Health Quality Ontario

Ontario Health Technology Assessment Series

Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

KEY MESSAGES

Repetitive transcranial magnetic stimulation (rTMS) is a technique used to stimulate focal areas of the outer layer of the brain with the use of magnetic pulses generated by a coil. In clinical practice, the patient is seated in a chair and an operator positions the coil on the scalp and applies rTMS pulses. rTMS does not cause seizures if used properly and does not require general anesthesia.

Many studies have investigated the effectiveness of this technique in the treatment of depression that does not respond to antidepressant medications by comparing it with electroconvulsive therapy or with a sham technique. rTMS can be applied using a variety of protocols and there are many combinations of such protocols. In this report, we focus on the rapid rate (high frequency) technique applied to the left side of the brain.

We reviewed 20 years' experience with rTMS and analyzed the results of published studies that compared this technique with electroconvulsive therapy or sham treatment. We considered changes in depression severity after treatment to compare these techniques and also calculated number of patients in each arm who reached a healthy mood state or who had their depression symptoms reduced by 50% or more. Our findings suggest that the clinical benefit of rTMS is inferior to that of electroconvulsive therapy and marginally effective when compared to the sham technique. The most common side effects of rTMS were headache, scalp discomfort, muscle twitching, and gastrointestinal and eye problems.

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ABSTRACT

Background

To date, several randomized controlled trials (RCTs) have shown the efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depression.

Objective

This analysis examined the antidepressant efficacy of rTMS in patients with treatment-resistant unipolar depression.

Methods

A literature search was performed for RCTs published from January 1, 1994, to November 20, 2014. The search was updated on March 1, 2015.

Two independent reviewers evaluated the abstracts for inclusion, reviewed full texts of eligible studies, and abstracted data. Meta-analyses were conducted to obtain summary estimates. The primary outcome was changes in depression scores measured by the Hamilton Rating Scale for Depression (HRSD), and we considered, a priori, the mean difference of 3.5 points to be a clinically important treatment effect. Remission and response to the treatment were secondary outcomes, and we calculated number needed to treat on the basis of these outcomes. We examined the possibility of publication bias by constructing funnel plots and by Begg's and Egger's tests. A meta-regression was undertaken to examine the effect of specific rTMS technical parameters on the treatment effects.

Results

Twenty-three RCTs compared rTMS with sham, and six RCTs compared rTMS with electroconvulsive therapy (ECT). Trials of rTMS versus sham showed a statistically significant improvement in depression scores with rTMS (weighted mean difference [WMD] 2.31, 95% CI 1.19–3.43; $P < .001$). This improvement was smaller than the pre-specified clinically important treatment effect. There was a 10% absolute difference between rTMS and sham in the rates of remission or response. This translates to a number needed to treat of 10. Risk ratios for remission and response were 2.20 (95% CI 1.44–3.38, $P = .001$ and 1.72 [95% CI], 1.13–2.62, $P = .01$), respectively, favouring rTMS. No publication bias was detected.

Trials of rTMS versus ECT showed a statistically and clinically significant difference between rTMS and ECT in favour of ECT (WMD 5.97, 95% CI 0.94–11.0, $P = .02$). Risk ratios for remission and response were 1.44 (95% CI 0.64–3.23, $P = .38$) and 1.72 (95% CI 0.95–3.11, $P = .07$), respectively, favouring ECT.

Conclusions

Overall, the body of evidence favoured ECT for treatment of patients who are treatment-resistant. Repetitive transcranial magnetic stimulation had a small short-term effect for improving depression in comparison with sham, but follow-up studies did not show that the small effect will continue for longer periods.

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BACKGROUND

Objective of Analysis

This analysis examined the antidepressant efficacy of repetitive transcranial magnetic stimulation in patients with treatment-resistant unipolar depression.

Clinical Need and Target Population

Transcranial magnetic stimulation (TMS) was originally used as a research tool to investigate brain function and in physiologic studies of various neuropsychiatric illnesses. Soon after the technique was introduced into research, several patients told researchers about their improved mood after TMS stimulation. This initial observation led to investigating TMS for depression treatment. Scientific investigation in the field of depression started in 1987 when Bickford et al[1] studied the possibility of mood elevation in normal volunteers receiving single-pulse stimulation.

Continuing progress of TMS technology soon made it possible to deliver multiple pulses within short periods; the technique now is known as repetitive transcranial magnetic stimulation (rTMS). The antidepressant effect of rTMS was initially reported by Pascual-Leone et al in 1996[2] and, soon after, neuropsychiatric centres around the world began to investigate the effectiveness of rTMS in treatment of major depression. Because technical parameters and the depression profile of patients were broad and because many factors needed to be considered, studies investigated a variety of stimulation paradigms and of depression profiles. The stimulation paradigm varied among studies in terms of the rTMS device used, coil shape, location of the coil on the scalp, frequency and intensity of stimulation, number of trains, train duration, number of sessions, and number of total pulses.

In addition to treatment for depression, rTMS has been used as a research tool investigating the potential for treating such other psychiatric disorders as bipolar disorder, panic disorder, obsessive-compulsive disorder, auditory hallucination in schizophrenia, catatonia, post-traumatic stress disorder, and addiction. Its potential to alleviate pain in conditions such as migraine, neuropathic pain, and fibromyalgia has been the subject of many investigations. The potential for benefit from rTMS treatment in other health conditions such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, and spasticity has also been investigated.

Description of Disease/Condition

According to criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., depressive disorders include the following conditions:

- Disruptive mood dysregulation disorder
- Major depressive disorder, single and recurrent episodes
- Persistent depressive disorder (dysthymia)
- Premenstrual dysphoric disorder
- Substance- and medication-induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorder
- Unspecified depressive disorder

Although depression can be effectively treated with antidepressant medications, patients generally respond to these medications differently. For some patients, it takes time to find the correct medication and dosage. Antidepressant medications generally take about 4 to 8 weeks to show the full effect.

When, for some patients, the first antidepressant does not show benefit, the physician can prescribe different classes of antidepressants to target a range of brain chemicals (i.e., neurotransmitters) linked to mood. In another approach (called augmentation), the physician can add other classes of medications intended to treat other psychological conditions (such as anxiety or psychosis) to antidepressant medication to boost the effectiveness of antidepressants. In many patients psychological counselling that allows patients to move toward a healthier emotional state and overcome negative emotions, such as sadness or anger, has proven effective and beneficial.

If symptoms of depression continue despite antidepressant trials and psychotherapy or other treatments, it is critical that the physician first ensure that patients have had an adequate dose of medication for long enough to take effect and then re-evaluate the diagnosis before labeling the condition as treatment-resistant depression.

Multiple definitions have been used to characterize the outcome of treatment for depression. Some researchers define treatment-resistant depression as inadequate response to a trial of at least one class of antidepressant of adequate dosage and duration. However, even the definition of an adequate response varies, ranging from failure to achieve response to failure to achieve full symptom remission. Most experts currently agree that inadequate response is the failure to achieve full symptom remission.[3]

Prevalence and Incidence

Prevalence of Depression in Canada

The Canadian Community Health Survey: Mental Health and Well-being (CCHS 1.2), conducted by Statistics Canada between May and December 2002, has reported prevalence estimates and descriptive epidemiology for major depression.[4] The target population included people 15 years of age or older and excluded people living in health care institutions, on Indian reserves, on government-owned land, in one of the three northern territories, and in remote regions. The overall annual prevalence of major depressive episode was 4.8% (95% confidence interval [CI] 4.5%–5.1%) and the lifetime prevalence was 12.2% (95% CI 11.7%–12.7%). The point prevalence was 1.8% (95% CI 1.6%–1.9%). After excluding people with bipolar disorder, the annual prevalence, lifetime prevalence, and point prevalence of major depressive disorder was 4.0% (95% CI 3.7%–4.2%), 10.8% (95% CI 10.3%–11.3%), and 1.3% (95% CI 1.1%–1.4%). Major depressive disorders were more common in women, in younger people, in singles (never married), in previously married people who divorced or separated, in those who had one or more chronic medical conditions, and in those unemployed within the past year.

The National Comorbidity Survey Replication[5] showed higher prevalence of major depressive disorder in the United States than in Canada; the 12-month prevalence of major depressive disorder in the United States was estimated as 6.6% (95% CI 5.9–7.3) and the lifetime prevalence as 16.2% (95% CI 15.1–17.3).[5]

Prevalence of Treatment-Resistant Depression

Data from the STAR*D trial,[6] which was conducted in both psychiatric and primary care practice settings, show that the prevalence for Stage 1 treatment-resistant depression (failure to achieve response after one course of adequate treatment) is about 50% using response criteria and about 70% using remission criteria. Data extrapolated from the trial show the prevalence of Stage 2 treatment-resistant depression (failing to achieve response after two courses of adequate treatment) as approximately 35%.[7]

Ontario Context

Using the figures of 4.0%[4] as the prevalence for unipolar major depression and 35%[7] as the prevalence of Stage 2 treatment-resistant depression, we can estimate that about 160,837 persons 15 years or older in Ontario have depression that is resistant to two courses of antidepressant treatment. Repetitive transcranial magnetic stimulation is not covered by the Ontario Health Insurance Plan.

Status of Technology in Other Provinces of Canada

In two provinces of Canada (Quebec and Saskatchewan), rTMS is an insured service, and in one province (Alberta), the technology is under review by the Expert Advisory Group of the Health Technology Decision Process at the time of writing.

Technology/Technique

Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation delivers magnetic pulses into the brain cortex and is a variant of the TMS technique of earlier studies, which used single-pulse stimulations. rTMS applies repetitive stimulations to modulate cortical activity.[8]

The aim of rTMS therapy is to stimulate the area of the brain associated with mood regulation. In this technique, a stimulating coil is placed directly on the scalp to deliver magnetic pulses to the underlying brain tissue and to depolarize the local neurons. Neuronal excitability depends on the frequency and intensity of stimulation applied. The antidepressant effect of rTMS has been studied using single pulse, paired pulse, and repetitive pulses, and also using low-frequency or high-frequency stimulation.

Repetitive transcranial magnetic stimulation has been used as an alternative to electroconvulsive therapy (ECT) for depression. Unlike ECT, rTMS does not require anesthesia and does not cause seizure in general if used properly and in compliance with the safety guidelines. Repetitive transcranial magnetic stimulation can be applied relatively painlessly to conscious patients and can be used for outpatients or for inpatients.

Various types of stimulating coils have been designed, each of which produce different magnetic field patterns. Circular coil (round coil) was the original design, but it could not deliver stimulation deep into the brain. Other types of coils have been designed to generate more focal and deeper stimulation. A double-cone coil conforms to the shape of the head to deliver deeper stimulation, and a figure 8 design (butterfly coil) produces a more focal pattern of activation. An H-coil has been designed for deep rTMS.

Equipment for rTMS includes a comfortable chair with an electromechanical head support system that allows reliable positioning of the coil over the head. The body of the chair should provide maximum comfort and lumbar support during rTMS treatment. Safety guidelines and contraindications are reported in Appendix 3.

Safety Guidelines

Several scientific societies have commissioned groups of experts and conducted comprehensive reviews of the evidence on safety of rTMS. The current guideline[9] on safe practice of rTMS is based on a consensus conference in Certosa di Pontignano, Siena (Italy) on

March 7 to 9, 2008, which was held to update the previous safety guidelines for application of TMS in research and clinical settings.

Clinical guidelines with respect to the margin of safety with rTMS were originally based on the evidence provided by Wassermann[10] that was subsequently updated by Rossi et al.[9] The US Food and Drug Administration cited the work by Wassermann and by Rossi et al as a clinical guide to avoid stimulation parameters that fall outside safety recommendations and that can cause adverse effects such as seizure or syncope. Appendix 3 shows maximum safe duration of trains and inter-train interval recommended in the guideline.

Contraindications

The rTMs technique is contraindicated for use in patients who have implanted ferromagnetic devices or other magnetic-sensitive metal implants close to the magnetic coil. However, given the lack of detailed information as to what constitutes a safe distance between the rTMS coil and the implanted stimulator and the role of other factors (such as the shape of the coil or coil angulation that might influence this relation), rTMS should be performed in patients with implanted stimulators only if there are scientifically or medically compelling reasons justifying its use.[9]

A very rare, but serious, complication of rTMS is the occurrence of seizure. In most reported seizures, the stimulation parameters did not follow the published guidelines. In addition, concomitant use of some medications could have resulted in a lower seizure threshold, leading to seizure.[11]

According to the safety guideline by Rossi et al,[9] the only absolute contraindication to rTMS is the presence of metallic hardware in close contact with the discharging rTMS coil. In such instances there is a risk that these implanted devices will malfunction. The safety guideline by Rossi et al[9] lists several conditions of increased or uncertain risk of inducing epileptic seizure related to protocol stimulus:

- any novel paradigm (i.e., that is not a classic method of high- or low-frequency rTMS, performed with a flat figure 8 coil and biphasic pulse waveform), pre-conditioning (i.e., priming), TMS applied on more than a single scalp region, and prolonged paired associative stimulation protocols
- conventional high-frequency rTMS protocol with parameters of stimulation (intensity, frequency, train length, or inter-train duration) exceeding the safety limits reported by Rossi et al (see Tables 4–6 in Section 7.2)

Rossi et al[9] also list increased or uncertain risk of inducing epileptic seizure related to the disease or patient's condition:

- A history of epilepsy (untreated patients with one or a few past episodes, or treated patients).
- Vascular, traumatic, tumoral, infectious, or metabolic lesion of the brain, even without a history of seizure, and without anticonvulsant medication.
- Administration of drugs that potentially lower seizure threshold without concomitant administration of anticonvulsant drugs that potentially protect against seizure occurrence.
- Sleep deprivation or a history of alcoholism.

Increased or uncertain risk of other events is related to such conditions as implanted brain electrodes, pregnancy, and severe or recent heart disease.

Regulatory Status

According to Health Canada, the only rTMS device currently indicated for treatment of depressive episodes in Canada is the Deep TMS system manufactured by Brainsway. Other devices listed in Table 1 are indicated for treatment of psychiatric and neurologic disorders, but are also used for rTMS.

Table 1: Devices Licensed by Health Canada and Their Intended Use

Company Name	Licence Name	Licence Number	Issue Date	Class	Intended Use
Brainsway Ltd	Deep TMS System	90504	2013-01-11	3	Indicated for treatment of depressive episodes in patients suffering from major depressive disorder who have failed to benefit from or are intolerant to antidepressant drugs.
Tonica Elektronik A/S	Magpro Compact Magnetic Stimulator	12164	2013-01-18	3	For magnetic stimulation of the central nervous system.
Tonica Elektronik A/S	Magpro X100 Magnetic Stimulator System	60608	2012-02-24	3	For noninvasive stimulation of nerves in the central and peripheral nervous systems. Used short-term to examine the physiology of motor pathways, to ascertain function of motor nerves stimulation, to examine human cortical physiology, to change muscle function in a therapeutic manner, and to change brain activity in a therapeutic manner.
Tonica Elektronik A/S	Magpro R30 Magnetic Stimulator	68484	2008-01-09	3	Electrophysiologic aid for assessment, diagnosis, and prognosis and to monitor diseases of the nervous system.
Magstim Company Limited	Magstim model 2002	70387	2006-02-02	2	Nerve stimulator that induces electrical current through electromagnetic pulses. Capable of stimulating neural tissue.

In October 2008, the US Food and Drug Administration cleared the first rTMS brain-stimulating device (NeuroStar) for treating patients with depression who have failed to respond to one trial of antidepressant medication. In January 2013, the Food and Drug Administration approved the Brainsway Deep TMS System based on substantial equivalence with the previously approved TMS device NeuroStar. However, the coil in Brainsway device is an H-coil that has the ability to stimulate deeper brain tissue.

Alternative Technologies

Electroconvulsive Therapy

Electroconvulsive therapy is considered the most effective treatment for very severe depression that has not responded to any other treatment. The technique uses a machine to send brief electrical stimulus to the brain to induce a seizure.

Electroconvulsive therapy requires general anesthesia and use of muscle relaxant to prevent muscle spasm, pain, or injury during the procedure. Physicians titrate doses to ensure patients will receive adequate stimulus and to avoid overdosing. In recent years the technique has greatly improved and can more safely provide relief for patients with severe depression. According to the Canadian Psychiatric Association position paper,[12] ECT has well-defined indications and established standards for practice. With the present-day technique, many of the previously significant medical complications of ECT have been eliminated.

CLINICAL EVIDENCE REVIEW

Research Methods

For the purpose of this analysis, we searched for randomized controlled trials that applied high-frequency (≥5 Hz) repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex in adult patients with unipolar depression refractory to antidepressant medications. We included all studies that compared rTMS with electroconvulsive therapy (ECT) or sham treatment. Daily left prefrontal rTMS has been approved by the US Food and Drug Administration for treatment of adult patients with unipolar depression whose current episode did not respond to one adequate dose of antidepressant medication. In consultation with experts in the field, we established that treatment-resistant depressive patients are the population most appropriate for rTMS treatment.

Given ongoing debate over the precise definition of treatment-resistant depression, our focus was not based on the number of treatments that failed; rather, we included all stages of treatment resistance so we could stratify patients and perform a subgroup analysis if possible.

Because results of earlier studies[2] showing acute effects at 1 week (after five treatment sessions) were not replicated in subsequent studies, longer duration of treatment was justified by the subsequent studies. We, therefore, included only studies in which the duration of treatment was not less than 2 weeks or 10 sessions.

Earlier studies also showed that stimulation at or above a patient's motor threshold produces much greater benefit than stimulation below the motor threshold (e.g., 80%).[13] However, we included studies on all percentages of motor threshold to further investigate the effect of the technical parameters.

We selected the Hamilton Rating Scale for Depression to measure the outcomes of treatment because this scale is the most commonly used tool for clinical assessment of treatments for depression.[14] The Hamilton Rating Scale for Depression is a multidimensional and clinician-rated scale that has become the standard for clinical trials of depression. For the 17-item version of the Hamilton Rating Scale for Depression, scores can range from 0 to 54. It is generally accepted that scores between 0 and 6 do not indicate the presence of depression, scores between 7 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression.[14] A decrease in scores of at least 50% typically indicates response, and scores of 7 or less after treatment indicate remission.[14]

Given high interest during the last 20 years in determining the most effective technical parameters of rTMS to treat depression, many studies experimented with various technical parameters. However, some of these studies used parameters outside the safety guidelines for current practice and therefore have no clinical relevance. We have provided estimates without and with the inclusion of two sham trials and one trial of ECT that used rTMS technical parameters outside safety guidelines. Forest plots including these studies are shown in the Appendices.

Literature Search Strategy

A literature search was performed on November 20, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative

Index to Nursing & Allied Health Literature (CINAHL), PsychInfo, and EBM Reviews, for studies published from January 1, 1994, to November 20, 2014. (Appendix 1 provides details of the search strategies.) The search was updated on March 1, 2015, through the AutoAlert function of the search.

Abstracts were assessed by two reviewers independently and, for all studies meeting the eligibility criteria, full-text articles were obtained and assessed by two reviewers. Any disagreement about inclusion was resolved by consensus once feedback was received from a consulting third party. The reference lists of the included studies were hand-searched by two reviewers to identify other relevant studies.

