Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis

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Objective: To systematically review the literature pertaining to rapid-rate repetitive transcranial magnetic stimulation (rTMS) compared with sham therapy for the treatment of a major depressive episode in order to arrive at qualitative and quantitative conclusions about the efficacy of rapid-rate rTMS. **Methods:** MEDLINE, the Cochrane Library, the metaRegister of Controlled Trials and abstracts from scientific meetings were searched for the years 1966 until July 2003. The search terms "transcranial magnetic stimulation" and "transcranial magnetic stimulation AND depression" were used. Eighty-seven randomized controlled trials investigating the efficacy of rTMS were referenced on MEDLINE. Nineteen of these involved treatment of a major depressive episode, and these were reviewed. Six met more specific inclusion criteria including the use of rapid-rate stimulation, application to the left dorsolateral prefrontal cortex, evaluation with the 21-item Hamilton Rating Scale for Depression (HAM-D) and use of an intent-to-treat analysis. Scores on the 21-item HAM-D after treatment and standard deviations were extracted from each article for treatment and control subjects. A random-effects model was chosen for the meta-analysis, and the weighted mean difference was used as a summary measure. **Results:** Six studies that met the inclusion criteria were identified and included in the meta-analysis. Two of these reported a significantly greater improvement in mood symptoms in the treatment versus the sham group. When combined in the meta-analysis, the overall weighted mean difference was –1.1 (95% confidence interval –4.5 to 2.3), and the results of a test for heterogeneity were not significant ($\chi^2_5 = 5.81$, $p = 0.33$). **Conclusions:** This meta-analysis suggests that rapid-rate rTMS is no different from sham treatment in major depression; however, the power within these studies to detect a difference was generally low. Randomized controlled trials with sufficient power to detect a clinically meaningful difference are required.

Objectif : Recenser systématiquement les publications qui traitent de la magnétostimulation transcrânienne répétitive (MSTr) rapide comparativement à une thérapie simulée pour traiter un épisode dépressif majeur afin de tirer des conclusions qualitatives et quantitatives sur l'efficacité de la MSTr rapide. **Méthodes :** On a recherché dans MEDLINE, la Cochrane Library, le metaRegister of Controlled Trials et des résumés de réunions scientifiques de 1966 jusqu'à juillet 2003 les expressions «transcranial magnetic stimulation» et «transcranial magnetic stimulation AND depression». MEDLINE contenait des références sur 87 essais contrôlés randomisés portant sur l'efficacité de la MSTr. Dix-neuf de ces études portaient sur le traitement d'un épisode dépressif majeur et ont été analysées. Six satisfaisaient à des critères d'inclusion plus spécifiques, y compris la stimulation rapide, l'application au cortex préfrontal dorsolatéral gauche, l'évaluation au moyen de l'échelle de dépression de Hamilton à 21 questions et l'utilisation d'une analyse de l'intention de traiter. Pour chaque article, on a extrait des résultats de l'échelle de dépression de Hamilton à 21 questions après le traitement et les écarts types pour les sujets traités et les sujets témoins. Un modèle d'effets aléatoires a été retenu pour la méta-analyse et la différence moyenne pondérée a servi de mesure sommaire. **Résultats :** Six études satisfaisaient aux critères d'inclusion et ont été incluses dans la méta-analyse. Deux de ces études ont signalé une amélioration beaucoup plus marquée des symptômes thymiques chez les sujets traités par rapport à ceux qui ont reçu la thérapie stimulée. Combinée à la méta-analyse, la différence moyenne pondérée globale s'est établie à

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–1,1 (intervalle de confiance à 95 % –4,5 à 2,3) et les résultats d'un essai d'hétérogénéité n'étaient pas significatifs (χ^2_5 = 5,81, p = 0,33). **Conclusions :** Cette méta-analyse indique que la MSTr rapide n'est pas différente du traitement simulé dans des cas de dépression majeure, mais la capacité de ces études à détecter une différence était généralement faible. Des essais contrôlés randomisés comportant

