A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression

Holtzheimer P E, Russo J, Avery D H

Authors' objectives
To determine the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression.

Searching
MEDLINE (search terms provided) and the Avery-George-Holtzheimer Database of rTMS Depression Trials were searched for published and unpublished studies. No language restrictions were imposed. The reference lists of pertinent articles were searched and the authors placed a request on a TMS listserv to identify further studies.

Study selection
Study designs of evaluations included in the review
Sham-controlled studies, with crossover or parallel groups, were eligible for inclusion. Studies using other treatments for depression as a control, such as medication alone or electroconvulsive therapy, were excluded.

Specific interventions included in the review
Studies of rTMS using the left or right dorsolateral prefrontal cortex (DLPFC) as the site of stimulation were eligible for inclusion. In the included studies, the frequency and intensity of stimulation, train duration, number of trains given per session, and the number of sessions varied (further details provided in the paper). The control condition received sham stimulation with the placement of a coil at an angle of 45 or 90 degrees.

Participants included in the review
Studies of patients diagnosed with depression (including major depressive disorder or bipolar disorder) were eligible for inclusion. Studies of patients resistant to medication, or receiving other medication in addition to rTMS, were included. Further patient characteristics were not provided.

Outcomes assessed in the review
Studies assessing the change from baseline for the 17-, 21-, or 25-item Hamilton Depression Rating Scale (HDRS) were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two authors simultaneously selected the articles for inclusion. However, it was not stated whether they were blinded to the source or results of the studies, or how any disagreements were resolved.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the mean decrease in HDRS score and standard deviation were extracted from the individual studies and used to calculate a standardised mean difference effect size (ES). Data were also extracted on the number of patients achieving a greater than 50% decrease in HDRS score. Additional study characteristics extracted were: the frequency and intensity of stimulation, train duration, number of trains given per session and the number of sessions, and whether the patients were resistant to medication or receiving medication.

Methods of synthesis
How were the studies combined?
The results from individual studies were combined using a random-effects meta-analysis and the pooled weighted ES was presented with 95% confidence intervals (CIs). In studies that evaluated more than one treatment condition, an ES
was calculated for each condition using the same sham-control group.

How were differences between studies investigated?
The homogeneity of the included studies was assessed statistically using the chi-squared test. Additional subgroup analyses were performed for studies using left DLPFC stimulation and parallel studies using left DLPFC stimulation. The impact of stimulation frequency and intensity, and the number of sessions, were analysed separately.

Results of the review
Twelve studies (16 comparisons; 264 patients) were included in the analysis comprising eight parallel studies (212 patients) and four crossover studies (52 patients). One study was excluded as it did not provide adequate details on the stimulation parameters or a measure of variability.

The use of rTMS was associated with a statistically-significant decrease in HDRS score in comparison with sham control (ES 0.81, 95% CI: 0.42, 1.20, P<0.001). There was evidence of statistical heterogeneity (data not provided). No significant correlation was found between stimulation frequency, intensity or the number of sessions and the ES (data not provided).

The subgroup analysis in studies using left DLPFC stimulation rTMS found a statistically-significant decrease in HDRS score in comparison with sham control (ES 0.89, 95% CI: 0.44, 1.35, P<0.001), based on 194 patients in 11 studies (14 comparisons). Of the studies that used parallel design, rTMS was associated with a statistically-significant decrease in HDRS score in comparison with sham control (ES 0.88, 95% CI: 0.22, 1.54, P<0.01), based on 142 patients in seven studies (nine comparisons).

The proportion of patients who reported a decrease in HDRS score of greater than 50% was 13.7% for rTMS and 7.9% for sham control.

Authors’ conclusions
rTMS was statistically superior to sham control in the treatment of depression, but this improvement was of modest clinical significance.

CRD commentary
The authors reported a clear review question with well-defined inclusion criteria. The search included sources to identify relevant published and unpublished trials, and an attempt was made to limit language bias. However, since only two electronic databases were searched, other relevant studies may have been missed. Two authors reviewed the studies for inclusion, which minimised selection bias, but details of the data extraction process were not reported.

The authors did not assess the validity of the included studies, although they did acknowledge that this may potentially affect the review's findings. The variability in the results of the individual studies and the limited details of the patient characteristics made it difficult to assess whether it was clinically appropriate to pool the data, although heterogeneity was assessed statistically and a random-effects model was used.

The authors' conclusion that the review's findings have modest clinical meaning, and their recommendation for further research to identify the patients who are likely to benefit the most from rTMS, appear to be appropriate.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further sham-controlled, parallel studies with adequate follow-up periods were required to determine the antidepressant effects of rTMS. These studies should collect data on patient characteristics (such as age, handedness, age at onset of depression, scalp-cortical distance, severity of depression, treatment resistance and concurrent medication) and stimulation characteristics (such as location, intensity, frequency, train duration, number of trains per session and number of sessions) to allow the identification of patients who are likely to benefit the most from rTMS.

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