Data were abstracted independently by two reviewers for relevant clinical outcomes. All the following variables were extracted:

- Demographic and clinical characteristics of patients (number of patients in each arm, mean age, medication resistance, use of medication during trial, percentage of patients with bipolar disorder, percentage of patients with psychosis)
- Study design, study power, and statistical analysis approach
- Technical parameters for rTMS (frequency and intensity of stimulation, number of trains, train duration, duration of inter-train interval, number of sessions, number of pulses per session, number of total pulses, device name, shape of the rTMS coil, and duration of treatment)
- Technical parameters for ECT (laterality, number of sessions)
- Clinical outcomes (depression scores, remission rate, response rate, and relapse rate; all based on scores from the Hamilton Rating Scale for Depression); adverse events were extracted as reported

Inclusion Criteria

- Randomized controlled trials
- Studies comparing rTMS with ECT or sham treatment in adult patients (age ≥ 18 years)
- Studies in which at least 80% of patients were resistant to treatment
- Studies that applied high-frequency rTMS (≥5 Hz) to the left dorsolateral prefrontal cortex and complied with rTMS safety guidelines
- Studies that included unipolar patients only or that reported the proportion of bipolar patients as ≤20%
- Studies in which patients received at least 10 sessions of rTMS treatment

Exclusion Criteria

- Nonrandomized trials
- Studies of stimulation sites other than left dorsolateral prefrontal cortex
- Studies that used frequencies of rTMS outside the range for this review
- Studies on bilateral rTMS or bilateral versus unilateral rTMS
- Studies on sequential combined low-frequency and high-frequency rTMS
- Studies on newer techniques (synchronized rTMS, pulsed rTMS, deep rTMS, rTMS with priming stimulation)

- Studies that evaluated the effect of rTMS on cognitive functions
- Studies that evaluated the effectiveness of rTMS in depression due to specific conditions (i.e., poststroke depression, postpartum depression)
- Studies that did not report the important outcomes for this review, did not define the reported outcomes, or provided insufficient data

Outcomes of Interest

Primary Outcome

- Changes in depression scores measured by the Hamilton Rating Scale for Depression

Secondary Outcomes

- Remission rate measured by the Hamilton Rating Scale for Depression
- Response rate measured by the Hamilton Rating Scale for Depression
- Relapse rate
- Adverse events

Research Questions

- What is the effectiveness of rTMS compared with ECT or sham rTMS in reducing depression scores?
- What is the effectiveness of rTMS compared with ECT or sham rTMS in improving remission and response rates?
- How long can the antidepressant effect of rTMS persist?
- What are the adverse effects of rTMS treatment?

Statistical Analysis

We conducted a series of meta-analyses to determine the summary estimates for the effectiveness of rTMS, comparing rTMS with ECT or sham treatment. All analyses were performed using STATA 11, StataCorp LP, in College Station, Texas.

We calculated changes in depression scores measured by Hamilton Rating Scale for Depression from baseline to the end of treatment and conducted a meta-analysis on the mean changes in scores for the rTMS treatment and control groups. Pooled effect sizes for depression scores were calculated using weighted mean difference, and we considered a priori the mean difference value of 3.5 points on the Hamilton Rating Scale for Depression to be a clinically relevant treatment effect.[15] We performed a sensitivity analysis based on weighted mean difference (WMD) to increase our level of confidence in the point estimate. We also calculated the effect size as the difference between the means of the two groups divided by the standard deviation (SD), a statistical method known as standardized mean difference (SMD) using Cohen's method. We used Cohen's conventional definition of small, medium, and large effect size as 0.2, 0.5, and 0.8, respectively. Cohen noted that, with the effect size of 0.2, the two populations will have an overlap of about 85% and the overlap between the two populations will be 67% and 53% for effect sizes of 0.5 and 0.8, respectively. Two studies used different rTMS parameters but did not report a combined estimate for depression scores; therefore, we

included only the parameter that was most frequently reported by other studies and had more clinical relevance to avoid duplication of data in the meta-analysis.

For binary outcomes, we calculated remission and response rates, as well as the pooled risk ratios and risk differences as the summary effect estimates along with their corresponding 95% confidence intervals (CIs) around the point estimates. We also calculated the number needed to treat for remission and response rates based on the sham trials as the inverse of the risk difference. Although the definition of response was consistent among the sham studies (all based on ≥50% reduction in depression scores), the definition of response varied in ECT trials and the definition of remission varied across the studies for both sham trials and ECT trials. Remission is a critical end point in management of patients with depression, but no universally agreed-upon remission rate currently exists. Remission is most frequently defined as scoring 7 or lower on the 17-item version of the Hamilton Rating Scale for Depression, proposed by McArthur Foundation group.[16]

We used a random effects model for all meta-analyses. The degree of statistical heterogeneity among studies was assessed using the I-squared (I^2) and chi-squared (χ^2) statistics. Higgins et al[17] have proposed a tentative classification of I^2 values with the purpose of helping to interpret its magnitude. They assigned adjectives of low, moderate, and high to the I^2 of 25%, 50%, and 75%.[17] We preferred to report outcomes via intention-to-treat analysis.

We examined the possibility of publication bias by constructing funnel plots based on weighted mean difference, remission rate, and response rate and by visualizing funnel plot asymmetry. We also performed tests for the presence of publication bias for these outcomes using Begg's and Egger's tests. We also conducted a cumulative meta-analysis to track accumulation of evidence on the effectiveness of rTMS over two decades.

Where applicable, we conducted meta-regression analyses to examine the potential effect of rTMS parameters on the effect estimates.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[18] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural method.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, three main factors that could raise the quality of evidence were considered: the large magnitude of effect, the dose-response gradient, and any residual confounding factors.[18] For more detailed information, please refer to the latest series of GRADE articles.[18]

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect

Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

Results of Evidence-Based Analysis

The database search yielded 2,253 citations published between January 1, 1994, and November 20, 2014 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis.

Twenty-nine randomized controlled trials (30 citations) met the inclusion criteria. The reference lists of the included studies were hand-searched to identify other relevant studies, and no additional citations were identified.

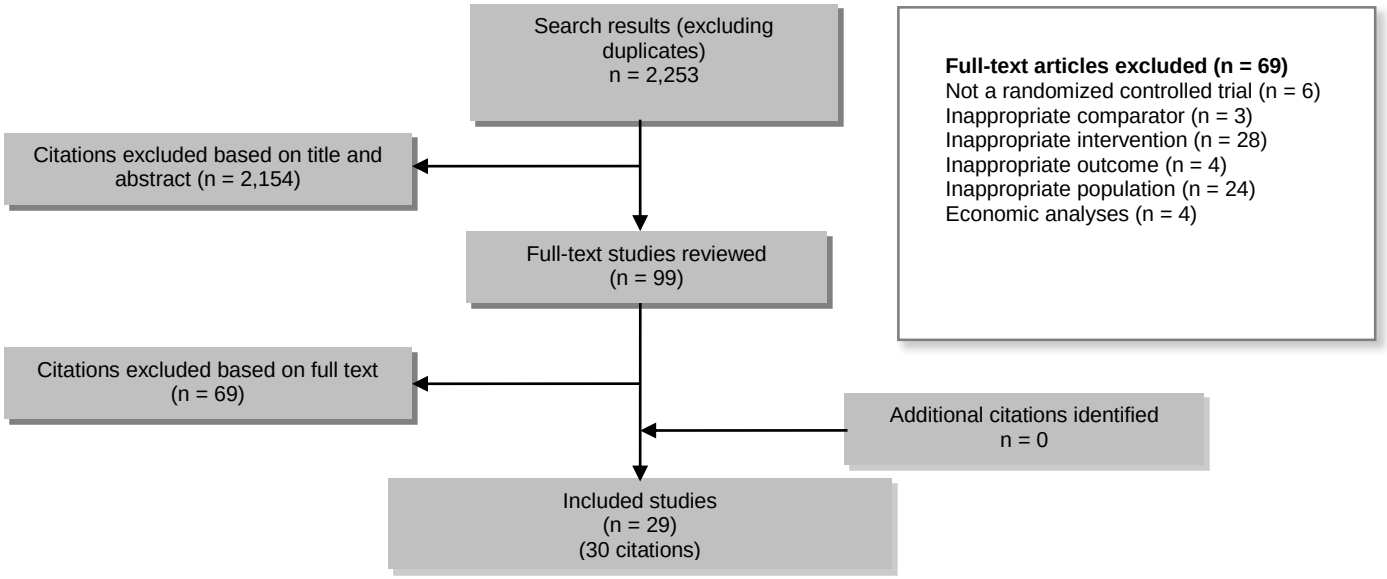


Figure 1: Citation Flow Chart

Twenty-three randomized controlled trials compared rTMS with sham rTMS, and six randomized controlled trials (seven citations) compared rTMS with ECT. Three studies (two for sham comparison and one for ECT comparison)[19-21] did not comply with the safety standards for the use of rTMS and exceeded the limit set by the safety guidelines.[9,10] We have presented the forest plots without these studies in this report and have included these studies in Appendices 3 and 4.

Repetitive Transcranial Magnetic Stimulation Versus Sham

Characteristics of Studies

Twenty-three studies conducted in nine countries met our inclusion criteria. A total of 1,156 patients were analyzed in these studies, from which 602 were assigned to rTMS and 554 to sham treatment. Only three studies performed allocation concealment either through sealed computer database or sealed envelope so that the person enrolling participants did not know in advance which treatment the next patient would receive.[15,22,23] All studies reported that the assessor of the outcomes was blinded to the intervention assignment, and all but four studies[19,21,24,25] reported that patients were also blinded to the intervention. Six studies reported statistical power of 80% or more to detect the true difference between the groups.[15,26-30]

We did not include the studies by Stern et al[21] and Padberg et al,[19] which did not comply with safety guidelines and exceeded the limit set by these guidelines for maximum duration of trains and number of pulses delivered; however, the forest plot in Appendix 4 includes these studies. A few studies[27,30-32] also exceeded the maximum duration of trains and delivered a slightly higher than recommended number of pulses. These studies were kept in the analysis. A few studies used an intensity of 80% MT. However, the safety guidelines did not address train duration at intensities below 90% MT.

Characteristics of Patients

In 11 studies, the mean depressive symptoms at baseline were above 25, indicating severe depression.[21-23,25,27,32-37] The mean depression scores for the remaining studies ranged from 19 to 24, indicating depression with moderate severity.

The mean age of patients in these studies ranged from 39 to 64 years. While in most studies (n = 16), patients had failed to benefit from two or more antidepressant medications, seven studies also included patients who had failed to improve with at least one antidepressant medication.[21,24,27,29,30,33,35] In 16 studies, patients received rTMS while receiving antidepressants, and in seven studies patients did not receive any antidepressant during rTMS treatment.[21,26,27,30,33,35,38]

Twelve of the studies did not include bipolar patients[21,22,26,27,30,31,34,36-40], while 10 studies did[15,23-25,28,29,32,33,35,41]; the proportion of bipolar patients in these studies ranged from 1.7% to 16.7%. One study[19] did not report whether bipolar patients were included. Twelve studies[21,22,26,27,29-32,34,37,38,41] clearly reported that no patients had psychosis. Three studies included patients with psychosis (all ≤7%),[15,28,33] and eight studies[19,23-25,35,36,39,40] did not report whether patients with psychosis were included.

Characteristics of the Intervention

The frequency of stimulation in these studies ranged from 5 to 20 Hz, and the intensity of stimulation was between 80% and 120% of the patients' motor threshold. Seven studies used intensities of less than 100% motor threshold only; the remaining studies used intensities of 100% to 120% motor threshold. The number of trains per session ranged from 15 to 75, and train duration ranged from 2 to 10 seconds. Number of pulses per session ranged from 800 to 3,000, and the total number of pulses during rTMS treatment ranged from 8,000 to 90,000. The inter-train interval varied across the studies, ranging from 22 to 58 seconds. Three studies did not report the train duration.[32,39,40] All studies reported that the active rTMS coil shape was a figure 8.

One study[32] investigated the effectiveness of two types of frequency (5 and 20 Hz), but did not report the combined data. We included only the higher frequency for continuous outcomes. Similarly, another study[31] investigated two types of intensity (80% and 110% motor threshold) and did not report the combined data. We therefore included the higher intensity for continuous outcomes. This approach was taken to avoid duplication of data in the analysis.

Reported Outcomes

A total of 16 studies reported depression scores at the baseline and at the end of treatment. Thirteen studies reported on remission rate, but the definition of remission varied among the studies (scores ranging from ≤7 to ≤10). Twenty studies reported on response rate, and all defined response as 50% or more reduction in depression scores. Three studies reported 3 or 4 months of follow-up, and only one study reported relapse rate. No study reported on a longer follow-up period. Table 2 shows study and patient characteristics, and Table 3 shows rTMS technical parameters used in studies that compared rTMS with sham rTMS.

Table 2: Study and Patient Characteristics: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Author	Year	Country	Age Mean (SD)		Failed Trials of AD (N)	AD Status During Trial	Depression Scale	Definition of Remission	Definition of Response	Study Power %	Follow-up Duration
			rTMS	Sham							
Chen et al[39]	2013	Taiwan	44.1 (4.4)	47.3 (3.5)	≥ 2	Add-on	HRSD-17	N/A	≥ 50% reduction	N/A	1 mo
Blumberger et al[22]	2012	Canada	48.9 (13.4)	45.8 (13.4)	≥ 2	Add-on	HRSD-17	≤ 10	≥ 50% reduction	N/A	N/A
Fitzgerald et al[40]	2012	Australia	43.4 (12.7)	44.9 (15.7)	≥ 2	Add-on	HRSD-17 MADRS	N/A	≥ 50% reduction	N/A	N/A
Bakim et al[31]	2012	Turkey	43.09 (8.18)	44.4 (10.2)	≥ 2	Add-on	HRSD-17 MADRS	≤ 7	≥ 50% reduction	N/A	N/A
George et al[27]	2010	USA	47.7 (10.6)	46.5 (12.3)	1–4 or intolerant to ≥ 3	No AD	HRSD-24 MADRS	2 consecutive scores < 10, one ≤ 3	≥ 50% reduction	80	N/A
Triggs et al[37]	2010	USA	46.7 (15.3)	Left 41.9 (14.1), right 46.6 (10.2)	≥ 2 or intolerant to ≥ 3	Add-on	HRSD-24	N/A	≥ 50% reduction	N/A	3 mo
Mogg et al[15]	2008	UK	55.0 (18.0)	52.0 (15.5)	≥ 2	Add-on	HRSD-17	≤ 8	≥ 50% reduction	90	4 mo
Bretlau et al[35]	2008	Denmark	53.1 (10.1)	57.8 (10)	≥ 1	No AD	HRSD-17	N/A	N/A	N/A	3 mo
O'Reardon et al[30]	2007	USA	47.9 (11.0)	48.7 (10.6)	≥ 1	No AD	HRSD-17/24 MADRS	< 8	≥ 50% reduction	90	N/A
Loo et al[29]	2007	Australia	49.8 (2.5)	45.7 (15)	1–2	Add-on	MADRS	≤ 10	≥ 50% reduction	80	N/A
Stern et al[21]	2007	USA	53.2 (12.0)	53.3 (9)	≥ 1	No AD	HRSD-21	≤ 10	≥ 50% reduction	N/A	2 wk
Avery et al[26]	2006	USA	44.3 (10.3)	44.2 (9.7)	≥ 2	No AD	HRSD-17	< 8	≥ 50% reduction	90	6 mo

Author	Year	Country	Age Mean (SD)		Failed Trials of AD (N)	AD Status During Trial	Depression Scale	Definition of Remission	Definition of Response	Study Power %	Follow-up Duration
			rTMS	Sham							
Su et al[32]	2005	Taiwan	5 Hz: 43.2 (10.6), 20 Hz: 43.6 (12)	42.6 (11.0)	≥ 2	Add-on	HRSD-21	< 8	≥ 50% reduction	N/A	N/A
Holtzheimer et al[38]	2004	USA, UK, Switzerland	40.4 (8.5)	45.4 (4.9)	≥ 2	No AD	HRSD-17	N/A	≥ 50% reduction	N/A	N/A
Mosimann et al[25]	2004	Germany	60 (13.4)	64.4 (13.0)	≥ 2	Add-on	HRSD-21	N/A	≥ 50% reduction	N/A	N/A
Fitzgerald et al[23]	2003	Australia	42.2 (9.8)	49.15 (14.24)	≥ 2	Add-on	MADRS	N/A	≥ 50% reduction	N/A	N/A
Hoppner et al[24]	2003	Germany	60.36 (2.12)	52 (3.69)	≥ 1	Add-on	HRSD-21	N/A	≥ 50% reduction	N/A	N/A
Boutros et al[34]	2002	USA	49.5 (8.0)	52.0 (7.0)	≥ 2	Add-on	HRSD-25	≤ 10[a]	≥ 50% reduction[a]	N/A	N/A
Padberg et al[19]	2002	Germany	100% MT: 62.1 (4.6) 90% MT: 60.3 (4.1)	52.7 (5.7)	≥ 2	Add-on	HRSD-21	< 9	≥ 50% reduction	N/A	N/A
Garcia-Toro et al[36]	2001	Spain	51.5 (15.9)	50.0 (11.0)	≥ 2	Add-on	HRSD-21	N/A	≥ 50% reduction	N/A	N/A
Berman et al[33]	2000	USA	45.2 (3.0)	39.4 (3.4)	≥ 1	No AD	HRSD-25	≤ 10[a]	≥ 50% reduction	N/A	N/A
Loo et al[28]	1999	Australia	45.7 (14.7)	50.9 (14.7)	≥ 2	Add-on	HRSD	N/A	N/A	95	N/A
Avery et al[41]	1999	USA	44.25 (5.1)	45 (5.0)	≥ 2	Add-on	HRSD-21	N/A	N/A	N/A	N/A

Abbreviations: AD, antidepressant; ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; MT, motor threshold; N/A, not available; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation.

[a]Not pre-specified by the authors, but outcomes were calculated on the basis of these thresholds.

Table 3: Technical Parameters Used in Studies Comparing Repetitive Transcranial Magnetic Stimulation With Sham Treatment

Author	Year	% MT	Frequency (Hz)	Trains (N)	Train Duration (s)	Inter-train Interval (s)	Pulses per Session (N)	Sessions (N)	Total Pulses (N)
Chen et al[39]	2013	90	20	20	2	N/A	800	10	8,000
Blumberger et al[22]	2012	100/120	10	29	5	30	1,450	15	21,750
Fitzgerald et al[40]	2012	120	10	30	5	N/A	1,500	15	22,500
Bakim et al[31]	2012	80/110	20	20	2	28	800	30	24,000
George et al[27]	2010	120	10	75	4	26	3,000	15	45,000
Triggs et al[37]	2010	100	5	50	8	22	2,000	10	20,000
Mogg et al[15]	2008	110	10	20	5	55	1,000	10	10,000
Bretlau et al[35]	2008	90	8	20	8	52	1,280	15	19,200
O'Reardon et al[30]	2007	120	10	75	4	26	3,000	30	90,000
Loo et al[29]	2007	110	10	30	5	25	1,500	20	30,000
Stern et al[21]	2007	110	10	20	8[a]	52	1,600	10	16,000
Avery et al[26]	2006	110	10	32	5	25–30	1,600	15	24,000
Su et al[32]	2005	100	5/20	40	8/2	N/A	1,600	10	16,000
Holtzheimer et al[38]	2004	110	10	32	5	30–60	1,600	10	16,000
Mosimann et al[25]	2004	100	20	40	2	28	1,600	10	16,000
Fitzgerald et al[23]	2003	100	10	20	5	25	1,000	10	10,000
Hoppner et al[24]	2003	90	20	20	2	30	800	10	8,000
Boutros et al[34]	2002	80	20	20	2	58	800	10	8,000
Garcia-Toro et al[36]	2001	90	20	30	2	20–40	1,200	10	12,000
Berman et al[33]	2000	80	20	20	2	58	800	10	8,000
Padberg et al[19]	2000	90/100	10	15	10[a]	30	1,500	10	15,000
Loo et al[28]	1999	110	10	30	5	30	1,500	10	15,000
Avery et al[41]	1999	80	10	20	5	> 55	1,000	10	10,000

Abbreviations: MT, motor threshold; N/A, not available.
[a]Outside the margin of safety set by safety guidelines.