Introduction

Transcranial magnetic stimulation (TMS) has recently emerged as a possible treatment for depression. It is a noninvasive method of brain stimulation in which magnetic fields are used to induce electric currents in the cerebral cortex, thereby depolarizing neurons.[1] An effective TMS device was first built in 1985 by Anthony Barker at the University of Sheffield in England.[1] It was designed as a neurodiagnostic tool that activated neurons in the motor cortex and produced an evoked potential in muscle tissue. More focused magnetic fields were then used to map cortical regions involved in the functions of memory, vision and muscle control.[2–4] Pascual-Leone et al[5,6] described epileptic seizures and increased excitability of neurons with high-frequency repetitive TMS (rTMS). These effects are reminiscent of electroconvulsive therapy (ECT), with the potential to remedy the putative defects of neuronal activation in depression.[7] Both rTMS and ECT use electrical energy to induce neuropsychiatric change; however, the magnetic fields in TMS are unaffected by the high impedance of the skull and, thus, TMS can be applied relatively painlessly to conscious patients without the need for sedation.[1]

Single-pulse TMS was first used as a possible therapeutic tool for depression in 1993.[1] Since then, depression continues to be the most commonly studied psychiatric condition in the application of rTMS.[7] The dorsolateral prefrontal cortex (DLPFC) has been the primary area of interest for stimulation for 2 reasons. First, networks of brain regions including the prefrontal, cingulate, parietal and temporal cortical regions, as well as parts of the striatum, thalamus and hypothalamus, are thought to regulate mood. Second, this region is the most accessible for treatment with rTMS of the areas thought to be important in mood disturbances.[7]

The first open studies using TMS in depression involved single-pulse stimulators at frequencies lower than 0.3 Hz.[8–10] The large, circular coil was positioned over the vertex, stimulating frontal and parietal areas bilaterally. Conca et al[11] reported an augmentation of the speed of response to antidepressant medication with an open trial of 2 weeks' duration of single-pulse TMS.

Once devices that produced rTMS became available, they essentially replaced single-pulse generators. George et al[12] were the first to administer rapid-rate rTMS to the left DLPFC in a series of 6 patients. Rapid-rate or fast rTMS is generally defined as a stimulation frequency greater than 1 Hz.[13] The Hamilton Rating Scale for Depression (HAM-D) was used to evaluate response, in which a decrease in score indicates improvement in depressive symptoms.[14] A drop of 50% has been considered to indicate response by some authors,[15] whereas others have considered a drop of 6 points to be clinically meaningful[16] (possible scores range from 0 to 66). In the study by George et al,[12] depression scores significantly decreased after treatment with rTMS. Many open trials followed. Figiel et al[17] found that 21 of 56 patients experienced at least a 60% decline in their HAM-D score after 5 days of treatment with daily rapid-rate rTMS. Triggs et al[18] found an average decrease of 41% in HAM-D scores in 10 patients with medication-resistant major depression using fast rTMS. In contrast, 1 open trial did not find antidepressant activity with rTMS.[19]

These open studies must be interpreted with caution. It is well known that depression is a condition that is highly susceptible to the placebo response, with rates ranging from 30% to 50% in drug trials.[20,21] Device-based treatments, like rTMS, may result in even higher placebo response rates because of the elaborate rituals and sophisticated technology involved.[22] Fortunately, several randomized controlled trials (RCTs) have now been conducted to investigate the efficacy of rTMS in the treatment of depression. The objectives of this paper are to review the literature systematically to arrive at qualitative conclusions about the efficacy of rapid-rate rTMS compared with sham therapy in treating a major depressive episode and to assess the results quantitatively in the form of a meta-analysis.

Methods

A review of the literature was performed using the database MEDLINE. The phrases "transcranial magnetic stimulation" and "transcranial magnetic stimulation AND depression" were used with and without the limits "review" and "randomized controlled trial." The Cochrane database of controlled trials (www.cochrane.org) and the *meta*Register of Controlled Trials (www.controlled-trials.com/mrct) were also used to locate articles. Review articles were obtained and the references scanned for further RCTs. Abstracts from several scientific meetings including those of the Society of Biological Psychiatry (2002, 2003) and the American Psychiatric Association (2000, 2001, 2002, 2003) were searched.

The following inclusion criteria were based on principles outlined in the *Cochrane Reviewers' Handbook* 4.1.4[23] and the *Users' Guides to the Medical Literature*.[24]

A. Criteria pertaining to study validity: (1) a randomized parallel or crossover design with sham control, (2) evidence of allocation concealment (investigators could not predict to which group patients were randomly allocated), (3) investigators and patients were blinded to whether patients were receiving the treatment or sham therapy, (4) use of an intent-to-treat analysis (ensures that data for all randomly allocated patients are analyzed at the completion of the study and is essential for validating the

randomization process) and (5) if a crossover design was used, then a test for interaction or carryover effect must be shown to be nonsignificant (if not done or significant, only the data from the first phase of the study were examined).

