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Comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression: A systematic review and multiple-treatments meta-analysis

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HIGHLIGHTS

- ECT was the most efficacious, but least tolerated.
- R-rTMS was the best tolerated treatment for MDD.
- B-rTMS appears to have the most favorable balance between efficacy and acceptability.

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ABSTRACT

Backgrounds: The effects of electroconvulsive therapy (ECT) and bilateral, left prefrontal, and right prefrontal repetitive transcranial magnetic stimulation (rTMS) on major depressive disorder (MDD) have not been adequately addressed by previous studies. Here, a multiple-treatments meta-analysis, which incorporates evidence from direct and indirect comparisons from a network of trials, was performed to assess the efficacy and acceptability of these four treatment modalities on MDD.
Method: The literature was searched for randomized controlled trials (RCTs) on ECT, bilateral rTMS, and unilateral rTMS for treating MDD up to May 2016. The main outcome measures were response and drop-out rates.
Results: Data were obtained from 25 studies consisting of 1288 individuals with MDD. ECT was non-significantly more efficacious than B-rTMS, R-rTMS, and L-rTMS. Left prefrontal rTMS was non −significantly less efficacious than all other treatment modalities. In terms of acceptability, R-rTMS was non-significantly better tolerated than ECT, B-rTMS, and L-rTMS. ECT was the most efficacious treatment with the cumulative probabilities of being the most efficacious treatment being: ECT (65%), B-rTMS (25%), R-rTMS (8%), and L-rTMS (2%). R-rTMS was the best-tolerated treatment with the cumulative probabilities of being the best-tolerated treatment being: R-rTMS (52%), B-rTMS (17%), L-rTMS (16%), and ECT (14%). Coherence analysis detected no statistically significant incoherence in any comparisons of direct with indirect evidence for the response rate and drop-out rate.
Conclusions: ECT was the most efficacious, but least tolerated, treatment, while R-rTMS was the best tolerated treatment for MDD. B-rTMS appears to have the most favorable balance between efficacy and acceptability.

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1. Introduction

Major depressive disorder (MDD, major depression) is a debilitating mental disorder affecting up to 15% of the general population and accounting for 12.3% of the global burden of disease [1]. To date, increasing evidence from biochemical, neuropsychological, postmortem, and neuroimaging studies indicates that MDD is not likely caused by a single brain region or neurotransmitter system, but rather is a system-level disorder affecting several integrated pathways [2,3].

Electroconvulsive therapy (ECT) is a well-established and effective treatment method for MDD superior to both placebo and sham ECT (anesthesia only) [4,5]. Some researchers even consider ECT to be the most effective treatment for MDD [6]. Of MDD patients who receive ECT, approximately 70% to 80% show significant improvement [6], and ECT is effective in half of patients with treatment-resistant depression (TRD) [7]. However, ECT is complicated by a number of side effects including cognitive impairment; so many patients are reluctant to engage in ECT treatment due to the risks and stigma associated with cognitive side effects, which has motivated attempts at developing treatment alternatives [8].

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive method of brain stimulation for the treatment of patients with serious neuropsychiatric disorders including MDD [9]. Unlike ECT, rTMS does not require anesthesia or induction of seizures. RTMS is divided into bilateral rTMS (B-rTMS), left prefrontal rTMS (L-rTMS), and right prefrontal rTMS (R-rTMS) according to the stimulation location. Most studies of rTMS in MDD focus on high-frequency (5–20 Hz) stimulation to the left dorsolateral prefrontal cortex, and L-rTMS has been shown to have positive antidepressive effects [10,11]. Some randomized controlled trials (RCTs) have demonstrated that R-rTMS shows significantly greater improvement in depression scores compared with sham rTMS [12,13], and our previous research has shown that L-rTMS and R-rTMS have a similar efficacy on MDD patients [14]. Moreover, a 2012 systematic review showed that B-rTMS is a promising treatment for MDD [15], and our previous research also found that bilateral and unilateral rTMS had comparable efficacies on MDD patients [16].

