Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review

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CRD summary
This review aimed to determine whether repetitive transcranial magnetic stimulation (rTMS) was useful in treating depression, and examined whether potential confounder variables alter effectiveness. The authors concluded that predictors of effectiveness could not be found, and the studies were often very different from each other. Questions surrounding the review methodology cast doubt on the reliability of the authors’ conclusions.

Authors' objectives
To determine whether repetitive transcranial magnetic stimulation (rTMS) can make a clinically useful contribution to the treatment of depression, in particular, to examine whether potential confounder variables have an impact on efficacy.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched using the expression 'transcranial magnetic stimulation' or 'TMS' and 'depression'. The authors also appear to have screened reference lists.

Study selection
Only randomised (parallel or crossover), double-blinded studies investigating the effects of rTMS compared with a sham control were included.

Outcomes had to be reported using either the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale. Baseline and follow-up depression scores (and their standard deviations) from before and after the intervention had to be available (or, at the very least, other data from which these values could be derived).

Studies were required to include patients with a diagnosis of depression: major depressive disorder or bipolar disorder. The majority of the included participants had major depressive disorder. The mean ages of the participant groups were 49.14 for active TMS and 48.85 for sham TMS. The mean baseline HAM-D scores were 27.05 for active TMS and 25.86 for sham TMS.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of the studies was assessed using a checklist from a previous systematic review (see Other Publications of Related Interest no.1), which the current review authors revised. The revision entailed using 9 criteria, rather than 17, since some of those omitted already formed part of the review inclusion criteria (e.g. presence of randomisation, double-blinding or sham control).

The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted on the mean and standard deviations of outcome measures (both before and after treatment), sample characteristics, study design and treatment parameters (stimulation frequency and intensity, type of coil used, number of treatment sessions). In crossover studies, only data from the first stage of the study were used.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
A meta-analysis examining overall effect size (ES) was performed using a random-effects model. The studies appear...
to have been weighted, although the method used was not stated; heterogeneity for this analysis was investigated using the Q test. The relationship between trial quality and ES was also explored. Mean baseline depression scores for the sham and active groups were compared using a paired t-test. To examine possible confounding effects, studies were also classified by the following variables: mean age of all participants; treatment resistance; number of rTMS sessions; type of depressive disorder; potential medication effects; stimulation intensity; left dorsolateral prefrontal cortex stimulation frequency; psychotic features; and inclusion in the systematic review of Couturier et al. Separate subgroup meta-analyses examining possible confounding effects were also performed, although heterogeneity here was not reported. A simultaneous multiple regression analysis was carried out to determine whether any variables predicted magnitude of the ES in individual studies.

Publication bias in the included studies was not assessed, although the relationship between date of publication and ES was investigated.

**Results of the review**
Thirty-three randomised controlled trials (n=877) were included in the review. The samples sizes for individual studies were not stated.

The quality scores ranged from 4 to 9, with a mean of 7.19 criteria satisfied. There appeared to be no significant correlation between trial quality and ES.

Active rTMS was associated with a statistically significant reduction in depressive symptoms (ES 0.65, 95% confidence interval: 0.51, 0.79), although the test for heterogeneity was highly significant (Q=100.9, d.f.=32, p<0.0001). A paired samples t-test showed no significant difference in baseline depression scores between treatment groups. The results of subgroup analyses were tabulated.

The multiple regression analysis, of which few details were provided, did not yield any significant predictors of ES. Further analyses were reported in the paper.

**Authors’ conclusions**
Studies that have examined rTMS efficacy in the treatment of depression are heterogeneous in terms of outcome, sample characteristics and treatment parameters. Predictors of rTMS efficacy in treating depression could not be found, owing to significant heterogeneity between the studies.

**CRD commentary**
The review question and inclusion criteria were reasonably clear. However, it was unclear whether the authors searched for non-English language papers or unpublished studies, which might have led to language or publication bias in the review. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. The assessment of the validity of studies was not comprehensive: allocation concealment and intention-to-treat parameters were ultimately excluded from trial quality scores (because few studies explicitly addressed these issues), while drop-out rates and use of power calculations were not assessed, despite the authors noting that many trials recruited relatively small numbers of participants. Very little information was given about the individual studies, and the number of participants included in each study was not stated. Forest plot, tables and textual reporting of seemingly the same pooled ES differed (0.65 versus 0.71), making the results difficult to interpret. Having found significant heterogeneity, the authors did not explore the potential reasons for it. In summary, a lack of complete reporting of review methods and trial details, and uncertainty about between-study differences and analyses, casts doubt on the reliability of the authors’ conclusions.

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

Research: The authors stated that large, rigorously controlled studies are needed to arrive at definitive judgements about predictors of treatment outcome. They also stated that future studies should investigate the effects of rTMS on cognition using longer follow-up periods.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.