B. Criteria pertaining to the subjects: (1) adults with a major depressive episode, meeting the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[25]
C. Criteria pertaining to the intervention: (1) rapid rTMS, frequency ≥ 10 Hz, (2) application over the left DLPFC, (3) duration of 5–10 days, (4) intensity of ≥ 80% (defined as a percentage of the intensity required to cause a muscle contraction of the abductor pollicis brevis) and (5) the sham condition similar in each study, with the coil angled between 45° and 90° from the scalp.
D. Criteria pertaining to the outcome: (1) data reported in a usable form for the meta-analysis, with post-treatment scores with standard deviations, (2) the 21-item HAM-D[14] was chosen as the primary outcome measure to be included in the meta-analysis, because it is a well-validated scale and was used in most studies in this systematic review.

Several exclusion criteria were established: (1) open trials, (2) studies investigating primary psychotic disorders, major depressive episodes with psychotic features, or other psychiatric illnesses, (3) studies targeting specific populations such as the elderly or children (because these groups may introduce clinical heterogeneity in the causes and prognosis of a major depressive episode) and (4) studies investigating rTMS in combination with the initiation of a medication.

The meta-analysis was performed using RevMan 4.1 for Windows, according to guidelines in the *Cochrane Reviewers' Handbook* 4.1.4.[23] The weighted mean difference summary measure was used, because the data were continuous and the identical outcome measure was used across studies. Using this approach, only patients within the same trial are compared with each other. A random-effects model was chosen, because it is generally more conservative than a fixed-effects model. A random-effects model produces wider confidence intervals and is based on the premise that 1 true answer does not exist.

In order to determine whether combining the results was appropriate, a test for heterogeneity was performed. This test is generally of low power; however, if significant it indicates that a large amount of variation exists in the outcomes of the combination of studies and that combining them may not provide valid results. Significance was set at $p < 0.05$.

Results

No studies were obtained through the Cochrane Collaboration database or the *meta*Register of Controlled Trials. No RCTs were found in the abstracts of scientific meetings. When the phrase "transcranial magnetic stimulation" was entered, 2379 articles were found to be referenced on MEDLINE. When this was limited to human RCTs, 87 articles were listed. Several of these articles involved rTMS in the treatment of psychiatric disorders other than depression, including schizophrenia, mania, bipolar disorder and post-traumatic stress disorder. Nineteen RCTs used rTMS versus placebo for depression. Thirteen of these were excluded (Table 1). Of these 13 excluded articles, 1 specifically involved an elderly population.[26] Six studies did not employ an intent-to-treat analysis.[27–32] Of these 6 studies, 1 involved concurrently starting treatment with a medication,[28] another involved right-sided stimulation,[29] 1 reported data in a different scale as opposed to the 21-item HAM-D,[30] and 1 did not report data in a usable form.[31] Two other studies used a scale other than the preferred 21-item HAM-D.[33,34] One study measured acute mood changes before and after each treatment rather than after 5–10 days of treatment and used a different outcome measure as opposed to the 21-item HAM-D.[35] One study involved subjects with a psychotic depression, over 5 months of a multiple crossover design, with concurrent treatment with nimodipine.[36] Two studies were excluded based on methods that were different from those used in the other studies. One used bilateral prefrontal stimulation,[37] and the other used neuronavigation with positron emission tomography (PET) in order to localize the DLPFC.[38]

After these exclusions, 6 studies remained that met the strict inclusion criteria (Table 2).[15,16,39–42] Three of these were crossover trials, and all had examined the effects of treatment order. One of these found no significant effect for treatment order.[39] In contrast, Kimbrell et al[40] found an effect for order in 1 of the outcome measures, the Beck Depression Inventory, and Eschweiler et al[16] found interactions between treatment group and order. Therefore, a conservative approach was taken, and only the data from the first phase of all 3 crossover studies were analyzed. The other 3 of the 6 included studies had a parallel design.[15,41,42] Three of the 6 studies compared fast, slow and sham rTMS, but the data from the slow treatment were excluded from the meta-analysis.[15,40,42]