Analysis of Primary Outcomes

We calculated changes in depression scores measured by Hamilton Rating Scale for Depression from baseline to the end of treatment and conducted a meta-analysis on the mean changes in scores of the two groups of rTMS-treated and sham-treated patients. The weighted mean difference was 2.31 points (95% CI 1.19–3.43, $P < .001$ favouring rTMS) (Figure 2). There was a low degree of heterogeneity among the studies ($I^2 = 19.8\%$, $P = .233$). The mean difference was below the mean value deemed a priori to be clinically important (i.e., the value of at least 3.5 points on the Hamilton Rating Scale for Depression). On average, rTMS reduced depression scores by about two points more than sham rTMS.

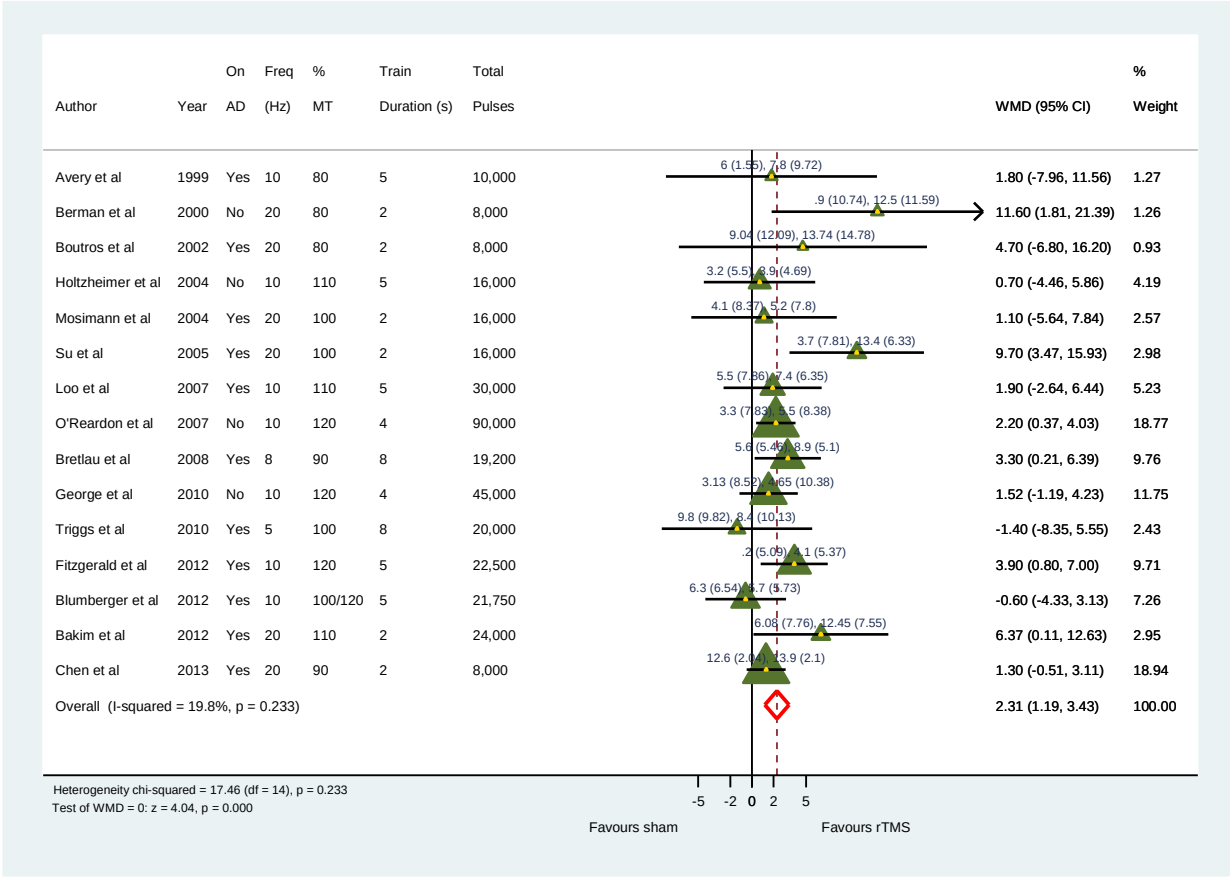


Figure 2: Weighted Mean Difference: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

We also computed the SMD using Cohen's method. The effect size was 0.33 (95% CI 0.17–0.5, $P < .001$), which would be considered small. There was a low degree of heterogeneity among the studies ($I^2 = 14.7\%$, $P = .289$) (Figure 3).

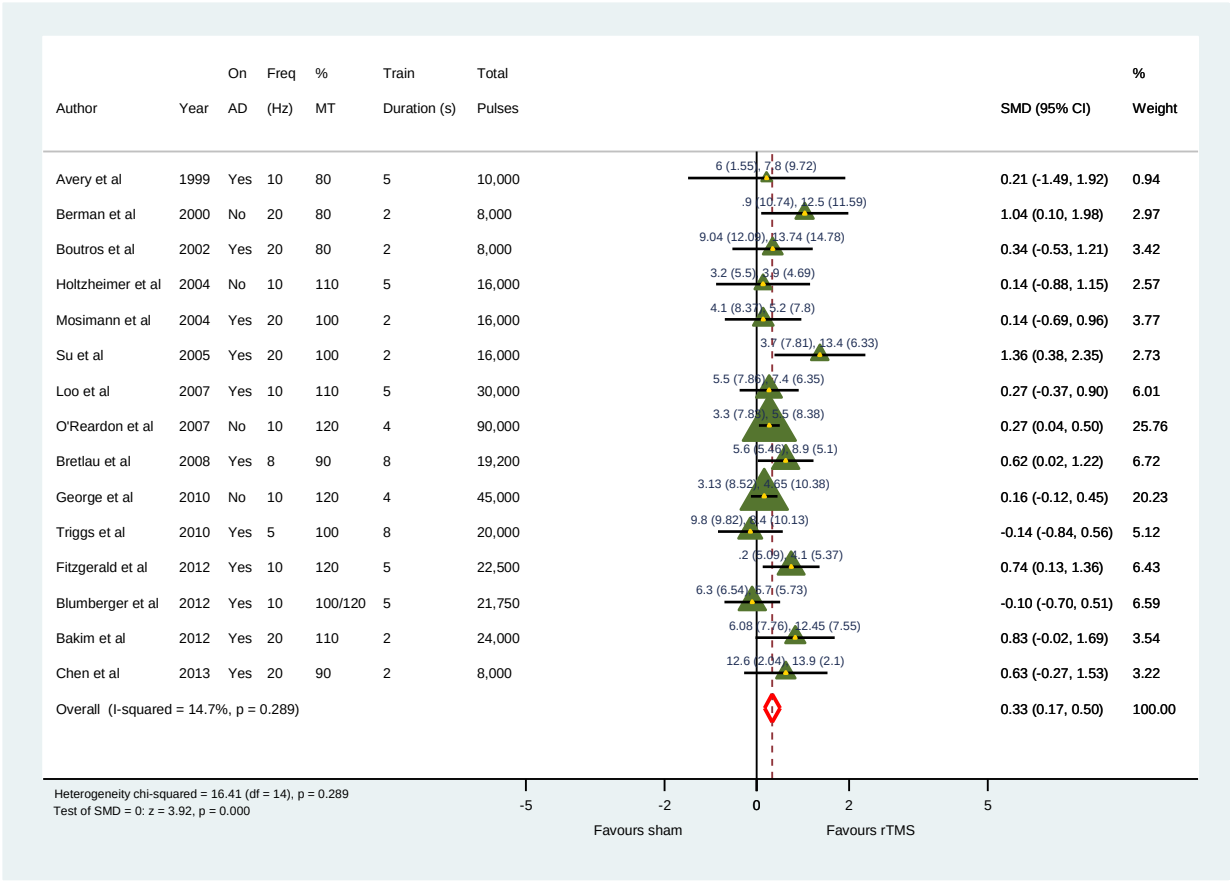


Figure 3: Standardized Mean Difference: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; rTMS, repetitive transcranial magnetic stimulation; SMD, standardized mean difference.

Subgroup Analysis

We performed three subgroup analyses for categories of frequency, total pulses, and total sessions to see whether these study or technical parameters influenced the outcome. The subgroup of studies that used a frequency of 20 Hz but with shorter train duration showed larger treatment effect than the other two subgroups (weighted mean difference 4.96, 95% CI 1.15–8.76, *P* = .011) (Figure 4).

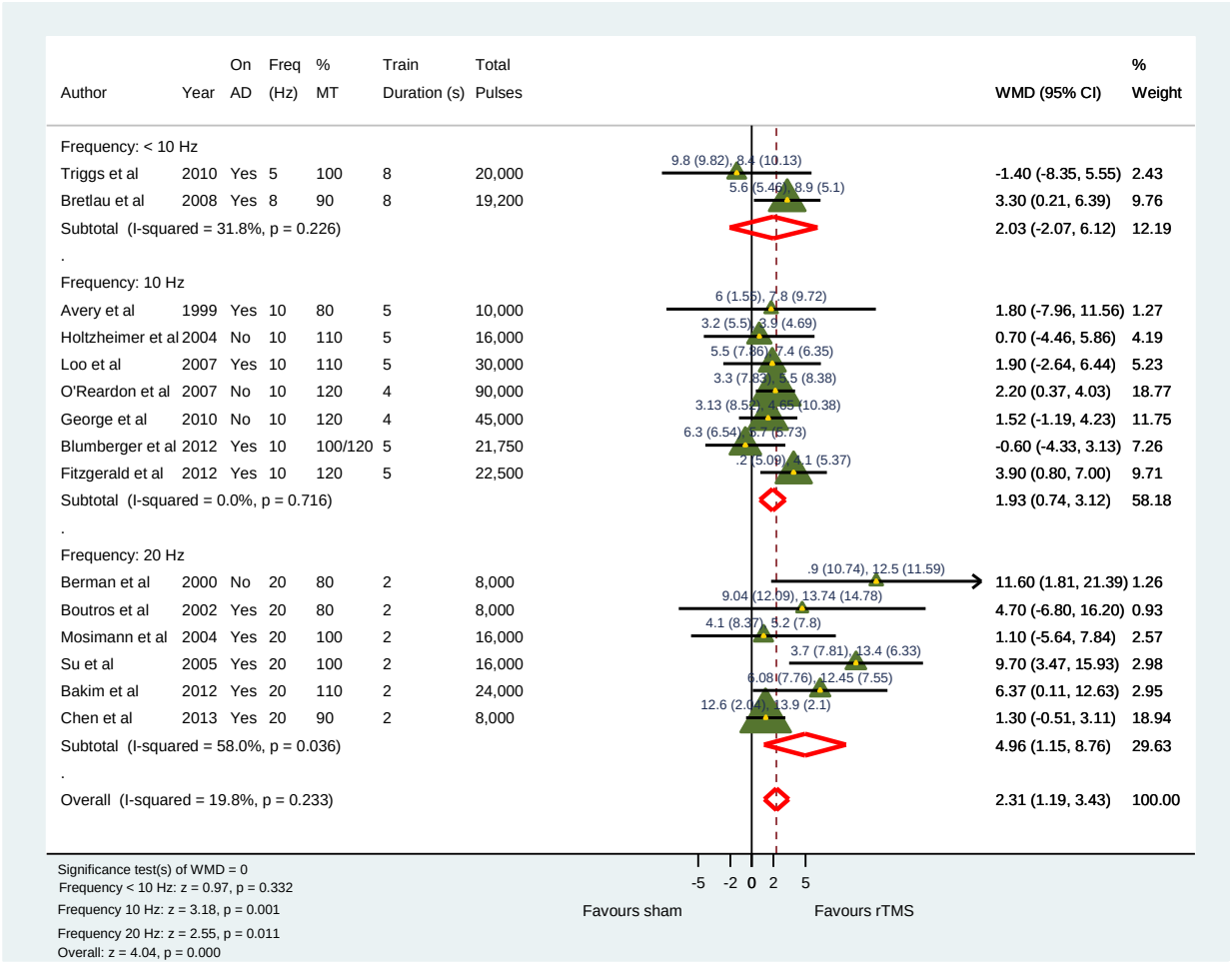


Figure 4: Weighted Mean Difference Stratified by Frequency of Stimulation: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

The subgroup analysis for total pulses applied during the entire course of rTMS treatment showed more heterogeneity among studies that used less than 10,000 or 10,000 to 16,000 pulses. However, the results for studies that used total pulses above 16,000 were more homogenous (I^2 = 0.0%, *P* = .450) (Figure 5).

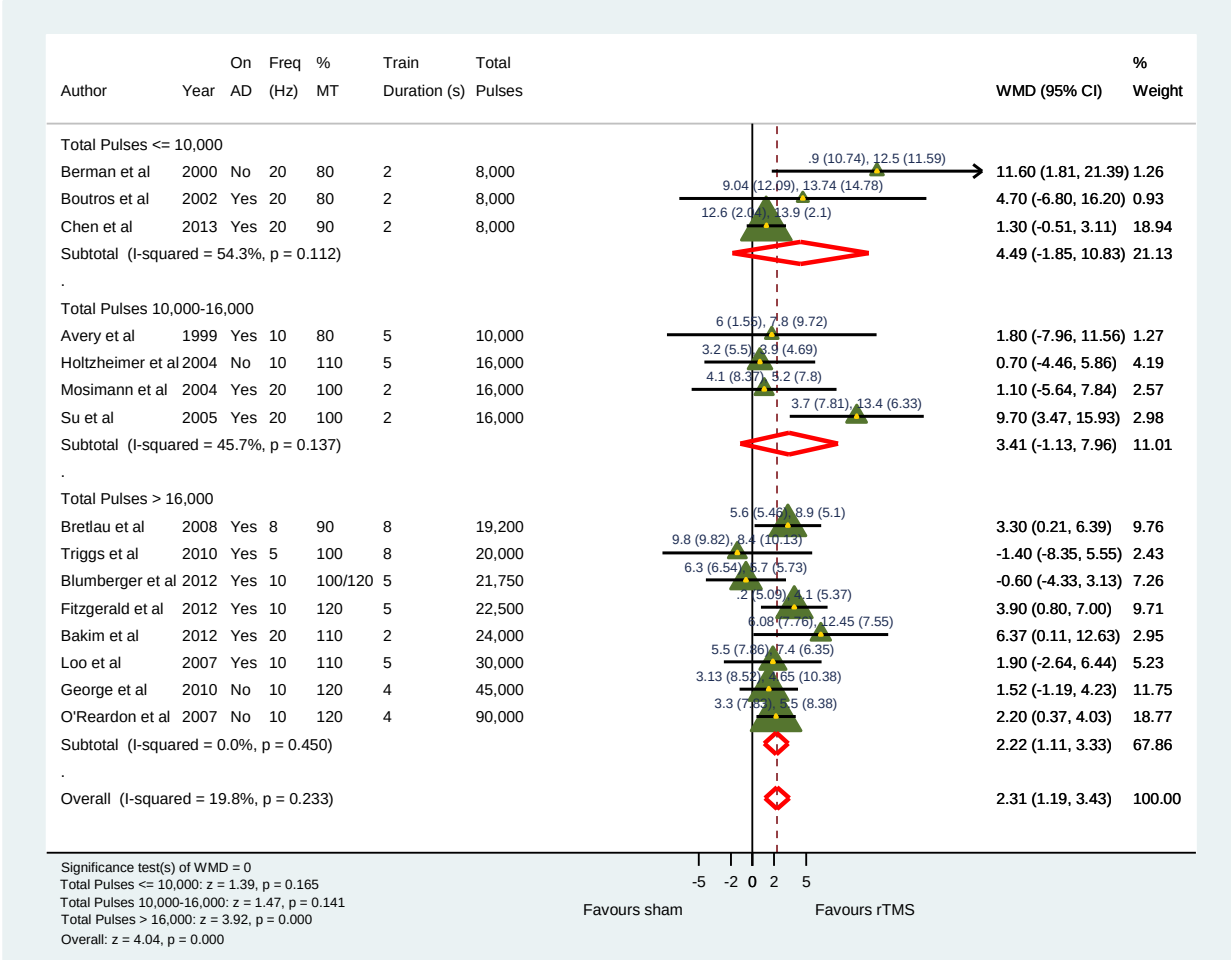


Figure 5: Weighted Mean Difference Stratified by Total Pulses: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

Most studies that used more than 16,000 pulses also seemed to be more precise in their estimates than studies in the other two categories. This observation led us to perform a sensitivity analysis to investigate the effect in studies with high precision only.

We also performed subgroup analysis for the number of rTMS sessions. The effect estimate was relatively higher for studies that had 30 sessions than for the other two groups. However, this effect was influenced by only one of the two studies in this category (Figure 6).

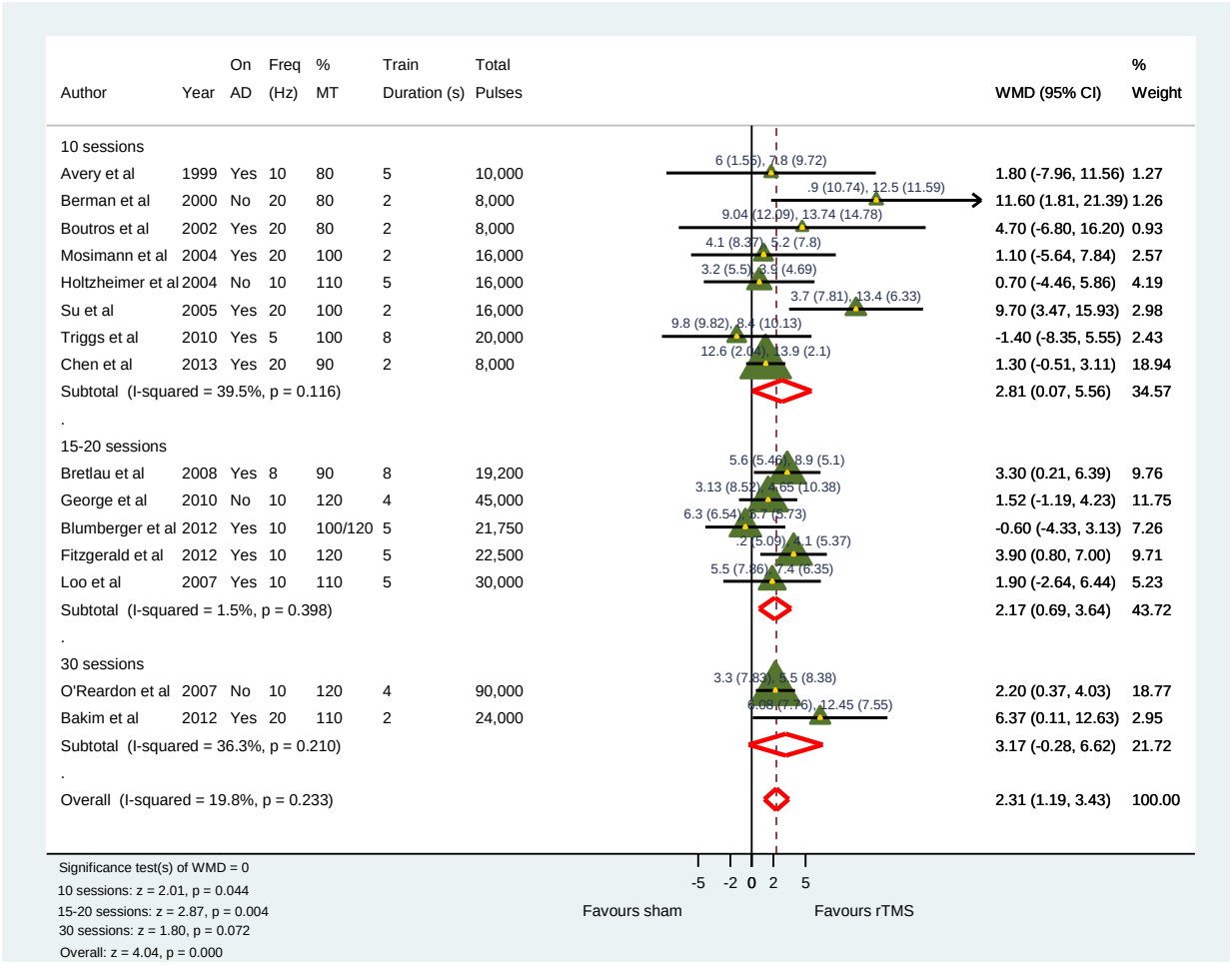


Figure 6: Weighted Mean Difference Stratified by Number of Sessions: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; Freq, frequency; On AD, using antidepressant during rTMS or sham treatment; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

Sensitivity Analysis

We performed a sensitivity analysis to explore the robustness of our results. For this purpose, we included only studies that produced estimates with higher precision. The summary estimates for these studies were slightly smaller than the overall summary estimate (weighted mean difference 1.93, 95% CI 0.96–2.90, $P < .001$) and there was no heterogeneity among these studies ($I^2 = 0.0\%$, $P = .582$) (Figure 7).