Hitherto, ECT has been traditionally viewed as the superior treatment modality vis-a-vis rTMS [17], but this conclusion has been primarily based on RCTs of ECT versus L-rTMS. There is still lack of quantitative data comparing the efficacy of ECT versus B-rTMS or R-rTMS in MDD. To this end, although standard meta-analyses are an effective tool, they can only compare two alternative treatments at a time; moreover, if no trials directly compare two interventions, it is impossible to compare their relative efficacies [18]. In contrast, multiple treatments meta-analyses use a technique that incorporates evidence from both direct and indirect comparisons from a network of trials of different interventions to better estimate summary treatment effects. Our group used this method to compare the efficacy and tolerability of antidepressants for MDD in children and adolescents, and the results has been published in *Lancet* in 2016 [19]. Therefore, here we applied a multiple-treatments meta-analysis to compare the efficacy and acceptability of B-rTMS, R-rTMS, L-rTMS, and ECT in the treatment of MDD.

2. Methods

2.1. Study selection

This systematic review and meta-analysis was conducted and reported according to the PRISMA statement (http://www.prisma-statement.org/). A comprehensive literature search of RCTs comparing ECT with rTMS was conducted up to May 2016 through the major scientific and medical databases, including international databases (PubMed, CCTR, Web of Science, and Embase) and two Chinese databases (CBM-disc and CNKI). The key search terms were "depression" AND ("transcranial magnetic stimulation" OR "TMS" OR "repetitive TMS" OR "rTMS") AND ("electroconvulsive therapy" OR "ECT"). No language or publication year limitation was imposed. To avoid omitting relevant trials, conference summaries and reference documents listed in the obtained articles were checked.

Among the identified studies, only those meeting the following criteria were selected for subsequent analyses: (i) RCTs comparing one treatment against another (B-rTMS, L-rTMS, R-rTMS, and ECT); (ii) assessing mood by the Hamilton Depression Rating Scale (HDRS), Montgomery-Åsberg Depression Rating Scale (MADRS), or Clinical Global Impression (CGI); (iii) patients over 18 years of age without metallic implants or foreign bodies, dementia, personal or family history of epileptic seizures, severe suicidal risk, organic brain damage, severe agitation or delirium, substance abuse, alcohol or drug dependence, and/or medically unfit for general anesthesia. Studies with pregnant patients were excluded because rTMS and ECT have unclear fetal side effects [20].

Studies were excluded if they: (i) had no random allocation; (ii) enrolled subjects with 'narrow' depression diagnoses (e.g., postpartum depression) or secondary depression diagnoses (e.g., vascular depression); (iii) used rTMS and ECT concomitantly with a new antidepressant without wash out period; and (iv) case reports and reviews.

2.2. Data extraction

Two reviewers independently verified all potentially suitable RCTs by the aforementioned inclusion and exclusion criteria and the completeness of data abstraction. Any disagreement was resolved by consensus and, if needed, a third reviewer was consulted. Data retrieved from the included RCTs were recorded in a structured fashion as follows: (i) sample characteristics: mean age, gender, mean depression score, treatment strategy used, presence of TRD; (ii) rTMS parameters: stimulation location, frequency, motor threshold, and duration; (iii) primary outcome measure: response was defined as at least a 50% reduction in the absolute HDRS or MADRS score from baseline, or significant improvement in the CGI, at the conclusion of therapy [21] with a preference for HDRS; and (iv) secondary outcome measure: overall drop-out rates at the study's end. For data that could not be directly retrieved, good faith efforts were applied to obtain the data by dispatching e-mails to the author, researching other studies citing the RCT in question, and researching associated conference summaries.

2.3. Bias risk in individual studies

Two reviewers independently assessed bias risk of the eligible studies according to the Cochrane handbook. We selected the following items to assess the bias risk: [1] did the authors conduct randomization? [2] did the authors conduct allocation concealment? [3] did the authors conduct blind treatment? and [4] were the baseline clinical characteristics matched between two groups. Studies with three or more 'NO' were still excluded.

2.4. Statistical analysis

In order to make the interpretation of current results easier for clinicians [22], the response rate (a dichotomous primary outcome for efficacy) was used instead of a continuous symptom score. If the baseline scores, standard deviations (SD), and endpoint means were provided instead of the dichotomous efficacy outcomes, we estimated the number of responding patients through a validated imputation method. [23] To perform a clinically sound analysis, we