as the control group will not be included.

Study designs to be included: This study will limit to peer-reviewed and published randomized controlled trials (RCTs), all relevant parallel-group RCTs, including the first phase of cross-over trials as well as cluster-randomized trials, will be considered eligible for this review.

Eligibility criteria: In order to ensure the quality of this systematic review, the eligibility criteria will be established in terms of participants, intervention, comparison, outcomes and study design (PICOS) approach.

Information sources: Studies will be identified through a computerized literature search of four English electronic databases (PubMed, Embase, Cochrane library, Web of Science) from their inception to search date. Only studies published in English with the full-reported available will be included. When several publications reported findings for the same participants, the most recent or most informative study will be chosen. Additionally, reference lists of included studies and previous published systematic reviews will be also searched to identify additional publications.

Main outcome(s): Primary outcomes will include reduction in the severity of depression and adverse drug reactions. Reduction in the severity of depression, measured at the endpoint of intervention period as a continuous variable on self-rating scales such as the Self-Rating Depression Scale (SDS), or on clinician-rated scales, such as the Hamilton Depression Rating Scale (HAMD). Adverse drug reactions, measured as a dichotomous variable by the total number of participants reporting adverse events associated with antidepressants, or measured at the endpoint of intervention period as a continuous variable on Treatment Emergency Symptom Scale (TESS) or Side Effects Rating Scale (SERS).

Additional outcome(s): Secondary outcomes will include remission rate, treatment response, treatment tolerability of antidepressants, change in dosages of antidepressants, social functioning. Remission rate, defined as the proportion of participants who achieved the criteria of being below the threshold in observer-rated scale (self-rated or assessor-rated) for depression at the endpoint of intervention period. Treatment response, defined as the proportion of participants who achieved the criteria of 50% or greater reduction in observer-rated scale (self-rated or assessor-rated) for depression at the endpoint of intervention period. Treatment tolerability of antidepressants, defined as the proportion of participants who discontinued treatment due to any adverse events during the delivery of the antidepressants. Social functioning, measured at the endpoint of intervention period as a continuous variable on any validated global assessment of functioning scales such as WHO Quality of Life-BREF (WHOQOL-BREF) scale or quality of life scales.

Data management: For studies fulfilling the eligibility criteria, two reviewers then independently will extract data from the selected studies about the general information (e.g. first author, publication year, country, sample size), participants characteristics (e.g. gender, mean age or range, diagnostic criteria of depression), intervention and comparison characteristics (e.g. type, frequency, total period, each session duration of acupuncture, antidepressants dosage), outcome measures (e.g. effectiveness, safety, dropout), notes (e.g. sources of funding, competing interests) and fill in the pre-designed electronic standardized data extraction Microsoft Excel form.

Quality assessment / Risk of bias analysis: The risk of bias of each included study will be assessed by two independent reviewers according to the risk of bias (ROB) assessment tool provided by the Cochrane Handbook for Systematic Reviews of Interventions. Any discrepancy in the study risk of bias assessment between the two reviewers will be arbitration by discussion. If the disagreement persists, a third

reviewer will be consulted to reach consensus. If there were incomplete information or unclear items that could affect the assessment of bias risk, we will contact the article authors to obtain more complete information.

Strategy of data synthesis: Meta-analysis of RCTs with available data will be performed using RevMan version 5.4 software (Cochrane, London, UK) to estimate the treatment effect. Results will be reported as mean difference (MD) for continuous outcomes or relative risk (RR) for dichotomous outcomes, with 95% confidence intervals (CIs), and standardized mean differences (SMDs) will be used when different scales were applied to measure the same outcome. Throughout the analyses, a two-sided tail test will be used and P-value$<$0.05 was considered statistically significant. If the data are not available for quantitative analysis or the information was insufficient, the evidence and report the findings will be summarized in a written narrative. Statistical heterogeneity across trials will be assessed based on Cochran's Q statistic and its related P-value. Furthermore, the I2 index will be used as a measure to categorise heterogeneity across the included RCTs. According to the Cochrane Handbook, when the P-value ≥0.1 and I2 index value ≤50%, the study will be considered to have no statistical heterogeneity, and the Mantel-Haenszel fixed-effect model will be employed. While the P-value$<$0.1 and I2 index value $>$50%, the study will be considered to have substantial heterogeneity, and the Mantel-Haenszel random-effect model will be selected, the sources of significant heterogeneity will be assessed by subgroup and sensitivity analysis.

Subgroup analysis: Subgroup analysis on outcomes of therapeutic effectiveness and adverse drug reactions will be performed to investigate possible sources of heterogeneity including the following characteristics: study period; nationality; severity of depression; diagnostic criteria; acupuncture subtypes (acupuncture or electroacupuncture); frequency, duration of acupuncture or electroacupuncture; form and dosage of antidepressant medication; mean age and gender of participants; sample size; the methodological quality of the selected RCTs.

Sensitivity analysis: Sensitivity analysis will be performed for outcomes of therapeutic effectiveness and adverse drug reactions to explore the robustness of the review conclusions where feasible. Meta-analysis will be repeated by excluding each of the related studies with small sample sizes, a high risk of bias, and incomplete results one at a time and re-evaluating the treatment effect size.

Language: English.

Country(ies) involved: China.

Keywords: Depression; acupuncture plus antidepressants; therapeutic effectiveness; adverse drug reactions; systematic review; meta-analysis; randomized controlled trials

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