INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Placebo response to Transcranial Magnetic Stimulation in randomized controlled trials for depression: A systematic review and meta-analysis

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Review question / Objective: **To conduct a systematic review and meta-analysis investigating placebo response of repetitive transcranial magnetic stimulation (rTMS) for depression treatment in randomized controlled trials (RCTs).**
Condition being studied: **Major depressive disorder (MDD) is a highly prevalent psychiatric disorder that is a leading cause of disability worldwide, with a lifetime prevalence of approximately 12%. MDD is projected to be the leading cause of disease burden by 2030 according to WHO. Despite the significant impact of MDD and the limitations of existing treatments, there is a need for new and effective therapies for this disorder. One such treatment is repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation technique that has been approved for use in the treatment of depression by FDA and other regulatory agencies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 December 2022 and was last updated on 26 December 2022 (registration number INPLASY2022120103).

INTRODUCTION

Review question / Objective: **To conduct a systematic review and meta-analysis investigating placebo response of repetitive transcranial magnetic stimulation (rTMS) for depression treatment in randomized controlled trials (RCTs).**

Rationale: Placebo effect is well noted in depression treatment. However, placebo responses to repetitive transcranial magnetic stimulation (rTMS) have not been systemically analyzed.

Condition being studied: Major depressive disorder (MDD) is a highly prevalent psychiatric disorder that is a leading cause of disability worldwide, with a lifetime prevalence of approximately 12%. MDD is projected to be the leading cause of disease burden by 2030 according to WHO. Despite the significant impact of MDD and the limitations of existing treatments, there is a need for new and effective therapies for this disorder. One such treatment is repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation technique that has been approved for use in the treatment of depression by FDA and other regulatory agencies.

METHODS

Search strategy: PubMed, Cochrane Library, EMBASE, PsycINFO, ClinicalTrials.gov and CINAHL Library will be systematically and independently searched by two reviewers. The following search terms will be used: Transcranial Magnetic Stimulation, Magnetic Stimulation, Transcranial, Magnetic Stimulations, Transcranial, Stimulation, Transcranial Magnetic, Stimulations, Transcranial Magnetic, Transcranial Magnetic Stimulations, Transcranial Magnetic Stimulation, Single Pulse, Transcranial Magnetic Stimulation, Paired Pulse, Transcranial Magnetic Stimulation, Repetitive, Depressive Disorder, Depression, Depressive Disorders, Depressive, Depressive Neuroses, Depressive Neurosis, Endogenous Depression, Endogenous Depressions, Depressive Syndrome, Depressive Syndromes, Neurotic Depression, Neurotic Depressions, Melancholia, Unipolar Depression, Unipolar Depressions, Depressive Symptoms, Depressive Symptom, Emotional Depression, randomized controlled trial, randomized, placebo, Randomized controlled trials, RCT, RCTs, placebos. The publications are in English, reporting from January 1, 1996, to January 1,2022. We will re-run the search prior to the final analysis. Also, reference lists of articles and reviews on TMS efficacy will be hand-searched for relevant reports.

Participant or population: Adult patients with an depression diagnosis are defined by DSM-IV, DSM-V or ICD-10. Studies will be excluded if depression is exclusively a comorbid disorder of a medical condition (e.g., post-stroke depression; depression after heart attacks). We will also exclude depression trials enrolling only geriatric (>65 years old) patients and children (<18 years old).

Intervention: Repetitive transcranial magnetic stimulation (rTMS).

Comparator: We are investigating the control group response.

Study designs to be included: Randomized controlled trials (RCTs) with accessible and meta-analyzable data. Case reports/series, qualitative reports, observational trials, non-randomized studies, reviews and meta-analyses will be excluded.

Eligibility criteria: Following the PICOS acronym, the eligibility criteria are as follows: Participants(P): adult patients with depression diagnosed according to standardized diagnostic criteria, such as the Diagnostic Statistical Manual of Mental Disorders(DSM), or the International Statistical Classification of Diseases and Related Health Problems(ICD).Studies will be excluded if depression is exclusively a comorbid disorder of a medical condition (e.g., post-stroke depression; depression after heart attacks).We also will exclude depression trials enrolling only geriatric (>65 years old) patients and children (<18 years old), as well as relapse prevention or maintenance studies, as it is not possible to draw comparisons between trials studying unique populations or with confounding differences in experimental design. Intervention (I): TMS.Comparison (C): the study group was treated with TMS with a definite treatment plan, including a

different sequence and frequency of neurophysical stimulation; the placebo group received sham stimulation but no restrictions in other treatments they received (except other physical treatments such as ECT, tDCS, etc.), including conventional treatment and waiting for treatment. The placebo groups had to have a minimum of 20 patients. For the trials with more than two randomized treatment conditions, we will calculate each TMS or placebo arm separately.Outcomes (O): The primary outcome measure is within group effect sizes (d), which is defined as the mean difference from pre-to post-treatment divided by the pooled standard deviation. The secondary outcome measure is percent symptom reduction, the ratio of change score and baseline score.Most often, ratings were based on the Hamilton (HDRS) or Montgomery-Åsberg Depression Rating Scales (MADRS), or Beck Depression Inventory (BDI) when these measures were not available. We will consider the factors that might influence outcomes, including the number of subjects and collaborating sites, location, gender, age, initial depression ratings, trial duration, dropout rates, medication status, and year of reporting. Study design (S): RCTs with accessible and meta-analyzable data. Case reports/series, qualitative reports, observational trials, non-randomized studies, reviews and meta-analyses will be excluded.