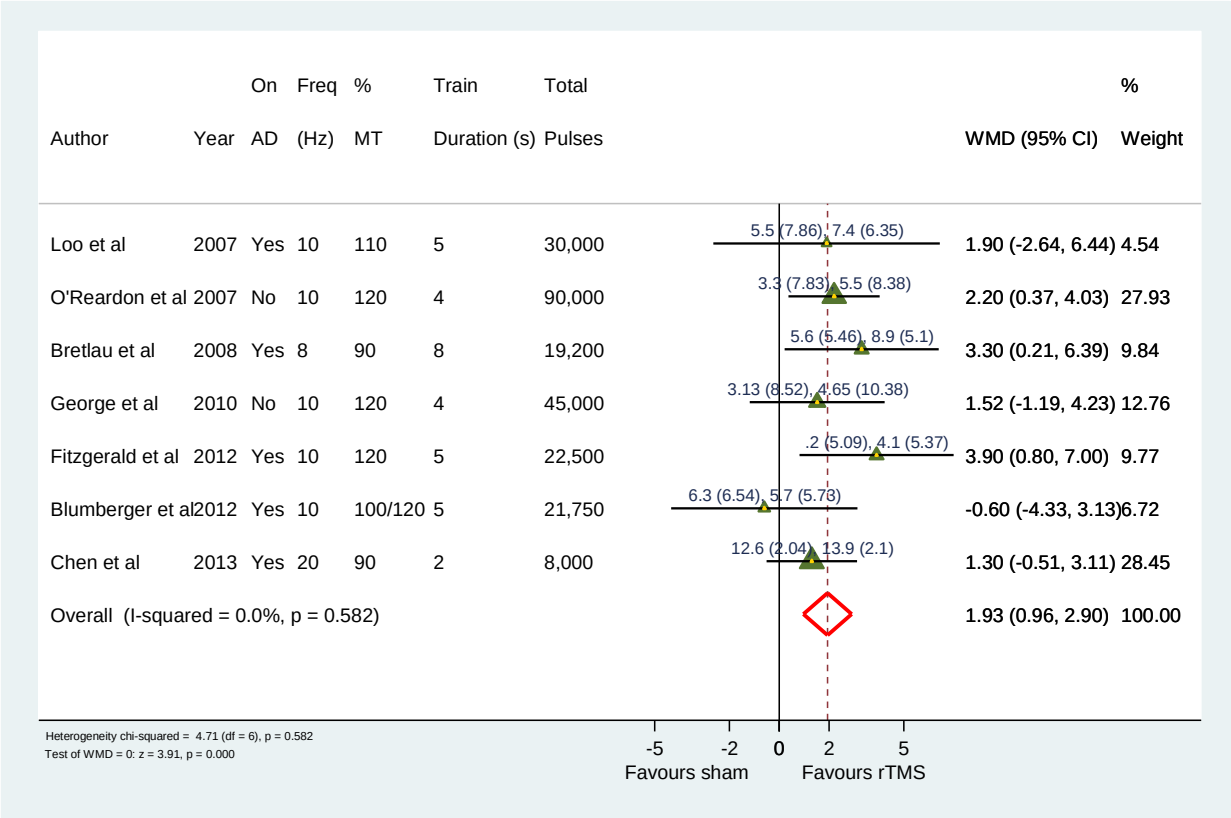


Figure 7: Weighted Mean Difference at End of Treatment: Studies With High Precision

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

Publication Bias Analysis

We investigated the possibility of publication bias in two ways. We constructed a funnel plot on the basis of depression scores to visually inspect the graph and tested for publication bias with Begg's and Egger's tests. For the funnel plot, we plotted the mean difference in scores on the horizontal axis and its standard error on the vertical axis. Because larger studies have smaller standard errors, we reversed the Y axis on the graph to place 0 at the top. As shown in Figure 8, smaller studies with larger standard error scatter widely at the bottom of the graph while the spread narrows among larger studies at the top of the plot. The solid vertical line represents the summary effect estimate.

Overall, the funnel seems to be symmetrical, giving us no reason to suspect the presence of a publication bias. Note that we have constructed the plot considering two periods in which studies were published (1999–2006 and 2007–2015) so that visual inspection of the graph will indicate whether the treatment effect estimates reported by earlier studies are different from those reported in more recent studies (Figure 8).

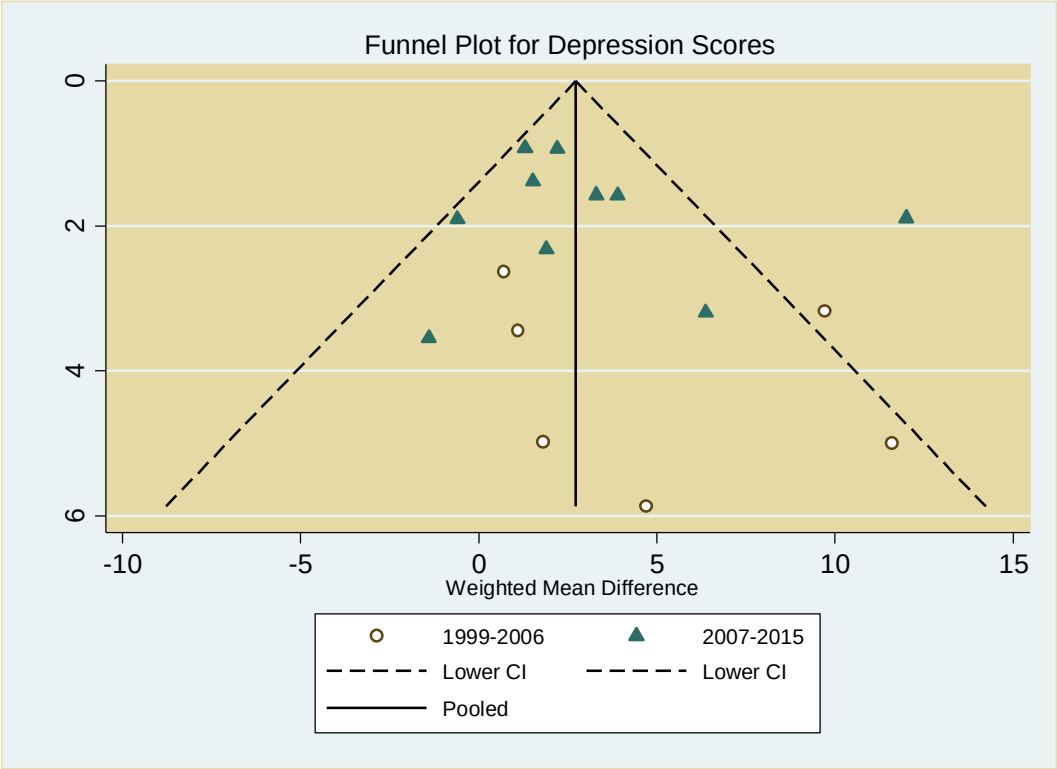


Figure 8: Funnel Plot for Depression Scores: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; se, standard error; WMD, weighted mean difference.

We also performed tests for the presence of publication bias for depression scores using Begg's and Egger's tests. No evidence of publication bias was observed for depression scores (Begg's test: Kendall's score = 26.0, SD of score = 22.21, *P* = .26; Egger's test: bias coefficient = 0.977, SD of bias coefficient = 0.849, *P* = .269).

Meta-Regression Analysis

We performed a meta-regression analysis including all studies to investigate whether rTMS technical parameters or duration of treatment influences the treatment effect. We speculated that the following study-level covariates could be associated with the treatment effect: frequency of stimulation, intensity of stimulation as percentage of motor threshold, train duration (seconds), and total number of sessions. We used the restricted maximum likelihood as the method of estimation of between-study variance. The joint test for all four covariates gave a *P* value of .010, indicating evidence for association of some of these covariates with the size of treatment effect. From all covariates in the model, frequency of stimulation, intensity of stimulation, and train duration were significantly associated with the treatment effect (*P* = .002, .008, and .001, respectively). This finding would not be considered definitive, but suggests a direction for additional research.

Analysis of Secondary Outcomes

Remission and Response Rates

Most studies (n = 20) reported on response rate, but only 13 studies reported on remission rate.

The pooled risk ratio for remission rate among studies that complied with the safety standards was 2.20 (95% CI 1.44–3.38, *P* < .001). No heterogeneity was observed among the studies reported on remission rate (I^2 = 0.0%, *P* = .809) (Figure 9).

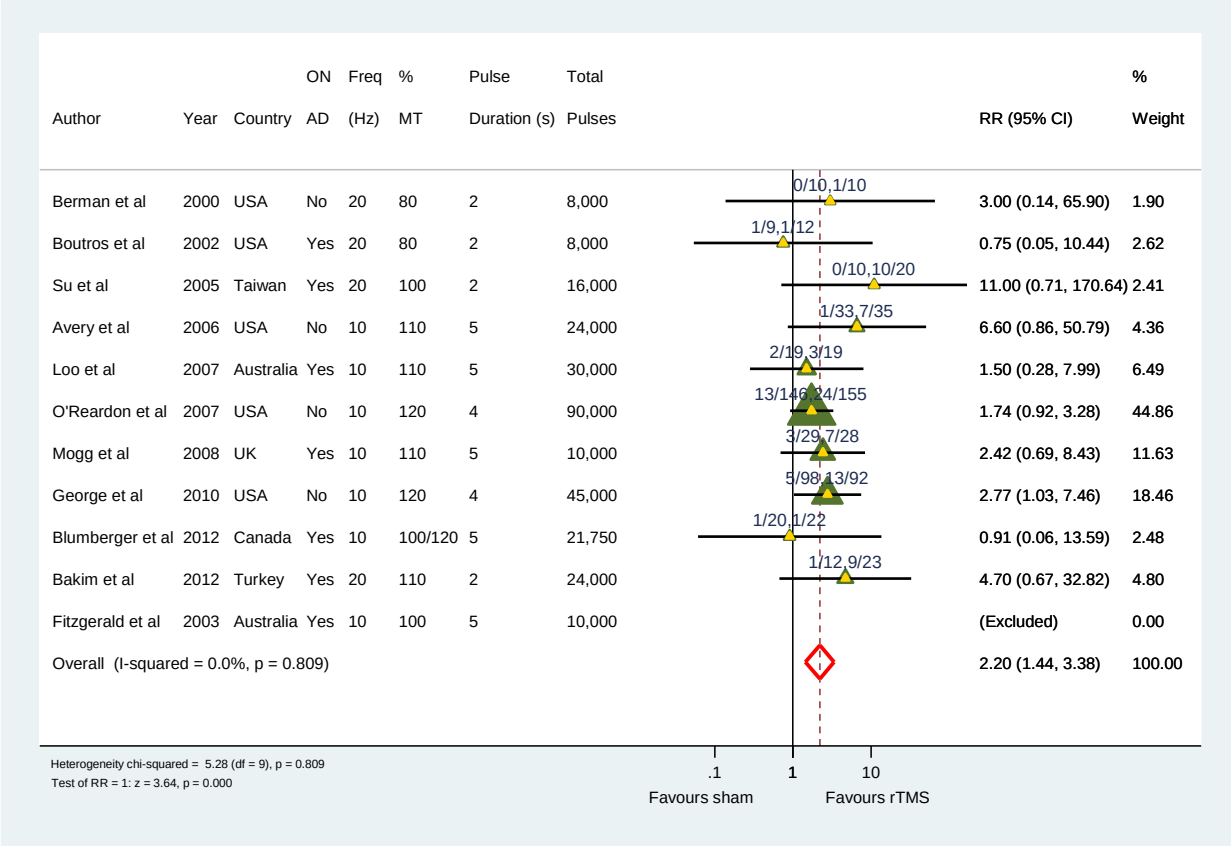


Figure 9: Remission Rate at End of Treatment: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; RR, risk ratio; rTMS, repetitive transcranial magnetic stimulation.

The pooled risk ratio for response rate was 1.72 (95% CI 1.13–2.62, *P* = .011). There was a moderate degree of heterogeneity among the studies reported on response rate (I^2 = 46.4%, *P* = .022) (Figure 10).

Note that the two studies[23,38] in which no patient in either arm responded to the treatment did not contribute to the remission or response summary estimates (marked as excluded in the forest plots).

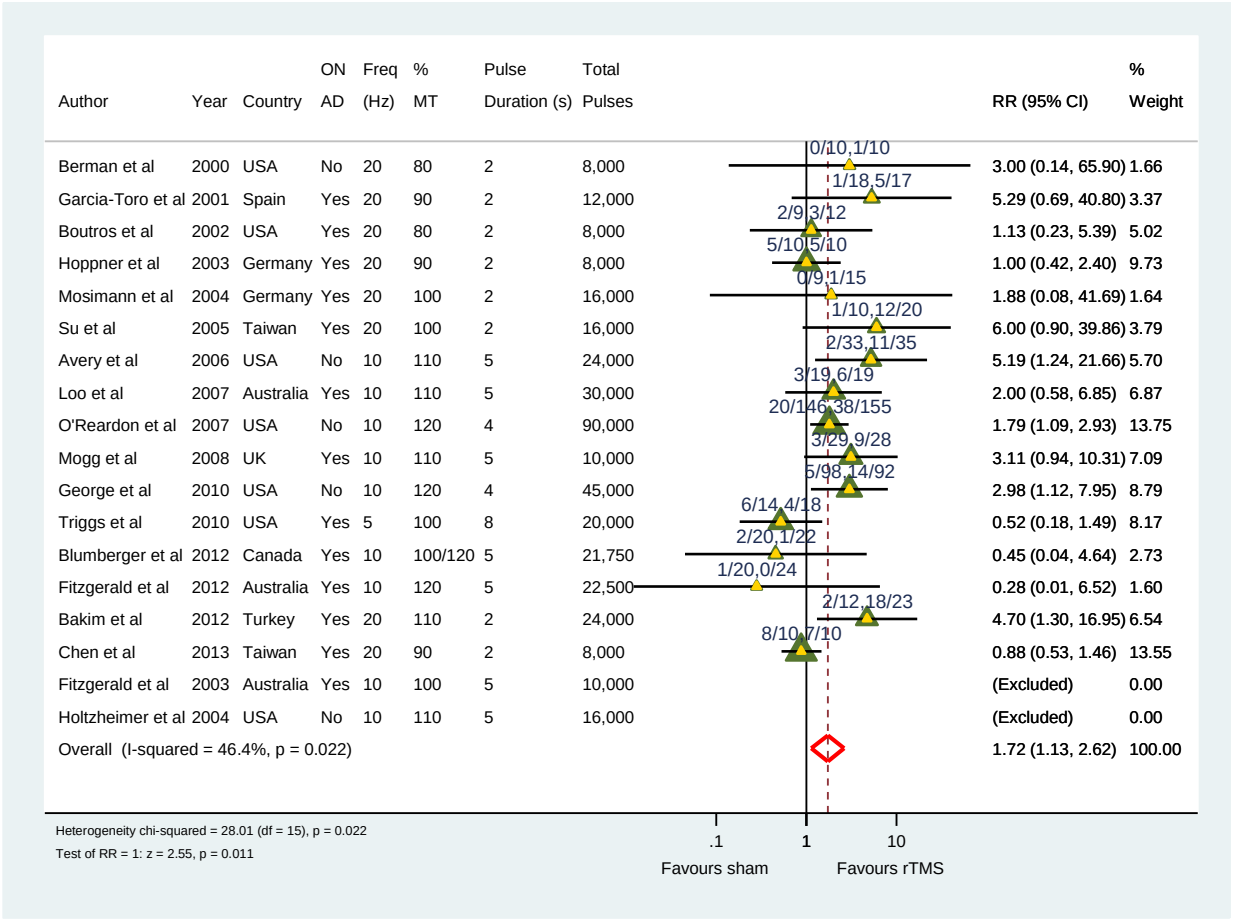


Figure 10: Response Rate at End of Treatment: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; RR, risk ratio; rTMS, repetitive transcranial magnetic stimulation.

Forest plots for remission and response rates that include the two studies that used parameters outside of the limits set by the safety guidelines are shown in Appendix 4.

Benefit Difference

The benefit difference (alternative terminology to risk difference for remission outcome) comparing rTMS with sham rTMS was 0.10 (95% CI 0.03–0.17, *P* = .003), indicating a 10% benefit increase in remission rate favouring rTMS over sham rTMS. There was a moderate degree of heterogeneity among the studies (I^2 = 56.1%, *P* = .012) (Figure 11).