Three studies indicated a significantly greater improvement in mood symptoms in the treatment group compared with the sham group.[15,16,39] George et al[39] reported a 5-point improvement on the HAM-D in the treatment group versus a 3-point worsening in the control group. Similarly, Eschweiler et al[16] reported a decrease of 5.4 points on the HAM-D compared with an increase of 1.6 points in the sham group. Although George et al[15] reported significantly more responders in the active versus the sham group, when comparing per cent change on the HAM-D there were no statistically significant differences between the fast rTMS group compared with the sham group. Avery et al[41] reported that although the sample was small, the data suggested greater improvement in the group that received rTMS. They noted a 10.5-point drop on the HAM-D in the treatment group compared with a 4.5-point drop in the control group. In contrast, Kimbrell et al[40] and Padberg et al[42] did not find any clinically meaningful antidepressant efficacy of rapid rTMS.

A meta-analysis was conducted of the 6 studies that met the inclusion criteria (Fig. 1). Only the data from the first phase of the crossover trials were used along with the parallel trials. The result of the χ^2 test for heterogeneity was not significant ($\chi^2_5 = 5.81$, $p = 0.33$), indicating that combining these studies was appropriate. The overall weighted mean difference was

–1.1 (95% confidence interval [CI] –4.5 to 2.3). As this confidence interval includes zero, it is not a statistically significant result. The test for overall effect was also not statistically significant ($z = 0.62$, $p = 0.5$). Therefore, there was no evidence to suggest that rapid rTMS was any better than placebo.

Discussion

The results of this meta-analysis indicate that rapid-rate rTMS does not appear to be any more efficacious than sham therapy in treating depression. These results are in partial agreement with those of a meta-analysis by Martin et al[43] who found an effect in favour of rTMS after 2 weeks of treatment (standardized mean difference = –0.35), but no significant difference at a 2-week follow-up. Martin et al[43] included 14 RCTs and concluded that the trials were generally of low quality and provided insufficient evidence to support the use of rTMS in the treatment of depression. These results are in contrast with those of another meta-analysis conducted by McNamara et al.[44] They found a beneficial effect of rTMS compared with placebo when 5 RCTs were included in a meta-analysis, with a difference in the rate of improvement between the treated and control group of 43% (95% CI 25%–61%). The results of a test for heterogeneity were not significant. This meta-analysis included 2 of the studies excluded from the present study. One of these involved rTMS given to the right DLPFC using a

Table 1: Randomized controlled trials that were excluded from the meta-analysis (*n* = 13)

Study	Participants	Methods	Outcome measures	Conclusions	Reason for exclusion
Berman et al[34]	20 Adults: major depression Failed to benefit from 1 trial of antidepressants	Parallel study Intent-to-treat analysis Left DLPFC 80% intensity 20 Hz for 10 weekdays 20 trains for 2-s duration with a 28-s intertrain interval Sham at 30°–45°	25-item HAM-D HAM-A BDI	Statistically significant, but clinically modest, reductions of depressive symptoms	Outcome measure not the 21-item HAM-D
Boutros et al[30]	22 Adults: major depression Failed to benefit from 2 trials of antidepressants	Parallel study Left DLPFC 80% intensity 20 Hz for 10 weekdays 20 trains for 2-s duration with 58-s intertrain interval Sham at 90°	25-item HAM-D	No significant differences between sham and treatment	Outcome measure not the 21-item HAM-D No intent-to-treat analysis
Garcia-Toro et al[27]	40 Adults: major depression Failed to benefit from 2 trials of antidepressants	Parallel study Left DLPFC 90% intensity 20 Hz for 10 weekdays 30 trains for 2-s duration with a 20–40-s intertrain interval Sham at 90°	21-item HAM-D HAM-A CGI BDI	TMS associated with significant decrease on HAM-D	No intent-to-treat analysis
Garcia-Toro et al[28]	28 Adults: major depression	Parallel study Left DLPFC 90% intensity 20 Hz for 10 weekdays Sham at 90°	21-item HAM-D	TMS does not add efficacy over the use of standard antidepressant medication	No intent-to-treat analysis Concurrent treatment with sertraline
Herwig et al[38]	25 Adults: major depression	Parallel study Intent-to-treat analysis Left DLPFC 110% intensity 15 Hz for 10 weekdays 30 trains for 2-s duration with a 4-s intertrain interval Sham at parieto-occipital transition	21-item HAM-D MADRS BDI	Moderate antidepressant effect	Neuronavigation with PET used to localize DLPFC (different method from other studies) Sham conditions not the same as in the other studies
Hoppner et al[32]	30 Adults: major depression	Parallel study Left DLPFC compared with right DLPFC and sham 90% intensity 20 Hz for 10 weekdays 20 trains for 2-s duration with a 60-s intertrain interval Sham at 90°	21-item HAM-D BDI	No significant differences between sham and treatment	No intent-to-treat analysis
Klein et al[29]	70 Adults: major depression	Parallel study Right DLPFC 1 Hz for 10 weekdays Sham at 90°	17-item HAM-D MADRS CGI	Significantly greater improvement on depression scales with rTMS	Right DLPFC 1-Hz frequency No intent-to-treat analysis