Information sources: PubMed, Cochrane Library, EMBASE, PsycINFO, ClinicalTrials.gov and CINAHL Library will be systematically and independently searched. Authors will be contacted for unreported or pending confirmation data. Also, reference lists of articles and reviews on TMS efficacy will be hand-searched for relevant reports.

Main outcome(s): Variation of depression severity rating scores after rTMS treatment or rates of response to treatment or of remission. The primary outcome will be defined among these measures depending on which is reported in a greater number of studies. If this criterion does not allow for the differentiation between measures, the variation of depression severity rating scores after rTMS treatment will be presented as the primary outcome.

Additional outcome(s): We will consider as many factors as possible that may influence outcomes, including the number of subjects and collaborating sites, location, gender, age, initial depression ratings, trial duration, dropout rates, medication status, and year of reporting.

Data management: EndNote will be used, if necessary, as a research and reference manager to detect and eliminate duplications. Relevant data will be independently extracted by two authors, recording in excel spreadsheets. Any discrepancies will be resolved by consensus or a discussion with the third author. If necessary and possible, we will contact the authors of the original studies to request additional material or clarifications. Extracted data will include:
a) metadata: authorship; publication date
b) demographics: sample size in each group; age; gende
c) general methodological details: the number of subjects and collaborating sites; randomization protocol; blinding assessment; location; trial duration; dropout rates; medication status; sample size; trial arms
d) depression characteristics: diagnosis; diagnostic criteria; current episode duration; the age of onset; illness duration; use of antidepressants; use of ECT; scales, interviews and checklists used for depression diagnosis and assessment of severity; mean and standard deviation (SD) scores of depression rating scales at baseline and endpoint (or change scores); number or percentage of responders; TRD details (categorical, as presence or absence of TRD patients; or ordinal, as no TRD patients, resistant to one or more, and two or more antidepressants)
e) rTMS characteristics: type of rTMS intervention; intensity (% of motor threshold); frequency; coil position; number of coils; duration of an intervention;

number of interventions; number of sessions; number of pulses per session
f) characteristics of sham procedures: such as stimulator type; coil positioning method; coil type and size, and further specifications, e.g., angle of the coil.

Quality assessment / Risk of bias analysis: Study quality will be assessed by two researchers via the Cochrane risk of bias and Jadad scale. Any discrepancies will be resolved by consensus or a discussion with the third author. The Cochrane risk of bias will be used to assess the aspects of selection bias (random sequence generation and allocation concealment), reporting bias (selective reporting), blinding, attribution bias, and other sources of bias, while the Jadad scale will assess the randomization, blinding, and withdrawals and dropouts of participants. The total score of the Jadad scale ranges from 1 to 5, with a higher score indicating higher quality. The score < 3 is considered as low quality; otherwise, it is considered as high quality.

Strategy of data synthesis: Pre–post-effect sizes(d) for the TMS and placebo groups will be calculated to detect moderate treatment effects. These effect sizes were defined as the mean difference from pre-to post-treatment divided by the pooled standard deviation. Percent symptom reduction is defined as the ratio of change score to baseline score, which takes into account variation in baseline and different measurement scales. Mean TMS-placebo difference is the difference between TMS percent symptom reduction and placebo percent symptom reduction, which attempts to determine the relationship between changes in measures of TMS-placebo difference and the symptom reduction on placebo. In instances where placebo has a greater percent symptom reduction than TMS, this measure will be negative. The heterogeneity across included studies will be assessed using I2 index, with I2 of 25%, 50% and 75% indicating mild, moderate, and high heterogeneity between studies, respectively. If significant heterogeneity for primary outcome exists, a sensitivity analysis, i.e., one outlying (SMD > 1.5) study will be removed to explain the heterogeneity source. According to studies heterogeneity, we will use a random or fixed-effect model. Correlations will employ nonparametric Spearman rank methods (rs) to avoid effects of non-normally distributed data and potential nonlinear relationships. We will carry out meta-regression and multivariate multiple regression modeling to evaluate associations of selected covariates with placebo response. Funnel plots, fail–safe-rates and Egger's test will be performed for publication bias of primary outcome.

Subgroup analysis: Subgroup analyses will be performed if sufficient data is available. We intend to perform meta-regression analyses to identify factors that might influence outcomes, such as demographic characteristics (age, gender), depression characteristics (age of onset, duration of the illness, baseline severity scores, use of antidepressants, use of ECT, degree of refractoriness), stimulation technique specificities (position of the coil, number of pulses per session, number of sessions, intensity) and year of reporting.

Sensitivity analysis: When significant heterogeneity for primary outcome exists, a sensitivity analysis, i.e., one outlying study will be removed to explain the heterogeneity source.

Language restriction: In English or Chinese.

Country(ies) involved: China.

Keywords: Placebo Response; Transcranial Magnetic Stimulation; Depression; Systematic Review; Meta-analysis.

Contributions of each author:
Author 1 - Yangting Xu - Author 1 will draft the review protocol, participate in the search, quality evaluation, data extraction and statistics, and draft the manuscript.
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