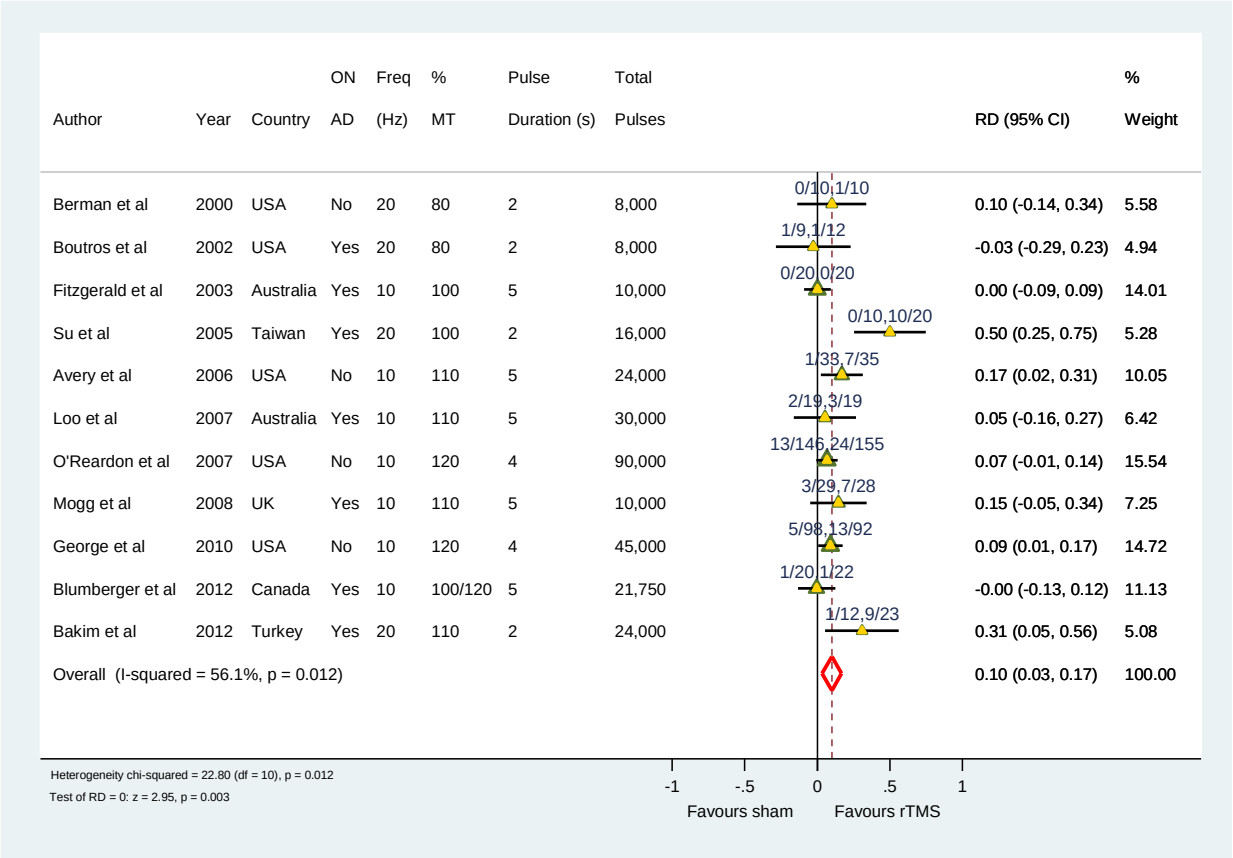


Figure 11: Risk Difference for Remission Rate: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; RD, risk difference; rTMS, repetitive transcranial magnetic stimulation.

The benefit difference (alternative terminology to risk difference for response to treatment outcome) for response rate was 0.11 (95% CI 0.03–0.18, *P* = .005), indicating 11% increase in response rate comparing rTMS with sham rTMS. There was a high degree of heterogeneity among the studies (I^2 = 65.6%, *P* < .001) (Figure 12).

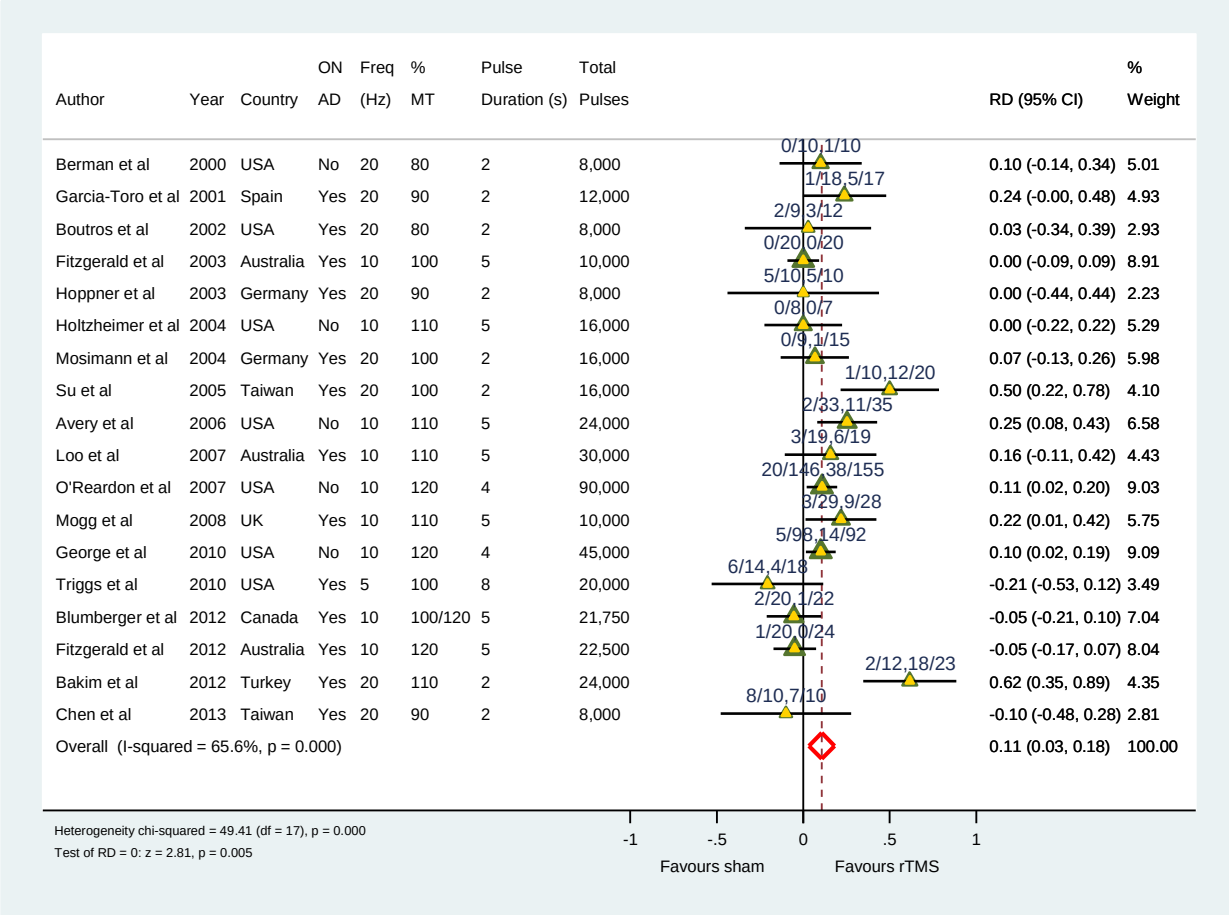


Figure 12: Risk Difference for Response Rate: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; RD, risk difference; rTMS, repetitive transcranial magnetic stimulation.

Number Needed to Treat

There was a 10% difference in the rates of remission or response. This translates to a number needed to treat of 10. If 10 patients are treated with rTMS, one will have a chance to have a response or remission. For comparison, a meta-analysis of 32 randomized trials in which the effects of treatment with combined psychotherapy and pharmacotherapy was compared with the effects of pharmacotherapy only in adults with depression obtained a number needed to treat of 4.2.[42]

Publication Bias Analysis

To investigate the possibility of publication bias for the remission and response rates, we constructed funnel plots. No evidence of publication bias was seen for these outcomes (Figures 14 and 15).

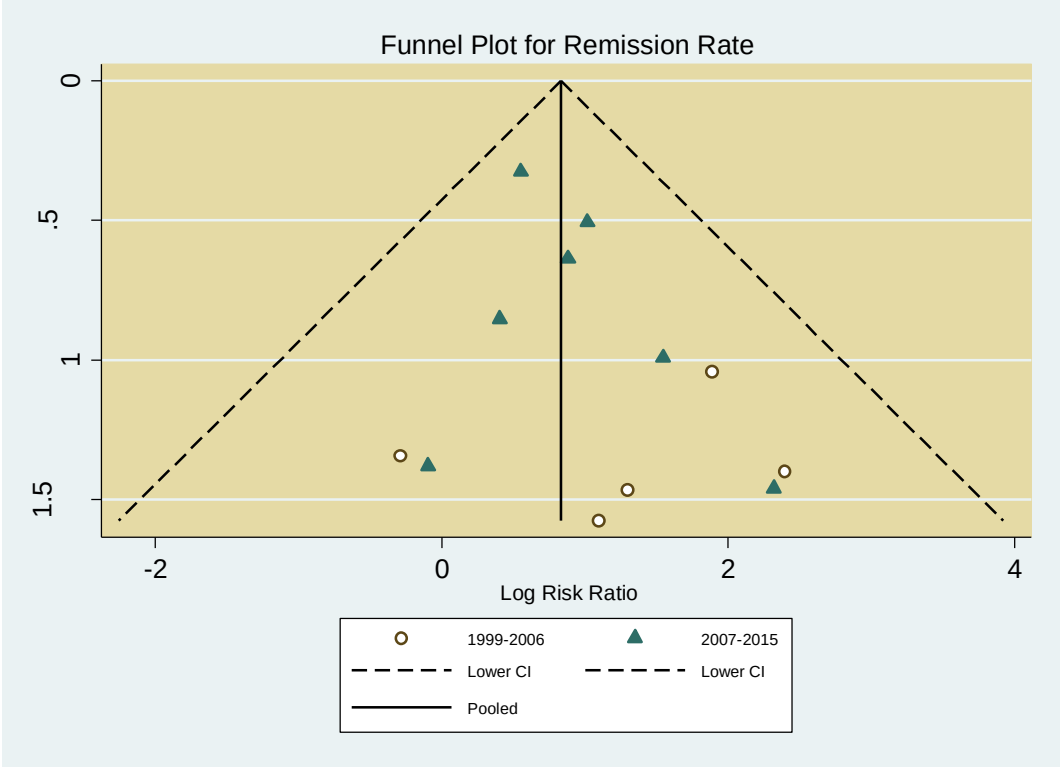


Figure 13: Funnel Plot for Remission Rate: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; se, standard error.

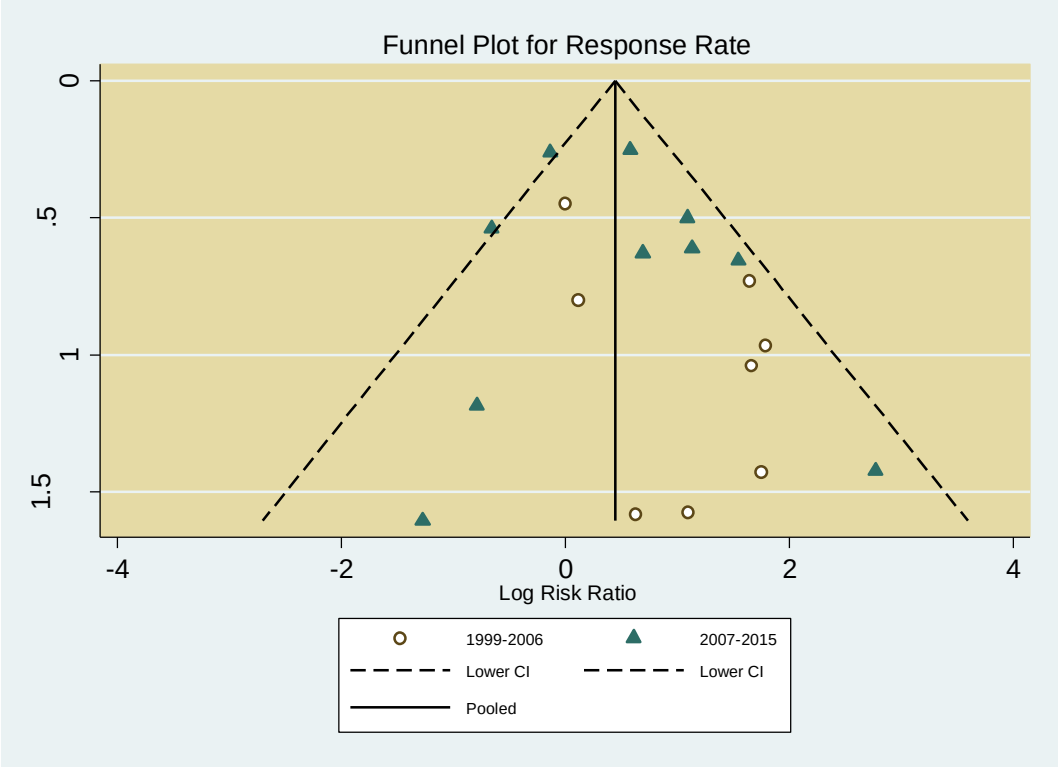


Figure 14: Funnel Plot for Response Rate: Repetitive Transcranial Magnetic Stimulation Versus Sham Treatment

Abbreviations: CI, confidence interval; se, standard error.

We also performed tests for the presence of publication bias for remission and response rates using Begg's and Egger's tests. No evidence of publication bias was observed for these outcomes (for remission, Begg's test: Kendall's score = 14.0, SD of score = 14.58, *P* = .37; Egger's test: bias coefficient 0.601, SD of bias coefficient 0.399, *P* = .16; for response, Begg's test: Kendall's score = 1.0, SD of score = 26.40, *P* = 1.0; Egger's test: bias coefficient 0.856, SD of bias coefficient 0.541, *P* = .13).

Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy

Characteristics of Studies

We found six studies (seven citations) that compared rTMS with ECT.[20,43-48] However, most of these studies were conducted in early 2000. A total of 266 patients (133 in each arm) were analyzed in these studies. Two of the studies[43,48] reported 6 months of follow-up.

Four studies[20,43,45,47] reported that the assessors of the outcomes were blinded to treatment assignment. In two studies,[44,46] the assessors were not blinded to treatment assignment. One of the studies did not comply with the safety guidelines and used a train duration that was twice the limit and delivered a higher number of pulses per session. Forest plots that include this study are shown in Appendix 5.

Characteristics of Patients

The mean age of the patients ranged from 34 to 68 years. In two studies, patients failed to benefit from two or more antidepressant medications,[20,46] and in two studies, patients who failed

to benefit from one or more antidepressant medications were included.[45,47] In one study, cases refractory to treatment were included, but the number of failed medications was not reported.[43] One study[44] included patients who failed medication or who were diagnosed with psychotic depression. In two studies, patients were free of antidepressant medications during the trial,[20,45] and antidepressant medication was limited during rTMS treatment in one trial.[47] Two studies[20,45] included nonpsychotic patients, while two other studies[43,44] reported that 47.5% and 15% of patients had psychosis. Two studies[46,47] did not report whether patients with psychosis were included.

Table 4 shows study and patient characteristics.

Table 4: Study and Patient Characteristics: Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy

Author, Year	Country	N	Age Mean (SD)		Dominant Hand	Failed Trials of AD, N	AD Status During Trial	Definition		Follow-up
			rTMS	ECT				Remission	Response	
Grunhaus et al 2000[44]	Israel	40	58.4 (15.7)	63.6 (15)	rTMS: N/A ECT: all right-handed	TRD /Not TRD	Receiving AD	N/A	≥ 50% reduction and a final GAF ≥ 60	N/A
Pridmore et al 2000[47] and Dannon et al 2002[48]	Australia	32	44 (11.9)	41.5 (12.9)	rTMS: all right-handed ECT: N/A	≥ 1	Receiving AD	≤ 8	N/A	6 mo
Grunhaus et al 2003[45]	Israel	40	57.6 (13.7)	61.4 (16.6)	N/A	≥ 1	No AD	≤ 8	≥ 50% reduction or a final rating of ≤ 10 and a final GAF ≥ 60	N/A
Rosa et al 2006[20]	Brazil	42	41.8 (10.2)	46 (10.6)	N/A	≥ 2	No AD	≤ 7	≥ 50% reduction	N/A
Eranti et al 2007[43]	UK	46	63.6 (17.3)	68.3 (13.4)	All right-handed	TRD	Receiving AD	≤ 8	≥ 50% reduction	6 mo
Keshtkar et al 2011[46]	Iran	75	34 (9.9)	35.6 (8.1)	N/A	≥ 2	Receiving AD	N/A	N/A	N/A

Abbreviations: AD, antidepressant; ECT, electroconvulsive therapy; GAF, global assessment of function; N/A, not available; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; TRD, treatment-resistant depression.

Characteristics of the Intervention

Most studies used a frequency of 10 Hz; a frequency of 20 Hz was used in only one study.[47] The study by Keshtkar et al did not report on the frequency of stimulation, but when we contacted the author, he indicated that it was probably 10 Hz. Three studies used intensity of rTMS of less than 100% motor threshold[44-46] and three used intensity of 100% to 110% motor threshold.[20,43,47] Number of pulses per session ranged from 408 to 2,500, and the total number of pulses ranged from 4,080 to 50,000. Train duration ranged from 2 to 10 seconds, and inter-train interval ranged from 20 to 55 seconds. All studies reported that the rTMS coil shape was Figure 8.

Number of sessions in the rTMS-treated group ranged from 10 to 20 sessions, and the mean number of sessions in the ECT-treated group ranged from 6.2 to 10.25 sessions. Table 5 shows technical parameters used in studies that compared rTMS with ECT.

Two studies used unilateral ECT[20,47] and bilateral ECT was performed in one study.[46] Three studies used both unilateral and bilateral ECT.[43-45]

Table 5 shows rTMS and ECT technical parameters used in studies that compared rTMS with ECT.

Reported Outcomes

Four studies reported depression scores at the baseline and at the end of treatment. Four studies reported on remission rate and four on response rate. Remission was defined as a score of 7 or more or 8 or more. Two studies defined response as 50% or more decrease in depression scores[20,43] and two used a definition that was based on two scales (Table 4).[44,45]

Table 5: Technical Parameters Used in Studies Comparing Repetitive Transcranial Magnetic Stimulation With Electroconvulsive Therapy

	rTMS					ECT	
Author, Year	Frequency, Hz	% MT	Total Pulses	Train Duration, s	Sessions N	Bilateral, %	Mean Sessions N
Grunhaus et al 2000[44]	10	90	8,000–24,000	2–6	20	40	9.6
Pridmore et al 2000[47] and Dannon 2002[48]	20	100	14,640–17,080	2	12	0	6.2
Grunhaus et al 2003[45]	10	90	24,000	6	20	35	10.25
Rosa et al 2006[20]	10	100	50,000	10[a]	20	0	10.0
Eranti et al 2007[43]	10	110	15,000	5	15	82	6.3
Keshtkar et al 2011[46]	N/A	90	4,080	N/A	10	100	10.0

Abbreviations: ECT, electroconvulsive therapy; MT, motor threshold; N/A, not available; rTMS, repetitive transcranial magnetic stimulation.
[a]Outside the margin of safety set by safety guidelines.

Analysis of Primary Outcomes

We calculated changes in depression scores from baseline to the end of treatment for patients who received rTMS and for those who received ECT. We conducted a meta-analysis on the mean changes in scores for the two groups. The weighted mean difference was 5.97 points (95% CI 0.94–11.0, P = .020) in favour of ECT. Its value was above the mean value deemed a priori to be clinically important (i.e., the value of at least 3.5 points on the Hamilton Rating Scale for Depression). There was a high degree of heterogeneity among the studies (I^2 = 72.2%, P = .013) (Figure 15).

