BMJ Open

Effect of repetitive transcranial magnetic stimulation (rTMS) for insomnia: a protocol for a systematic review

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ABSTRACT

Introduction Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation approach, might be a promising technique in the management of insomnia. A systematic review of the available literature on this topic is warranted. The systematic review described in this protocol aims to investigate the efficacy of rTMS as a physical therapy in patients with insomnia.

Methods and analysis This protocol was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. We will retrieve relevant literatures across the following electronic bibliographic databases: CENTRAL, PubMed, EMBASE, PsycINFO, CINAHL, PEDro, CBM, CNKI, WANFANG and VIP. A manual search of the reference lists of all relevant articles will be performed for any additional studies. We will include randomised controlled trials published in English and Chinese examining efficacy of rTMS on patients with insomnia. Two reviewers will independently complete the article selection, data extraction and rating. PEDro scale will be used to assess the methodological quality of the included studies. Narrative and quantitative synthesis will be done accordingly.

Ethics and dissemination Ethical approval will not be required for this review. The results of this review will be disseminated in a peer-review journal.

PROSPERO registration number CRD42018115033.

Strengths and limitations of this study

► Well-recognised approach for conducting and reporting of systematic reviews will be followed (Cochrane handbook).
► To our knowledge, this study will be the first to explore the efficacy of repetitive transcranial magnetic stimulation (rTMS) as a physical therapy in patients with insomnia.
► In the study, both primary and comorbid insomnia will be included.
► This work provides an overview of the current situation in this territory and will potentially be helpful for future evidence-based research to refine rTMS.
► The scarcity of randomised controlled trials and the methodological quality of studies may be the main limitations of the study.

have increased risk of errors and accidents, increased work absenteeism rates and healthcare use.[19 20] Insomnia has a large negative impact on function, health and quality of life, resulting in a major public health burden.[21]

General approaches in the management of insomnia include the evaluation and treatment of contributing medical or psychiatric comorbidities, and specific treatment strategies fall into two major categories: pharmacological treatments and cognitive behavioural therapy (CBT).[22] Due to potential adverse effects and limited supporting data of sleep-promoting medication, clinical practices and guidelines recommended CBT as the first-line treatment for insomnia, and pharmacotherapy may be used on a short-term basis if CBT is either inaccessible or ineffective.[23–26] However, CBT is rarely used in routine clinical practice, possible reasons include time consumption and lack of adequately trained providers, other barriers may be related to patient awareness and economic issues.[24 27 28] Given the limitations of both pharmacological therapy and CBT for insomnia, treating insomnia can be challenging. Other than improving access to CBT, many complementary therapies have

INTRODUCTION

Insomnia disorder is a patient-reported problem characterised by difficulty initiating sleep, difficulty maintaining sleep, early morning awakening or non-restorative or poor sleep quality.[1 2] It is a common sleep disorder, recent data show that the population prevalence of insomnia is estimated to be 5%–16%.[3–7] Compared with good sleepers, individuals with the disorder often experience clinically significant distress or daytime dysfunction such as fatigue, poor cognitive function, emotional disturbance and poor performance,[8] have higher risk for many physical health problems (cardiovascular diseases,[9] neurological disorders,[10] obesity,[11] diabetes[12 13] and so on) as well as mental health problems (such as depression, anxiety, suicide and substance use),[14–18] and

been used to improve sleep, and repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation approach, might be a promising technique.

TMS is a non-invasive method of stimulating the brain through the intact skull and scalp with little or no pain at the surface.[29–31] In TMS, a magnetic field is generated with a magnetic coil placed above the scalp, which efficiently passes through the skull and induces electrical currents in the underlying brain tissue beneath the coil, and the induced electrical stimulus activates neural elements in the cortex or subcortical white matter.[31 32] A single TMS pulse lasts only ~0.2–0.3 ms, which induces neuronal effects lasting only a fraction of a second, thus producing short responses. By contrast, longer rTMS pulse sequences, such as conventional 1 Hz or 20 Hz rTMS which have usually been delivered in trains, can cause prolonged neuroplastic changes that inhibit or excite the brain's activity.[30–32] rTMS has been reported to have therapeutic utility in many neurological and psychiatric conditions, such as stroke,[33] Parkinson's disease,[34] dystonia,[35 36] depression[37] and schizophrenia.[38]