low frequency,[29] and the other, a study with a multiple crossover design, included patients with psychotic features and treatment with nimodipine.[36] Therefore, the present study includes more homogeneous conditions of rTMS delivery and clinical presentation of patients. In addition, the present study used data in a continuous form instead of dichotomizing the responses, thereby conserving information.[45] Several new studies have been published since the meta-analysis by McNamara et al[44] was conducted, and these were included in the present meta-analysis.

There are several possible explanations for the lack of benefit found for rTMS versus sham therapy in the present meta-analysis. The first, and most obvious, is that this is a valid result and rTMS is no more efficacious than placebo. A second possibility is that the most effective combination of parameters of rTMS has not been delineated. Even in the 6 studies combined in this meta-analysis, there were differences in the frequency, intensity, duration of train of pulses and days of treatment. These parameters are analogous to the dosage of a medication. If the therapeutic dosage is unknown, establishing efficacy may be difficult, if not impossible. In addition, the optimal site for the delivery of rTMS for depression has not been found. There is no evidence that the DLPFC is the best location. However, almost all of the studies encountered

Table 1 continued

Study	Participants	Methods	Outcome measures	Conclusions	Reason for exclusion
Loo et al[37]	19 Adults: major depression Medication resistant	Parallel study Intent-to-treat analysis Bilateral PFC 90% intensity 15 Hz for 3 weeks 24 trains for 5-s duration with a 25-s intertrain interval	HAM-D MADRS	No significant differences between sham and treatment	Bilateral prefrontal stimulation
Loo et al[33]	18 Adults: 15 major depression 3 bipolar depression (1 with psychotic features)	Parallel study Intent-to-treat analysis Left DLPFC 110% intensity 10 Hz for 10 weekdays 30 trains of 5-s duration with 30-s intertrain intervals Sham at 45°	17-item HAM-D MADRS BDI	No significant differences between sham and treatment	Outcome measure not the 21-item HAM-D
Manes et al[26]	20 Elderly subjects: major depression Treatment refractory	Parallel study Left DLPFC 80% intensity 20 Hz for 5 days 20 trains of 2-s duration	HAM-D	No significant differences	Elderly subjects
Padberg et al[31]	31 Adults: major depression	Parallel study Left DLPFC 100% and 90% intensity 10 Hz for 10 weekdays 15 trains of 10-s duration with 30-s intertrain interval	21-item HAM-D MADRS CGI	Significant reduction in depression scores with treatment	No intent-to-treat analysis Data reported as means (and SEM) instead of means (and SD)
Pascual-Leone et al[36]	17 Adults: major depression with psychotic features	Multiple crossover study Intent-to-treat analysis Left DLPFC 90% intensity 10 Hz for 5 days 20 trains of 10-s duration with 1-min intertrain intervals Sham at 45° Patients also treated with nimodipine	21-item HAM-D	Significant decrease in depression scores	Psychotic subtype of depression Concurrent treatment with nimodipine
Szuba et al[35]	16 Adults: major depression	Parallel study Intent-to-treat analysis Left DLPFC 100% intensity 10 Hz for 2 weeks 20 trains of 5-s duration over 10 minutes Outcomes measured before and after each session of TMS Sham at 90°	HAM-6 YMR-6 POMS	Significantly greater improvement on the POMS in the TMS group	Outcome measure not the 21-item HAM-D Outcomes were measured before and after each treatment (not at the end of 2 weeks as in the other studies)