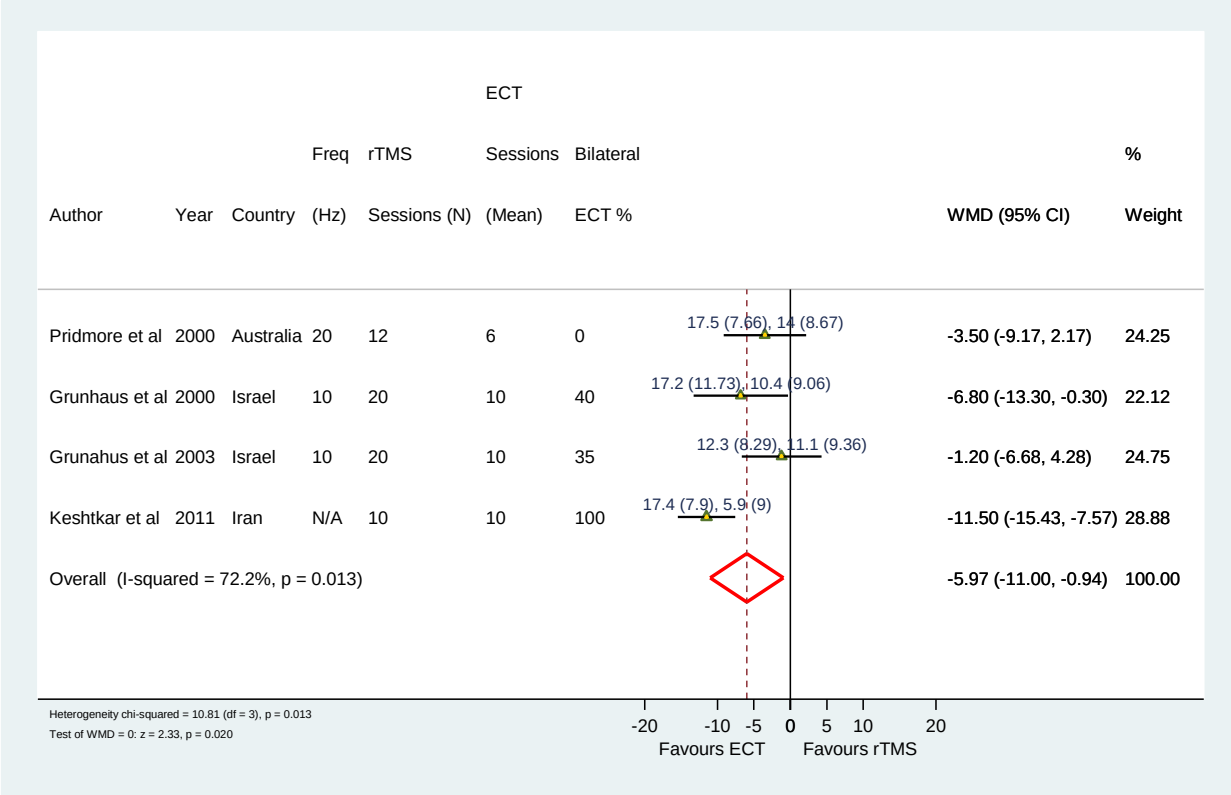


Figure 15: Weighted Mean Difference: Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy

Abbreviations: CI, confidence interval; df, degrees of freedom; ECT, electroconvulsive therapy; Freq, frequency; MT, motor threshold; N/A, not available; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

We also computed the SMD using Cohen's method. The effect size was 0.67 (95% CI 0.10–1.23, *P* = .021), in favour of ECT, which would be considered a large effect size. There was a high degree of heterogeneity among the studies (I^2 = 70.6%, *P* = .017) (Figure 16).

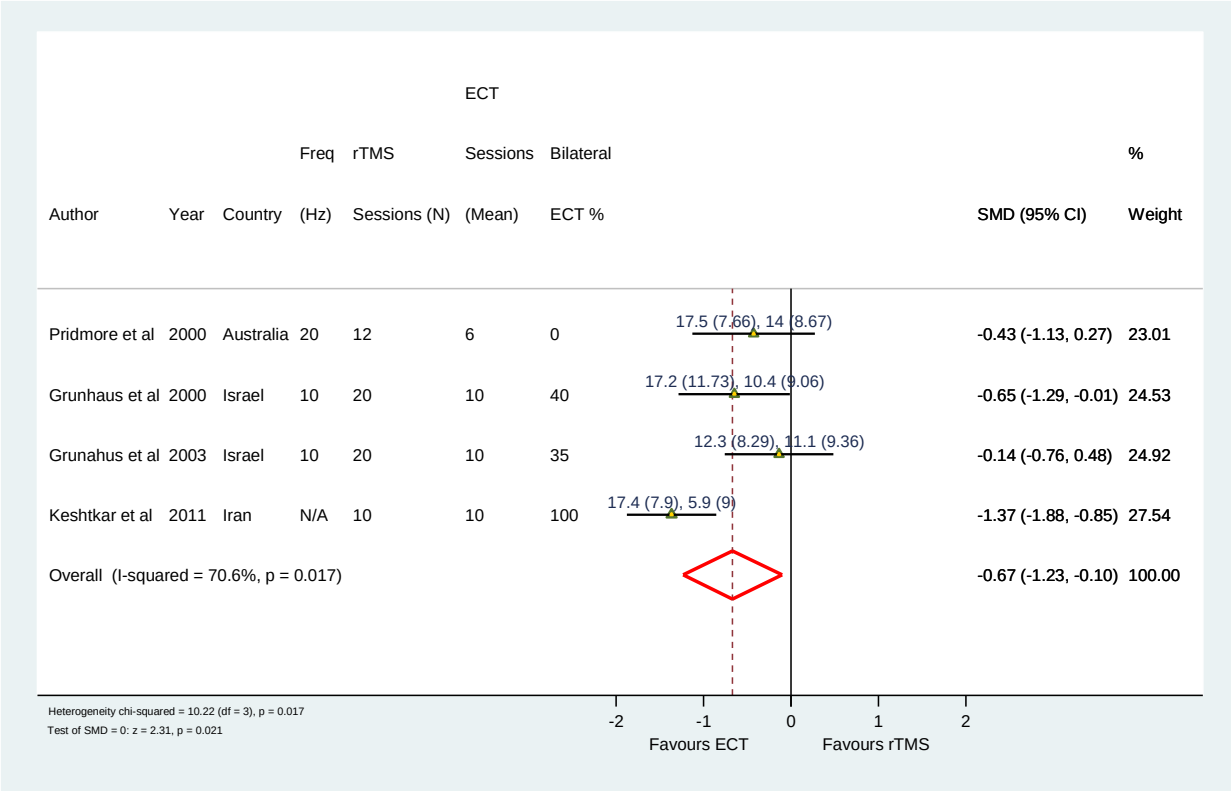


Figure 16: Standardized Mean Difference: Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy

Abbreviations: CI, confidence interval; df, degrees of freedom; ECT, electroconvulsive therapy; Freq, frequency; N/A, not available; rTMS, repetitive transcranial magnetic stimulation; SMD, standardized mean difference.

Subgroup Analysis

We performed a subgroup analysis for ECT electrode placement to see whether variation in this parameter influences the outcome. The subgroup of studies that used bilateral ECT in 40% or more of the patients showed larger treatment effect (weighted mean difference 9.89 [95% CI 5.52–14.26], *P* < .001) than studies that used only unilateral ECT or bilateral ECT in less than 40% of the patients (weighted mean difference 2.31 [95% CI 1.63–6.25], *P* = .25) (Figure 17).

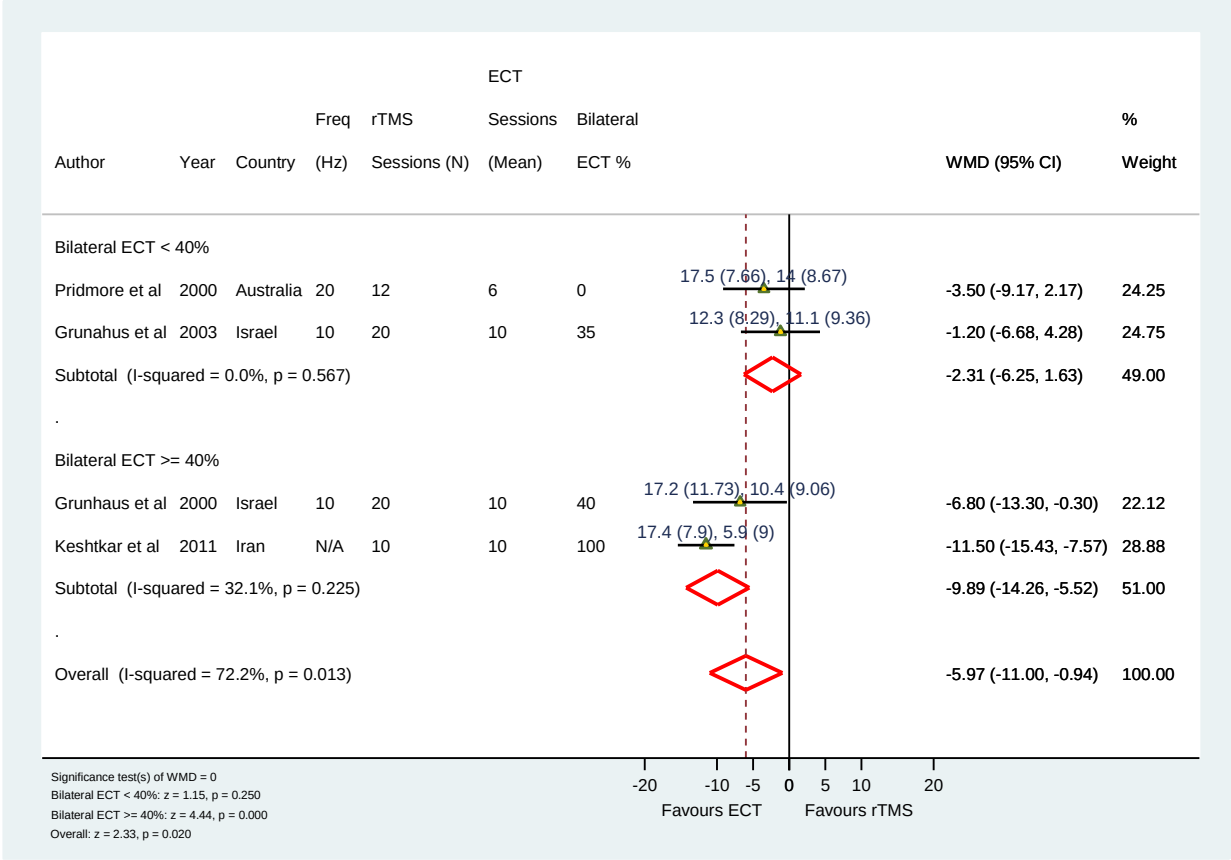


Figure 17: Weighted Mean Difference: Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy Stratified by Laterality of Electroconvulsive Therapy

Abbreviations: CI, confidence interval; Freq, frequency; ECT, electroconvulsive therapy; N/A, not available; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

Analysis of Secondary Outcomes

Remission and Response Rates

Three of the studies that complied with safety standards reported on remission rate and four reported on response rate. The pooled risk ratio for remission at the end of treatment was 1.44 (95% CI 0.64–3.23, *P* = .375), favouring ECT. The pooled risk ratio for response at the end of treatment was 1.72 (95% CI 0.95–3.11, *P* = .072), favouring ECT. There was a high degree of heterogeneity among the studies for both remission rate and response rates (remission: I^2 = 69.1%, *P* = .039; response: I^2 = 60.6%, *P* = .079), which could be explained in part by variation among studies with respect to the use of unilateral or bilateral ECT (Figures 18 and 19).

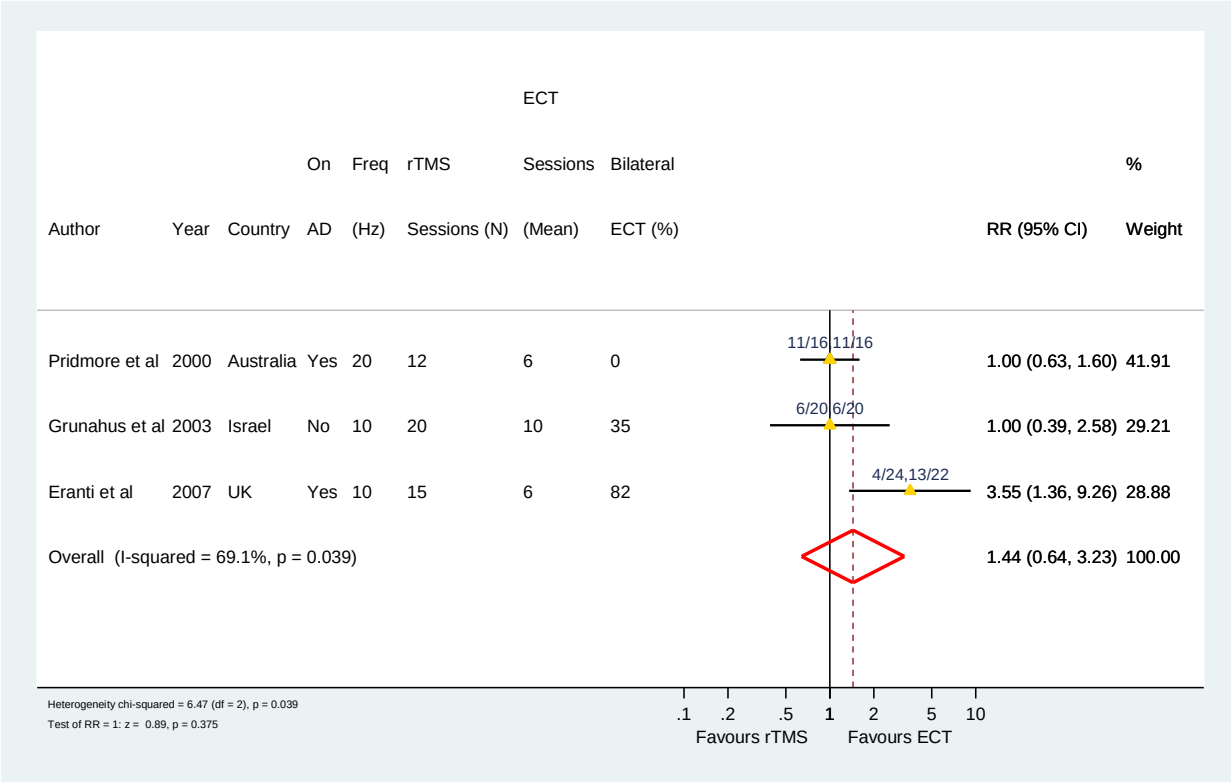


Figure 18: Remission Rate: Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy

Abbreviations: CI, confidence interval; df, degrees of freedom; ECT, electroconvulsive therapy; Freq, frequency; On AD, using antidepressant during rTMS or sham treatment; RR, risk ratio; TMS, repetitive transcranial magnetic stimulation.

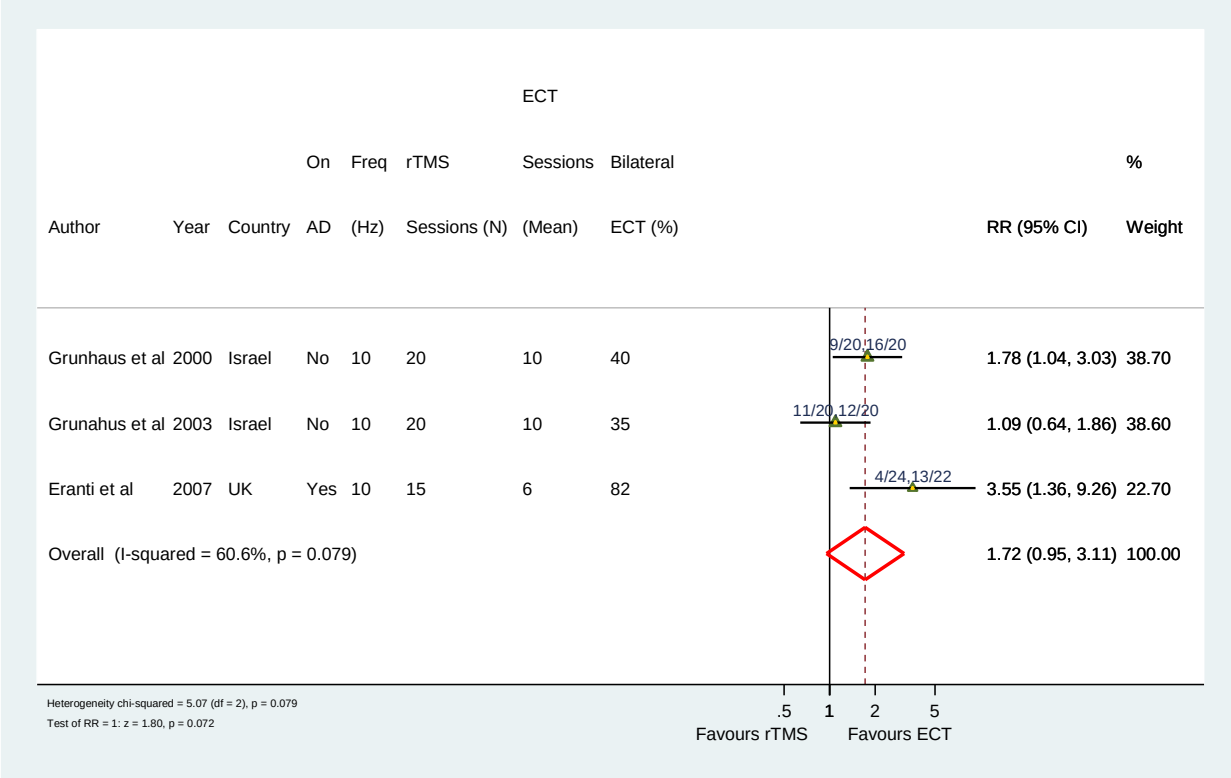


Figure 19: Response Rate: Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy

Abbreviations: CI, confidence interval; df, degrees of freedom; ECT, electroconvulsive therapy; Freq, frequency; On AD, using antidepressant during rTMS or sham treatment; RR, risk ratio; rTMS, repetitive transcranial magnetic stimulation.

Benefit Difference

The benefit increase (alternative terminology to risk difference for remission or response outcomes) in remission for rTMS versus ECT was 15% (95% CI -0.14–0.44, *P* = .310) favouring ECT. For response, the benefit increase was 29% (95% CI 0.07–0.5, *P* = .010) favouring ECT. Figures are not shown.

Follow-Up Studies

Follow-Up of rTMS Versus Sham rTMS Trials

Four of the sham trials provided follow-up information beyond 1 month. Two studies[35,37] reported that there was no difference between rTMS and sham treatment with respect to the mean scores or proportion of responders at 3-months' follow-up. One study[15] provided a graph for the mean scores and demonstrated lower scores in favour of the sham group (Table 6). One study[26] reported that about half of patients had relapsed at 6 months.

Table 6: Follow-up of Sham Trials

Author, Year	Follow-up (mo)	Outcome	rTMS	Sham	Effect Size, *P* value
Triggs et al 2010[37]	3	Depression scores, mean (SD)	16.3 (11.5)	17.9 (11.6)	NS
	3	Response, n/N (%)	6/18 (33.3)	4/14 (28.6)	N/A
Bretlau et al 2008[35]	2	Depression scores, mean (SD)	12.4 (5.8)	15.3 (6.4)	0.64 (0.04–1.24), *P* = .05
	3	Depression scores, mean (SD)	11.1 (6.7)	13.5 (7.2)	0.47 (−0.11 to 1.07), *P* = .22
Mogg et al 2008[15]	4	Depression scores, mean (graph)	Sham group had lower scores for about 2 points		N/A
Avery et al 2006[26]	6	Relapse rate n/N (%)	5/11 (45.5) responders	1/2 (50) responders	N/A

Abbreviations: N/A, not available; NS, not significant; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation.