Among several models of insomnia, hyperarousal is identified as a final common pathway of the pathophysiology.[39–41] In addition, studies using TMS to assess the trait of insomnia found that patients with insomia are characterised by disturbed intracortical excitability.[42 43] Reduction of overexcited state in patients with insomia can effectively improve their sleep.[44] The potential mechanisms of rTMS in improving sleep in patients with insomnia might involve inhibiting the hyperarousal state of the cerebral cortex, affecting metabolic activity and sleep-related hormones, and promoting hippocampal neurogenesis.[39 45 46] In the recent years, there is an increasing interest in application of rTMS in the treatment of patients with insomia, and it seems that rTMS might have the potential to improve sleep,[45 47 48] but negative results were also reported.[49] Until now, there is no systematic review about rTMS for insomnia. We seek to perform a systematic review of randomised controlled trials (RCTs) to evaluate the efficacy of rTMS as a physical therapy in patients with insomnia.

METHODS

This protocol was registered prospectively in PROSPERO, it was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[50 51]

Research question

The PICO (P=Patients, I=Intervention, C=Comparison, O=Outcomes) method will be used to define the major components of this systematic review:

► P: adults (>18 years of age) of any gender and ethnic background with insomnia diagnosed by standard criteria such as Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition,[52] Fifth Edition[1]), International Classification of Sleep Disorders (Second Edition,[53] Third Edition[2]), International Classification of Diseases (Tenth Edition),[54] Chinese Classification and Diagnostic Criteria of Mental Disorders (Third Edition).[55] In the study, both primary and comorbid insomnia will be included.

► I: the intervention used in the experimental group was rTMS alone or in combination with other therapy. The intensity of stimulation, frequency, target area, localisation method, dose and duration are not limited.

► C: comparison with placebo or sham control, other treatment, no intervention or no rTMS therapy under the same treatment programme.

► O: primary outcomes and secondary outcomes.
Primary outcomes:

► Polysomnography: sleep parameters such as total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), sleep onset latency (SO, rapid-eye movement (REM) latency, total arousal index, percentage of TST spent in each sleep stage (N1, N2, N3, REM), apnoea-hypopnoea index, mean arterial oxygen saturation (SaO_2), minimum SaO_2 and periodic limb movements index.

► Pittsburgh Sleep Quality Index.
Secondary outcomes:

► Other sleep-related scales: Insomnia Severity Index, Athens Insomnia Scale.

► Sleep parameters measured by actigraphy: activity mean, sleep duration, sleep onset latency, SE, WASO, daytime inactivity.

► Adverse events: number and type of self-reported and measured adverse events during the study period.

Thus, this systematic review aims to answer the following question: Is rTMS effective in improving quality of sleep compared with other forms of treatment or no intervention?

Eligibility criteria

In addition to the PICO components mentioned above, articles will be included for review if they were:

► Published in the English or Chinese language.

► RCTs.

Exclusion criteria

Articles will be excluded if:

► Insufficient data for the establishment of results were reported (eg, deficiency of the number of participants, the means and the SD or other relevant statistics regarding a continuous outcome).

► They were reported in books, conference proceedings or dissertations.

Search strategy

We will retrieve relevant literatures across the following electronic bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE, PsycINFO, CINAHL, Physiotherapy Evidence Database (PEDro), the Chinese Biomedical Literature

Database (CBM), China National Knowledge Infrastructure (CNKI), WANFANG database, and the Chinese Scientific Journal Database (VIP). We will develop the search strategy for MEDLINE (via Ovid) (see supplementary material online supplementary appendix 1. Search Strategy Example) and adapt this strategy for the other databases except for PEDro in which the term 'rTMS' and 'insomnia' will be used for simple search. The concepts of 'subjects' and 'intervention' will be combined with the 'AND' operator. Subjects are defined as individuals with insomnia, and intervention is defined as rTMS. For each concept, we will combine synonyms and Medical Subject Headings terms with the 'OR' operator. In addition to database searching, a manual search of the reference lists of all relevant articles will be performed for any additional studies.