Note: BDI = Beck Depression Inventory; CGI = Clinical Global Impressions scale; DLPFC = dorsolateral prefrontal cortex; HAM-6 = 6-Item Hamilton Rating Scale for Depression; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery–Asberg Depression Rating Scale; PET = positron emission tomography; POMS = Profile of Mood States; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; SEM = standard error of the mean; TMS = transcranial magnetic stimulation; YMR-6 = 6-item Young Mania Rating Scale.

in this systematic review used a procedure described by Pascual-Leone et al[36] in which the DLPFC is located by inducing muscle contractions in the abductor pollicis brevis and moving 5 cm anterior to this site. This method does not take into account variability in head size or shape.[7] In fact, studies using post hoc localization by magnetic resonance imaging (MRI) of coil position found considerable variability in coil distance from the middle prefrontal gyrus.[46,47] When the DLPFC was localized by PET before stimulation, Herwig et al[38] found a moderate improvement in depressive symptoms indicating that accurate localization is important.

A further confounding variable is the sham condition. Tilting the coil off the scalp is meant to stimulate the skin to reproduce the tactile sensation of real TMS along with the acoustic effects. However, inadequate tilting may in fact stimulate the cortex, exerting possible therapeutic effects.[48,49] This would reduce any possible differences in the treatment versus control groups, resulting in "negative" trials. Another difficulty arises in that the sensation of sham versus active rTMS may differ slightly, which could essentially unblind subjects in crossover trials.[7]

Another possible explanation for these negative findings is the low power in the 6 trials combined in the meta-analysis. For example, performing a sample size calculation based on the following assumptions, (1) a minimal clinically important decrease of 6 points on the HAM-D, (2) a standard deviation of 8 (an estimate from the 6 studies in this meta-analysis), (3) an alpha level of 0.05 and (4) power of 0.80, yields 56 subjects

Table 2: Randomized controlled trials that were included in the meta-analysis (*n* = 6)

Study	Participants	Methods	Outcome measures	Conclusions
Avery et al[41]	6 Adults: 5 with major depression 1 with bipolar II depression No psychotic features Condition resistant to 2 trials of antidepressants	Parallel study Left DLPFC 80% intensity 10 Hz for 10 weekdays 20 trains per session of 5-s duration with a 55-s intertrain interval Sham at 45°	21-item HAM-D BDI CGI SIGH-SAD	Sample too small Data suggest a greater improvement with TMS
Eschweiler et al[16]	12 Adults: major depression	Crossover study Left DLPFC 90% intensity 10 Hz for 5 days 20 trains of 10-s duration with a 50-s intertrain interval Sham at 90°	21-item HAM-D BDI	Statistically significant decrease on HAM-D in the treatment group No change in the sham group
George et al[39]	12 Adults: 11 major depression 1 bipolar II depression	Crossover study Left DLPFC 80% intensity 20 Hz for 10 weekdays 20 trains of 2-s duration over 20 minutes per day Sham at 45°	21-item HAM-D	Statistically significant improvement in mood in the treatment group compared with the sham group
George et al[15]	30 Adults: 21 major depression 9 bipolar I depression	Parallel study Left DLPFC 100% intensity 20 Hz for 10 weekdays 40 trains of 2-s duration with a 28-s intertrain interval over 20 minutes per day Sham at 45° Also involved a third group at 5-Hz frequency, but these data were not used	21-item HAM-D HAM-A CGI MMSE	Statistically significant greater improvement on the BDI and HAM-A in the treatment group
Kimbrell et al[40]	13 Adults: 9 major depression 1 bipolar II depression 3 bipolar I depression	Crossover study Left DLPFC 80% intensity 20 Hz for 10 weekdays 20 trains of 2-s duration with a 1-min intertrain interval (800 stimuli) Sham at 45° Also involved a third treatment condition at 1-Hz frequency, but these data were not used	21-item HAM-D BDI	Lack of overall response to 20-Hz TMS
Padberg et al[42]	18 Adults: major depression Condition resistant to 2 trials of antidepressants	Parallel study Left DLPFC 90% intensity 10 Hz for 5 days 5 trains of 5-s duration with a 30-s intertrain interval Sham at 90° Also involved a third group at 0.3-Hz frequency, but these data were not used	21-item HAM-D BDI MADRS	No clinically meaningful antidepressant effect of rTMS

Note: MMSE = Mini-Mental State Examination; SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorder version.