Follow-Up of rTMS Versus ECT Trials

Two ECT studies reported outcomes at 6-months' follow-up. The study by Eranti et al[43] showed relatively higher rate of remission at 6-months' follow-up for ECT than rTMS (27.3% versus 16.7%) and reported that 50% of patients relapsed during the first 6 months. The study by Grunhaus et al[44] and Dannon et al[48] showed no difference between ECT and rTMS at 3- or 6-month's follow-up, but relapse rate was lower in the ECT group (Table 7).

Table 7: Follow-up of Electroconvulsive Therapy Trials

Author, Year	Follow-up (mo)	Outcome	rTMS	ECT	Effect Size/*P* value
Eranti et al 2007[43]	6	Remission, n/N (%)	2/24 (8.3) remitters	6/13 (46.2) remitters	N/A
	6	Relapse rate, n/N (%)	2/4 (50) remitters	6/12 (50) remitters	NS
Grunhaus et al 2000[44]	3	Depression scores, mean (SD)	6.4 (4.91)	7.71 (5.03)	NS
Dannon et al 2002[48]	6	Depression scores, mean (SD)	7.9 (7.14)	8.4 (5.60)	NS
	6	Relapse rate, n/N (%)	4/9 (44.4) responders	4/16 (25) responders	N/A

Abbreviations: ECT, electroconvulsive therapy; N/A, not available; NS, not significant; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation.

Comparison of Current Study With Prior Meta-Analyses

Sham Trials

We found an effect size of 0.33 (95% CI 0.17– 0.5), which was relatively smaller than that reported by two other meta-analyses of sham-controlled trials, in part because inclusion criteria or method of statistical analysis differed. Schutter et al[49] included patients with or without resistance to drug treatment, but included only studies on high frequency (≥5 Hz) delivered over the left dorsolateral prefrontal cortex. These researchers found an effect size of 0.39 (95% CI 0.25–0.54), on the basis of changes in depression scores from baseline to the end of treatment (similar to the current study), and there was no significant heterogeneity among the studies. The study by Lam et al,[50] which included only patients with treatment-resistant depression but pooled results for both left- and right-brain stimulation, found a larger effect size (0.48 [95% CI 0.28–0.69]), with significant heterogeneity among the studies. However, this study calculated

the effect size on the basis of scores at the end of treatment. Sensitivity analysis restricted to studies that used higher intensity and high frequency delivered over the left dorsolateral prefrontal cortex did not change the effect size of 0.48 (95% CI 0.21–0.76), but the effect size dropped to 0.37 (95% CI 0.18–0.56) when researchers performed a sensitivity analysis of the entire sample for failing to benefit from two or more antidepressants. The small magnitude of effect shown in our study, in which most patients had failed to respond to two or more antidepressants, and also the findings by Lam et al,[50] suggest that greater drug resistance could negatively influence the outcomes.

In another meta-analysis[51] of high-frequency stimulation of the left dorsolateral prefrontal cortex in patients with or without treatment-resistant depression, the weighted mean difference was 1.1 (95% CI −2.3 to 4.5; *P* = .33), indicating that rTMS is no better than sham treatment. This mean difference was less than what we found in the present study (2.31, 95% CI 1.19–3.43). This study had more stringent inclusion criteria pertaining to the study validity and included only studies with evidence for allocation concealment. We found evidence for allocation concealment in only three of the included studies.[15,22,23] Another reason for observing a smaller effect size in the study by Couturier[51] might be the shorter duration of treatment in trials included in that study (10 session of rTMS treatment) while, in the present study, 8 of the 23 studies used 15 to 30 sessions.

The results of our analysis of remission and response outcomes for sham studies were similar to the results of the study by Lam et al.[50] Although our analysis included studies published since that publication and was also restricted to unipolar depression, the pooled remission rate of 17.4% and pooled response rate of 25.1% for rTMS-treated patients in our study are similar to the remission rate and response rate in the study by Lam et al[50] (17% and 25%, respectively). Our pooled remission and response rates of 6.7% and 12.3% for sham conditions were also close to the rates reported by Lam et al[50] (6% and 9%) (Table 8).

In another systematic review and meta-analysis[52] of a patient population not restricted to treatment-resistant cases of unipolar depression, the rate of remission was 18.3% in the group receiving active rTMS and 5% in the group receiving sham rTMS. These rates are close to the estimates of 17.4% for the rTMS and 6.7% for the sham groups in the current review. The proportions of responders in that study (rTMS 29.3% and sham 10.5%) were slightly different but not far from our estimates.

Table 8: Remission and Response Rates

Studies	Proportion of Patients (%)			
	Remitted		Responded	
Sham	**rTMS**	**Sham**	**rTMS**	**Sham**
Current review	17.4	6.7	25.1	12.3
Meta-analysis by Lam et al of TRD patients[50]	17.0	6.0	25.0	9.0
ECT	**rTMS**	**ECT**	**rTMS**	**ECT**
Current review	35.0	51.7	37.5	66.1
Meta-analysis by Berlim et al 2013[53]	33.6	52.0	N/A	N/A

Abbreviations: ECT, electroconvulsive therapy; N/A, not applicable; rTMS, repetitive transcranial magnetic stimulation; TRD, treatment-resistant depression.

ECT Trials

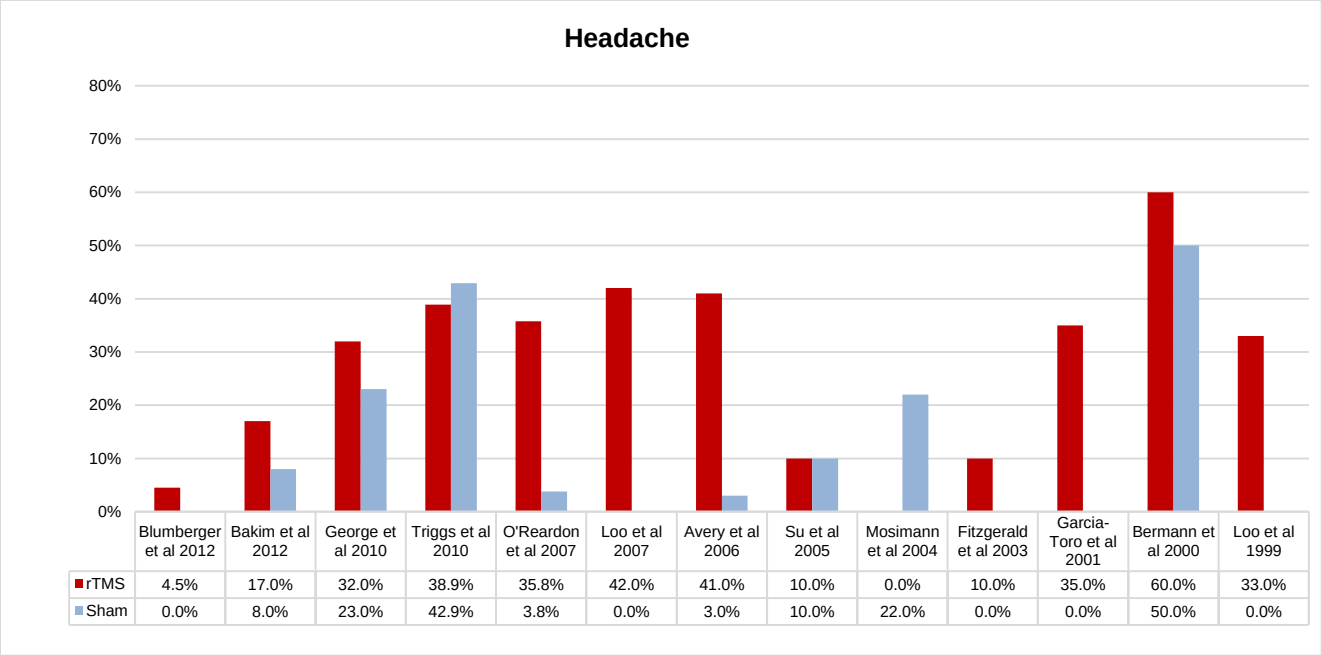
The remission rate of 52% for ECT-treated patients reported by a meta-analysis of trials that compared rTMS with ECT[53] was close to our estimated remission rate for ECT-treated patients (51.7%) (Table 8).

The remission rate of 68.8% for the rTMS group, reported by one of the rTMS-versus-ECT trials conducted in early 2000, was considerably higher than the rate in other trials. It approached the rate observed for ECT, whereas two other ECT studies found remission rates of 16.7% and 30% for rTMS group. Our pooled remission rate for the rTMS group in sham-controlled trials was 17.4%. We were unable to justify this discrepancy, but noted that patients in the first study were younger than in the other two ECT studies. Kedzior et al[54] have also noticed a considerably larger effect size (d = 1.28) in one rTMS versus sham trial in which patients were younger than 40 years of age, while the effect size for patients who were older than 40 years of age (d = 0.38) was close to our effect size in sham trials. Nahas et al[55] have shown that the skull-to-prefrontal-cortex distance increases with age, and Daskalakis et al[56] have emphasized the importance of coil-to-cortex distance in considering the stimulation intensity, as it might be insufficient to reach the targeted area. Frengi et al[57] have shown that age and treatment refractoriness are significant negative predictors of depression improvement when adjusting these variables to other significant predictors and confounders. Thus, several lines of evidence suggest that, in addition to the stimulation paradigm, the magnitude of the clinical effect of rTMS is also linked to the characteristics of the patients and the approach to stimulate the targeted area.

Reported Adverse Events

Studies Comparing rTMS With Sham rTMS

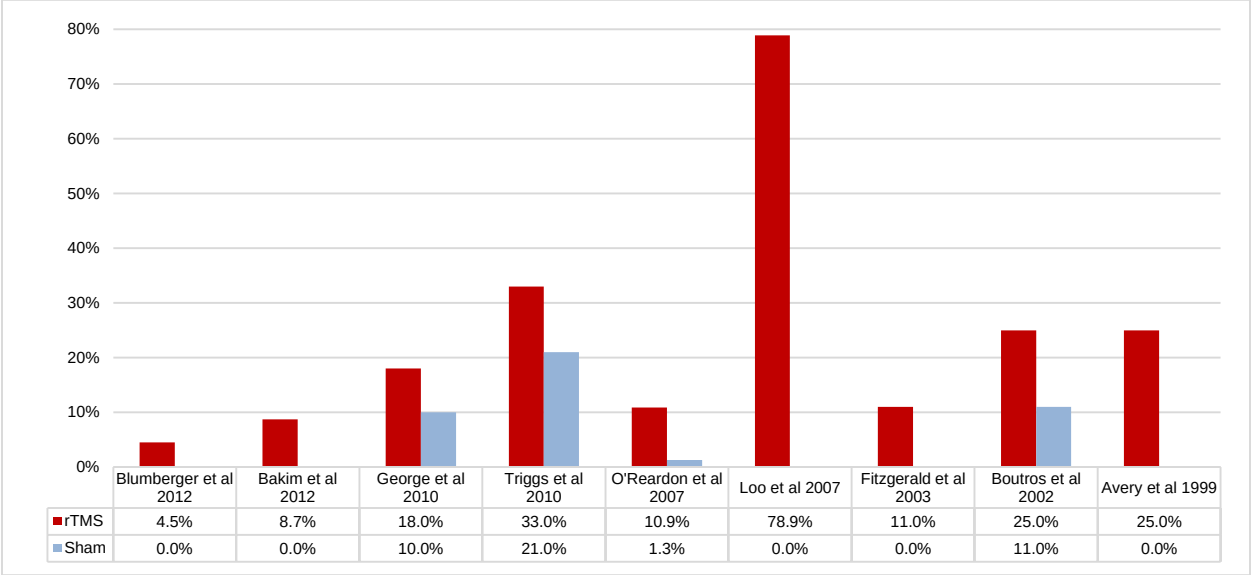
Sixteen studies reported the number of patients in each group who experienced adverse events. One study[35] provided scores on a side effect scale. One study[40] reported no serious adverse event in patients, and three studies[24,38,39] did not report on adverse events. Headache and scalp discomfort were the most frequently reported adverse events in these trials, and rates were higher in rTMS-treated than sham rTMS–treated patients. The occurrence of headache in patients who received sham treatment might in fact raise questions about the integrity of sham conditions (Figures 21 and 22).



	Blumberger et al 2012	Bakim et al 2012	George et al 2010	Triggs et al 2010	O'Reardon et al 2007	Loo et al 2007	Avery et al 2006	Su et al 2005	Mosimann et al 2004	Fitzgerald et al 2003	Garcia-Toro et al 2001	Bermann et al 2000	Loo et al 1999
rTMS	4.5%	17.0%	32.0%	38.9%	35.8%	42.0%	41.0%	10.0%	0.0%	10.0%	35.0%	60.0%	33.0%
Sham	0.0%	8.0%	23.0%	42.9%	3.8%	0.0%	3.0%	10.0%	22.0%	0.0%	0.0%	50.0%	0.0%

Figure 20: Rate of Headache

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

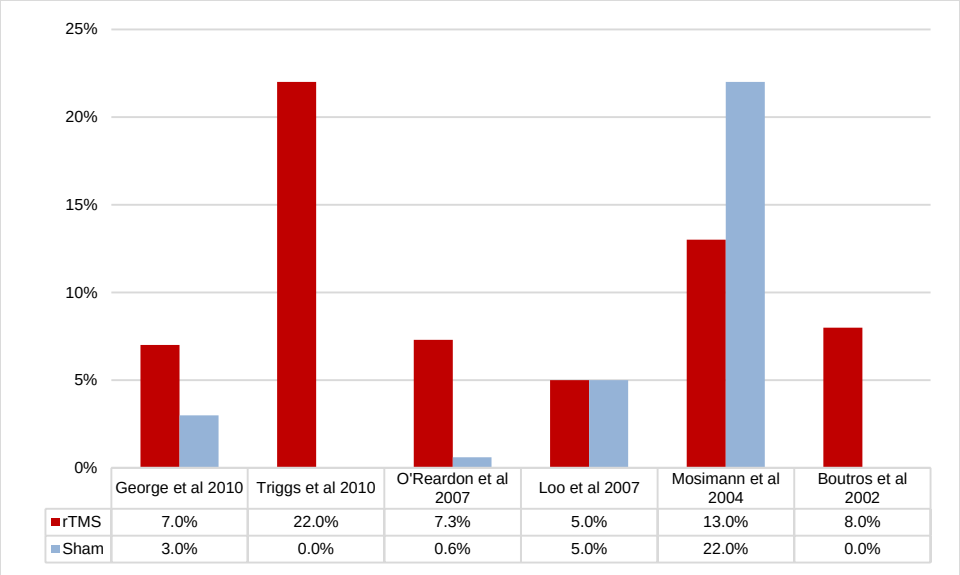


	Blumberger et al 2012	Bakim et al 2012	George et al 2010	Triggs et al 2010	O'Reardon et al 2007	Loo et al 2007	Fitzgerald et al 2003	Boutros et al 2002	Avery et al 1999
rTMS	4.5%	8.7%	18.0%	33.0%	10.9%	78.9%	11.0%	25.0%	25.0%
Sham	0.0%	0.0%	10.0%	21.0%	1.3%	0.0%	0.0%	11.0%	0.0%

Figure 21: Rate of Scalp Pain or Discomfort

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

Gastrointestinal problems were also more prevalent in the rTMS than in the sham-treated group (Figure 22).

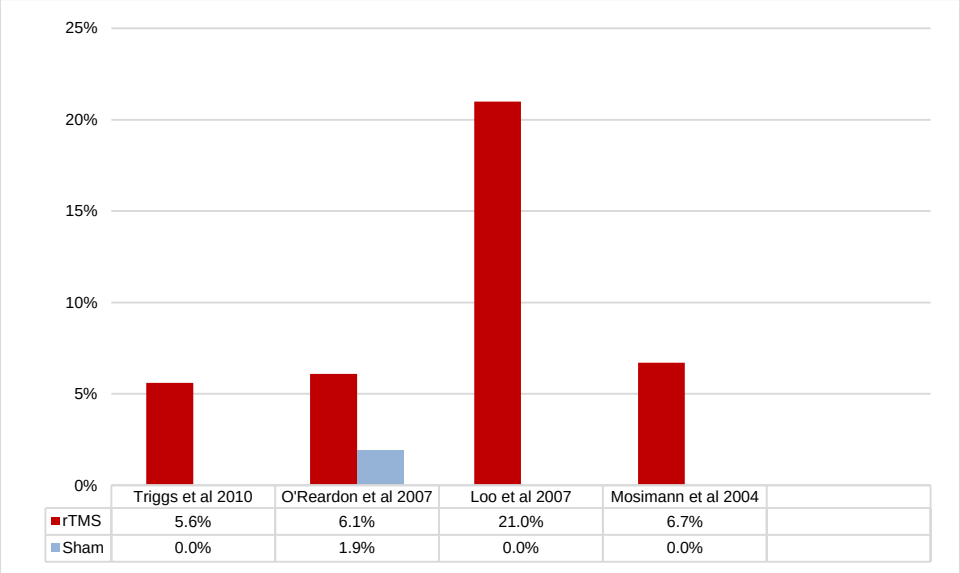


	George et al 2010	Triggs et al 2010	O'Reardon et al 2007	Loo et al 2007	Mosimann et al 2004	Boutros et al 2002
rTMS	7.0%	22.0%	7.3%	5.0%	13.0%	8.0%
Sham	3.0%	0.0%	0.6%	5.0%	22.0%	0.0%

Figure 22: Rate of Gastrointestinal Problems

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

Figure 23 shows the rate of eye problems (eye pain, conjunctivitis, or tearfulness).



	Triggs et al 2010	O'Reardon et al 2007	Loo et al 2007	Mosimann et al 2004	
rTMS	5.6%	6.1%	21.0%	6.7%	
Sham	0.0%	1.9%	0.0%	0.0%	

Figure 23: Rate of Eye Problems

Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

Figure 24 shows the rate of muscle twitching.

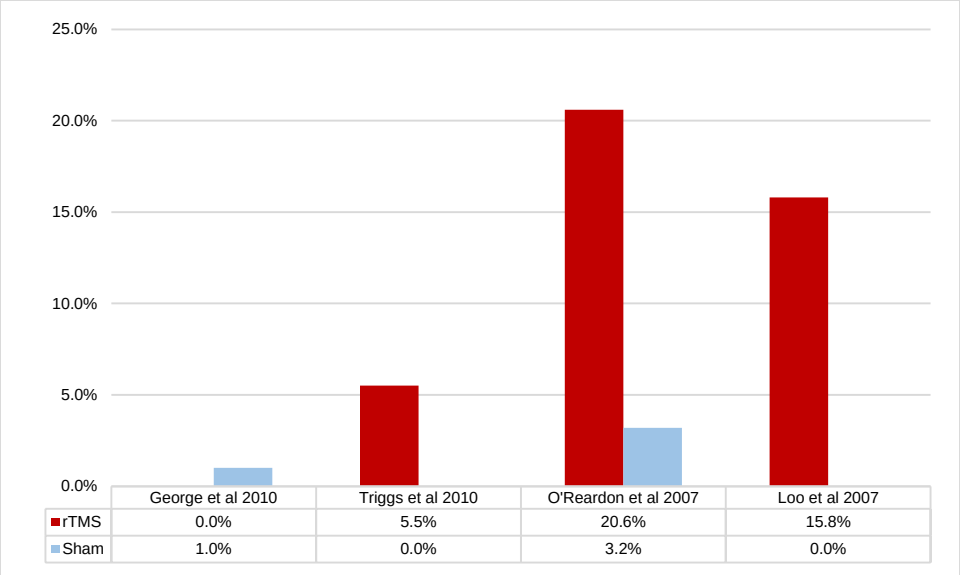


Figure 24: Rate of Muscle Twitching

Table 9 shows the other adverse events reported in rTMS versus sham trials.