Selection of studies

Duplicate articles generated by different databases will be removed using an electronic reference management tool Endnote X7 software. The title, abstract and keywords of every retrieved articles will be scanned independently by two authors (NS and YH) with predetermined eligibility criteria, in order to eliminate the irrelevant studies and determine which studies require further assessment. If there is any doubt regarding these criteria from scanning the titles and abstracts, the full article will be retrieved for clarification. Later, the full text of the remaining articles after preliminary screening will be reviewed in detail, and the criteria will be reapplied to these studies to determine the eligible ones. Discrepancies will be resolved by discussion (or with consultation of a third author); decisions will be arrived at by the authors in consensus.

Data extraction

Two authors (NS and YH) will independently extract relevant population and intervention characteristics from the included studies. The data will include the following items:

► General information: first author, title, journal, year of publication, country, setting, aim, ethical approval, register number and funding source.
► Trial characteristics: design, method of randomisation, allocation concealment, blinding (subjects, therapists, and assessors).
► Intervention(s): intervention(s) (stimulus frequency, number of TMS pulses delivered per session, target area, localisation method, number of sessions in a course of treatment), comparison intervention(s) (type, frequency, dose and duration).
► Participants: participant demographics, number of participants, inclusion/exclusion criteria, comorbidity, assessment of compliance and withdrawals.
► Outcomes: results, adverse events, duration of follow-up, intention-to-treat (ITT) analysis.

Methodological quality assessment

This review will use The Physiotherapy Evidence Database (PEDro) scale as methodological criteria.[56] The PEDro scale is an instrument for the methodological quality assessment of physiotherapy-based studies. It had been demonstrated that PEDro scale possesses moderate inter-rater reliability for assessing methodological quality of clinical trials.[56 57] This scale has 11 criteria, with scores range from 0 to 10 (the 1st item-specified eligibility criteria-is not included in the total score), and a higher score indicates that the trial has a better methodological quality (9–10=excellent, 6–8=good, 4–5=fair, and <4=poor). Responses to the 2nd to 11th item are summed to create a total score, which include randomisation, allocation concealment, baseline comparability, blinding (subjects, therapists, and assessors), follow-up of subjects (at least 85%), ITT analysis, between-group statistical comparisons, and reporting point measures and measures of variability.[56] The scores of each selected study will be determined by two authors (NS and YH) independently based on these criteria. Possible disagreement will be resolved by consensus (discussion or with consultation of a third author).

Data analysis and synthesis

The Cochrane Review Manager V.5 software will be used for meta-analysis. In our study, meta-analysis concerning effects of rTMS will be conducted if two or more studies used the same outcome measure or measured similar constructs.

For continuous data, standardised mean differences as well as 95% CI will be computed. For dichotomous data, OR as well as 95% CI will be computed. We will employ the χ^2 test to analyse the heterogeneity, a p value ≤0.1 will be considered statistically significant.[58] Heterogeneity between studies will be calculated using the I^2 statistic, which indicates the proportion of variation across studies.[59] If p>0.1, I^2<50%, fixed effects model will be used; Substantial heterogeneity is considered If p>0.1, I^2≥50%, and random effects model will be used in this case; If p≤0.1, statistical heterogeneity is considered, subgroup analysis or a narrative description will be conducted depending on the available data.[58]

If data permitted, we will carry out subgroup analyses on the following factors to assess whether the treatment effects are different in different subgroups: diagnostic subtypes (primary insomnia versus comorbid insomnia), age groups, site of stimulation, nature of the comparative treatment.[58]

When sufficient data are available, we will carry out sensitivity analyses on the following factors to assess the impact of study quality: concealed allocation, outcomes assessor blinding, drop outs, ITT analysis.[58]

The results of meta-analysis will be presented as forest plots. If ≥10 studies are included in the meta-analysis, potential publication bias will be assessed by graphing a funnel plot.[58]

The quality of the evidence in this review will be assessed by GRADEpro V.3 software and rated into high, moderate, low or very low, four levels according to the

Grading of Recommendations Assessment, Development and Evaluation system.[60]

Patient and public involvement

Not applicable. This systematic review protocol does not directly involve patients and the general public. Data will be collected from published articles retrieved from main databases and manual search.

ETHICS AND DISSEMINATION

Ethical approval will not be required for the performance of this review. Results of this research will be disseminated in a peer-review journal. These results will potentially be helpful for improving the therapeutic strategy of patients with insomnia.

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