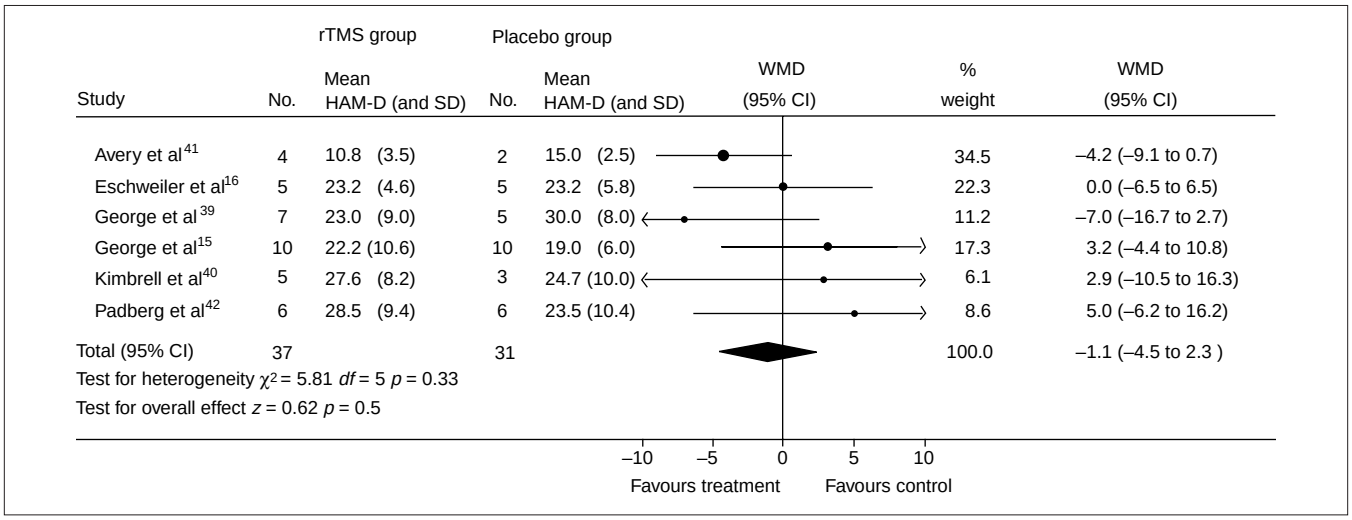

Fig. 1: Meta-analysis using a random-effects model and the weighted mean difference (WMD) of the efficacy of repetitive transcranial magnetic stimulation (rTMS) versus placebo as a treatment for depression measured with the Hamilton Rating Scale for Depression (HAM-D).

needed in a single trial (for formula see Friedman et al[50]). This is slightly fewer than the total of 68 subjects included in the 6 trials examined in this meta-analysis, indicating that the power of each of these trials was significantly below that needed to detect a difference of this magnitude in the HAM-D. Therefore, if this difference cannot be detected because of low power, a trial may produce negative results even if there really is a difference between the treatment and control groups (type II error).

The intention of this meta-analysis was to determine the efficacy of rTMS compared with sham therapy. The comparison of rTMS with ECT has also been investigated with open[51,52] and controlled[53] protocols. Unfortunately, these studies could not be included in this meta-analysis, because the question of whether rTMS is different from ECT is a separate issue. A future review and meta-analysis may look at comparing rTMS with ECT. Although studies comparing rTMS with ECT have suggested favourable results for rTMS with no statistically significant differences between these treatments, these studies are not designed to determine equivalence. In other words, "no significant difference" does not mean these treatments are equal. Perhaps future studies with the much larger sample sizes needed to determine equivalence might be helpful in clarifying this question.

In conclusion, when rTMS was first introduced, several open trials suggested a possible antidepressant effect. The RCTs that followed provided mixed results. This meta-analysis of 6 small, but generally well-designed, studies found that rapid-rate rTMS was no more efficacious than sham therapy in treating adults with a major depressive episode. Heterogeneity in these 6 studies was not significant, indicating that combining the data was appropriate. Further RCTs with larger samples and sufficient power are needed in which the DLPFC is precisely localized and the parameters of rTMS are of sufficient intensity, frequency and duration. In addition, true sham conditions must be delineated. These steps would help answer the question of whether rTMS is efficacious in treating depression.

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