Table 9: Other Reported Adverse Events

Adverse Event	Rates Reported by Studies: rTMS vs Sham (%)
Vertigo/dizziness	George et al 2010: 2 vs 2[27]
	Triggs et al 2010: 16.7 vs 14[37]
	Avery et al 2006: 2.9 vs 0[26]
	Mosimann et al 2004: 0 vs 6.7[25]
	Fitzgerald et al 2003: 5 vs 5[23]
	Mogg et al 2008: 0 vs 3[15]
Insomnia	Blumberger et al 2012: 4.5 vs 0[22]
	George et al 2010: 7.6 vs 10[27]
	Triggs et al 2010: 5.6 vs 7.1[37]
Muscle pain	George et al 2010 : 4% vs 4%[27]
	Triggs et al 2010 5.5% vs 0%[37]
Fatigue	George et al 2010: 5 vs 4[27]
	Triggs et al: 27.8 vs 14[37]
Difficulty concentrating	Triggs et al: 0 vs 7[37]
	Boutros et al 2002: 41.7 vs 0[34]
Anxiety/panic episode	Loo et al 2007: 10.5 vs 0[29]
	Su et al 2005: 5 vs 0[32]
Hypomania	Loo et al 2007: 5 vs 0[29]
	Su et al 2005: 5 vs 0[32]
Tinnitus	Boutros et al: 8 vs 0[34]
	Loo et al 1999: 11 vs 0[28]
	Mogg et al 2008: 0 vs 3[15]
Skin pain	George et al: 1 vs 1[27]
	O'Reardon et al: 8.5 vs 0.6[30]
Facial pain	O'Reardon et al: 6.7 vs 3.2[30]
Depersonalization	Boutros et al 2002: 25 vs 11[34]
Paranoid ideation	Boutros et al: 8 vs 11[34]
Crying	Mosimann et al: 13 vs 0[25]
Getting worse	Boutros et al: 8 vs 0[34]
Suicidal ideation	Mosimann et al: 6.7 vs 0[25]
Syncope	George et al: 1 vs 0[27]

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; vs, versus.

Studies Comparing rTMS With ECT

Eranti et al[43] provided detailed information about the side effects of the interventions. Keshtkar et al[46] reported that only one patient experienced headache after rTMS. Details of adverse events reported by studies that compared rTMS with ECT are summarized in Table 13.

Table 13: Adverse Events Reported for Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy

Study	Side Effect Scores	Self-Rating of Cognitive Complaints	Cognition Scores
Eranti et al 2007[43]			Total scores (Maximum = 107)
Baseline	rTMS: 13.2 (5.8) ECT: 14.2 (4.7)	rTMS: 2.1 (1.3) ECT: 2.4 (1.2)	rTMS: 85.3 (11.3) ECT: 83.2 (11.1)
End of Treatment	rTMS: 9.7 (4.6) ECT: 6.7 (6.4)	rTMS: 1.5 (1.2) ECT: 1.5 (1.4)	rTMS: 84.7 (17.4) ECT: 87.0 (14.8)
6 mo	rTMS: 8.9 (4.7) ECT: 7.1 (4.7)	rTMS: 2.1 (1.5) ECT: 1.2 (1.4)	rTMS: 84.8 (14.5) ECT: 86.1 (17.3)
***P* values**	.02[a]	.1	.07
Pridmore et al 2000[47]			
Baseline	rTMS: 8.1 (3.2) ECT: 6.1 (3.6)		
***P* value**	.1		
End of Treatment	rTMS: 3.9 (2.9) ECT: 5.3 (4.3)		
***P* value**	.3		
Rate of Adverse Events			
Grunhaus et al 2003[45]	rTMS: three (15%) patients had headache and two (10%) had sleep disturbance ECT: No adverse event occurred		
Grunhaus et al 2000[44]	rTMS: five (25%) had headache ECT: No adverse event occurred		

Abbreviations: ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation.
[a]Body of evidence favoured ECT.

CONCLUSIONS

High-Frequency rTMS of Dorsolateral Prefrontal Cortex Versus Sham

The mean difference in depression scores between high-frequency rTMS of the dorsolateral prefrontal cortex and sham treatment (the primary outcome) was small (WMD 2.31, 95% CI 1.19–3.43) and did not meet prespecified criteria for clinical significance. The standardized mean difference was also small (SMD = 0.33, 95% CI 0.17–0.5). The proportion of patients who remitted or responded (secondary outcomes) was higher in patients who received rTMS than in patients who received sham treatment (remission 17% versus 7% and response 25% versus 12%). The benefit increase in remission or response rates was 10%. This translates to a number needed to treat of 10, meaning that we need to treat 10 patients with rTMS to have one remission or response. For comparison, in a meta-analysis of 32 randomized trials, the effects of treatment with combined psychotherapy and pharmacotherapy were compared with the effects of pharmacotherapy only in adults with depression. The meta-analysis obtained a number needed to treat of 4.2. The risk ratios and corresponding 95% CIs for remission and response rates were 2.20 (1.44–3.38) and 1.72 (1.13–2.62), respectively.

Only a few studies provided follow-up data. However, three reported no difference between rTMS and sham treatment after 3 or 4 months of follow-up, and one reported that relapse occurred in about half of patients who responded to the treatment in spite of receiving antidepressant medications after the last rTMS treatment.

Overall, the body of evidence showed a small short-term effect of rTMS in comparison with sham for improving depression scores. There is limited data to assess the long-term effectiveness of rTMS.

High-Frequency rTMS of Dorsolateral Prefrontal Cortex Versus ECT

Trials of high-frequency rTMS of the dorsolateral prefrontal cortex versus ECT showed significantly more improvement in depression scores with ECT treatment than with rTMS treatment, and the effect estimate was also clinically significant (WMD 5.97, 95% CI 0.94–11.0, P = .020). The standardized mean difference was 0.67 (95% CI 0.10–1.23, P = .021), which would be considered a large effect size.

The remission and response rates were also higher in patients who received ECT than in those who received rTMS (remission 51.7% versus 35% and response 66.1% versus 37.5%). The benefit increase in remission and response rates were 15% (95% CI −0.14 to 0.44, P = .310) and 29% (95% CI 0.07–0.5, P = .01), respectively, favouring ECT. The risk ratios and corresponding 95% CIs for remission and response rates were 1.44 (0.64–3.23) and 1.72 (0.95–3.11), respectively. The pooled risk ratio did not reach significance level, as the studies used different ECT protocols and were very heterogeneous. At 6-months' follow-up of a blinded study, 27% of the ECT group and 17% of the rTMS group were still remitted, and the relapse rate among those who remitted was about 50% in either group.

LIST OF ABBREVIATIONS

CI	Confidence interval(s)
ECT	Electroconvulsive therapy
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
rTMS	Repetitive transcranial magnetic stimulation
SD	Standard deviation
SMD	Standardized mean difference
TMS	Transcranial magnetic stimulation
WMD	Weighted mean difference

APPENDICES

Appendix 1: Literature Search Strategy

Databases: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 2014, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2014, EBM Reviews - Cochrane Central Register of Controlled Trials October 2014, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2014, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2014, Ovid MEDLINE(R) Daily Update November 19, 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, Embase 1974 to 2014 November 19

#	Searches	Results
1	Depression/	341444
2	exp Depressive Disorder/ use prmz,acp,cctr,coch,clcmr,dare,clhta,cleed	92220
3	Major Depression/ use oemezd	37851
4	Treatment Resistant Depression/ use oemezd	742
5	(depressi* or dysthymic or melancholia or TRD or "involutional psychos*" or paraphrenia).ti,ab.	642939
6	or/1-5	783031
7	Transcranial Magnetic Stimulation/	22067
8	(((transcranial or trans-cranial) adj2 magnetic adj2 stimulation*) or rtms or tms).mp.	36404
9	or/7-8	36404
10	6 and 9	4766
11	limit 10 to yr="1994 -Current" [Limit not valid in DARE; records were retained]	4743
12	limit 11 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained]	4305
13	remove duplicates from 12	2734

Database: PsycINFO <1987 to November Week 3 2014>

#	Searches	Results
1	exp Major Depression/	93059
2	(depressi* or dysthymic or melancholia or TRD or "involutional psychos*" or paraphrenia).ti,ab.	180727
3	or/1-2	186314
4	exp Transcranial Magnetic Stimulation/	4565
5	(((transcranial or trans-cranial) adj2 magnetic adj2 stimulation*) or rtms or tms).mp.	6312
6	or/4-5	6312
7	3 and 6	1182
8	limit 7 to (english language and yr="1994 -Current")	1081

HEED

depressi* OR dysthymic OR melancholia OR TRD OR psychos* OR paraphrenia =all data
AND transcranial OR trans-cranial OR rtms OR tms =all data
5 results

Appendix 2: Evidence Quality Assessment

Table A1: GRADE Evidence Profile for Comparison of rTMS and Sham rTMS

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Depression scores							
15 (RCTs)	Serious limitations	Serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	⊕⊕⊕ Moderate/Low
Remission rate							
11 (RCTs)	Serious limitations	Serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	⊕⊕⊕ Moderate/Low
Response rate							
18 (RCTs)	Serious limitations	Serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	⊕⊕⊕ Moderate/Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; N/A, not applicable; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation.

Table A2: GRADE Evidence Profile for Comparison of rTMS and ECT

Number of Studies (Design)	Risk of Bias	Inconsistency[a]	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Depression scores							
4 (RCTs)	Serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	⊕⊕⊕ Moderate
Remission rate							
3 (RCTs)	Serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	⊕⊕⊕ Moderate
Response rate							
3 (RCTs)	Serious limitations	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	⊕⊕⊕ Moderate

Abbreviations: ECT, electroconvulsive therapy; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; N/A, not applicable; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation.
[a]Heterogeneity in results was mostly due to the different application of ECT among studies.

Appendix 3: Safety Guidelines

Table A3: Maximum Safe Duration of Single Trains of Repetitive Transcranial Magnetic Stimulation

Frequency (Hz)	Stimulus Intensity (% of Motor Threshold)[a]				
	90%	100%	110%	120%	130%
1	> 1,800	> 1,800	> 1,800	> 360	> 50
5	> 10	> 10	> 10	> 10	> 10
10	> 5	> 5	> 5	4.2	2.9
20	2.05	2.05	1.6	1.0	0.55
25	1.28	1.28	0.84	0.4	0.24

[a]Numbers preceded by > are the longest duration tested.

Data from Wassermann[10] Reprinted from Clinical Neurophysiology, *120/12, Rossi et al, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research, 2008–39, 2009, with permission from Elsevier.[9]*

Table A4: Updated Recommendations: Maximum Safe Duration of Pulses for Individual Trains at Each Stimulus Intensity

Frequency (Hz)	Stimulus Intensity (% of Motor Threshold)							
	100%		110%		120%		130%	
	Duration[a]	Pulses	Duration[a]	Pulses	Duration[a]	Pulses	Duration[a]	Pulses
1	> 270	> 270	> 270	> 270	> 180	> 180	50	50
5	10	50	10	50	10	50	10	50
10	5	50	5	50	3.2	32	2.2	22
20	1.5	30	1.2	24	0.8	16	0.4	8
25	1.0	25	0.7	17	0.3	7	0.2	5

[a]Duration per second.

Reprinted from Clinical Neurophysiology, *120/12, Rossi et al, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research, 2008–39, 2009, with permission from Elsevier.[9]*

Table A5: Safety Recommendations for Safe Inter-Train Interval for 10 Trains at < 20 Hz

Inter-train Interval (ms)	Stimulus Intensity (% of Motor Threshold)			
	100%	105%	110%	120%
5,000	Safe	Safe	Safe	Insufficient data
1,000	Unsafe (EMG spread after 3 trains)	Unsafe[a]	Unsafe (EMG spread after 2 trains)	Unsafe (EMG spread after 2 trains)
250	Unsafe[a]	Unsafe[a]	Unsafe (EMG spread after 2 trains)	Unsafe (EMG spread after 3 trains)

Abbreviation: EMG, electromyographic.

[a]These stimulus parameters are considered unsafe because adverse events occurred with stimulation of lower intensity or longer inter-train interval, but no adverse effects were observed with these parameters.

Reprinted from Clinical Neurophysiology, *120/12, Rossi et al, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research, 2008–39, 2009, with permission from Elsevier. [9]*

Appendix 4: Forest Plots for All Studies, Including Those With Intensive Protocols: rTMS Versus Sham

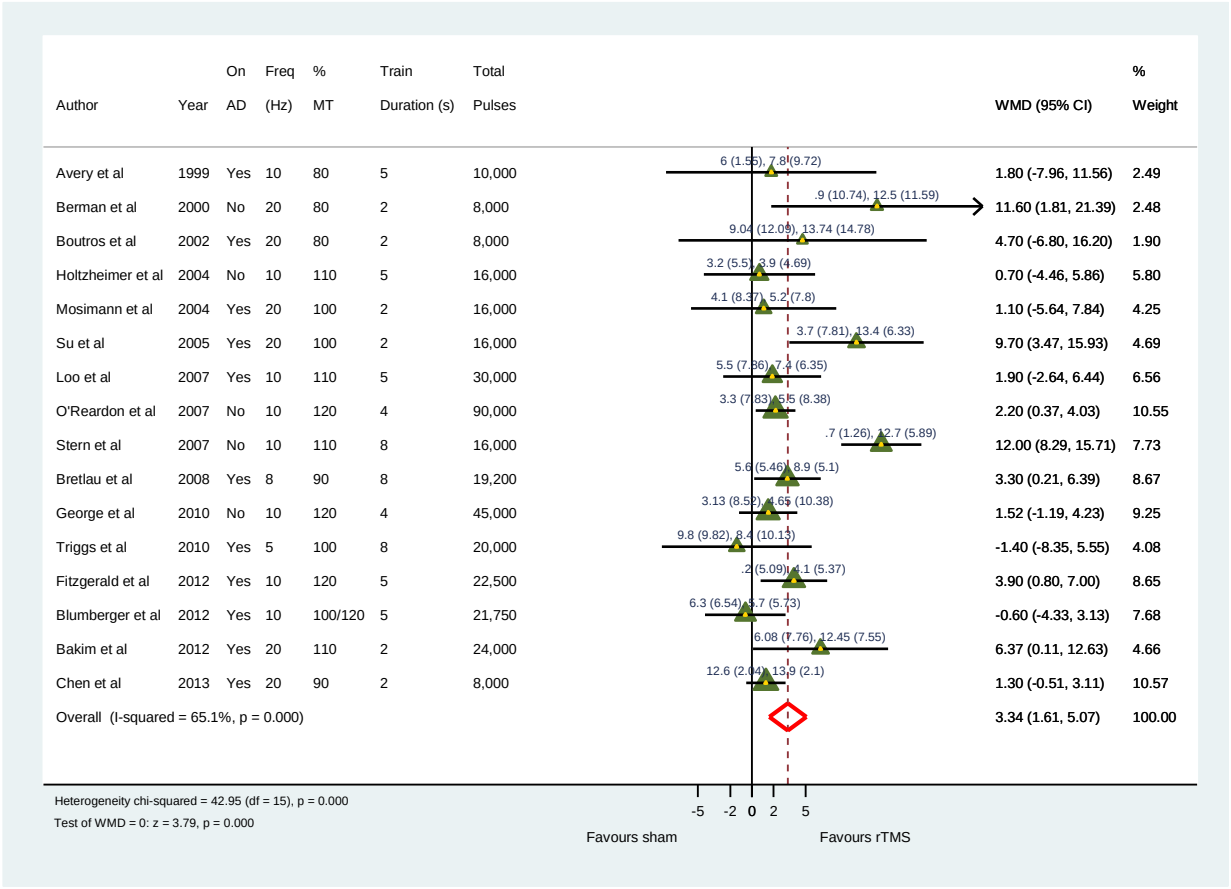


Figure A1: Weighted Mean Difference in Depression Scores for rTMS Versus Sham

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

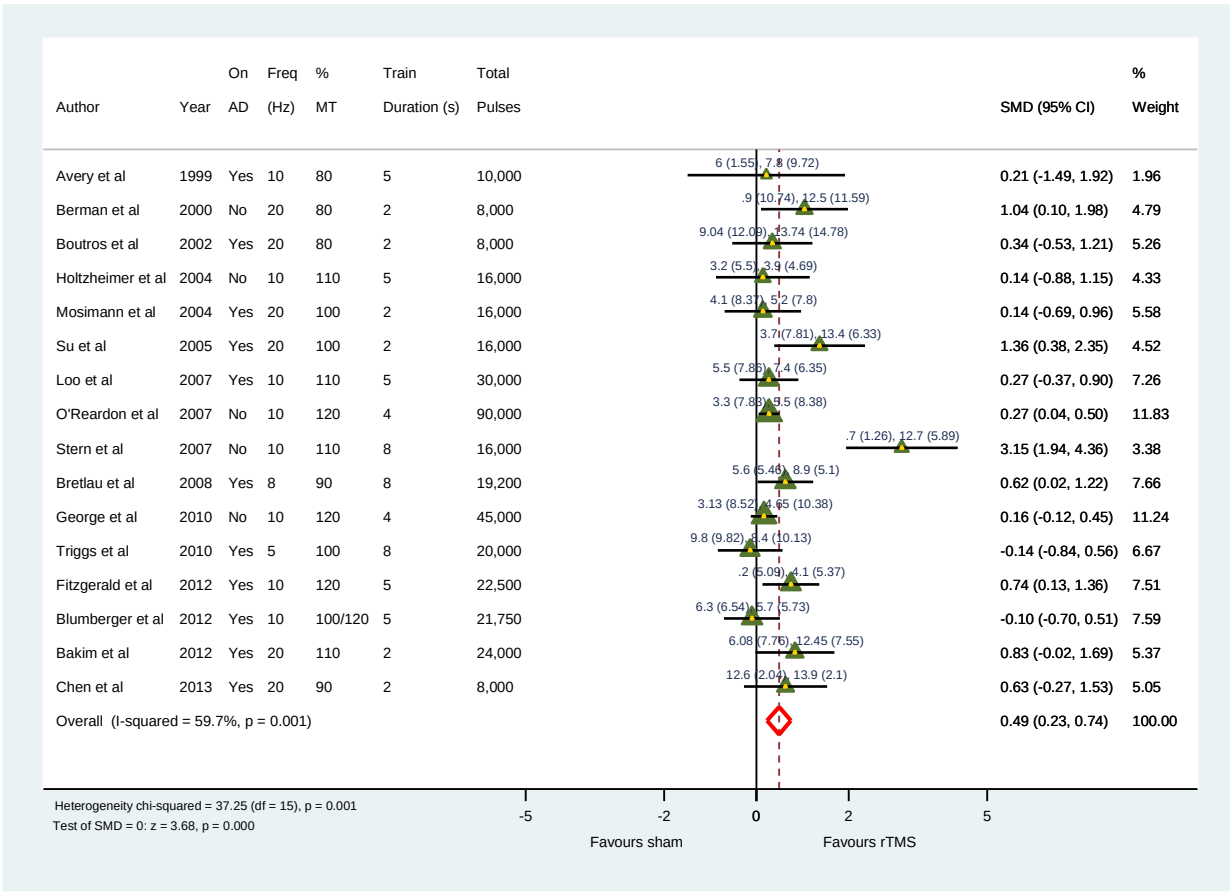


Figure A2: Standardized Mean Difference in Depression Scores for rTMS Versus Sham

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; rTMS, repetitive transcranial magnetic stimulation; SMD, standardized mean difference.

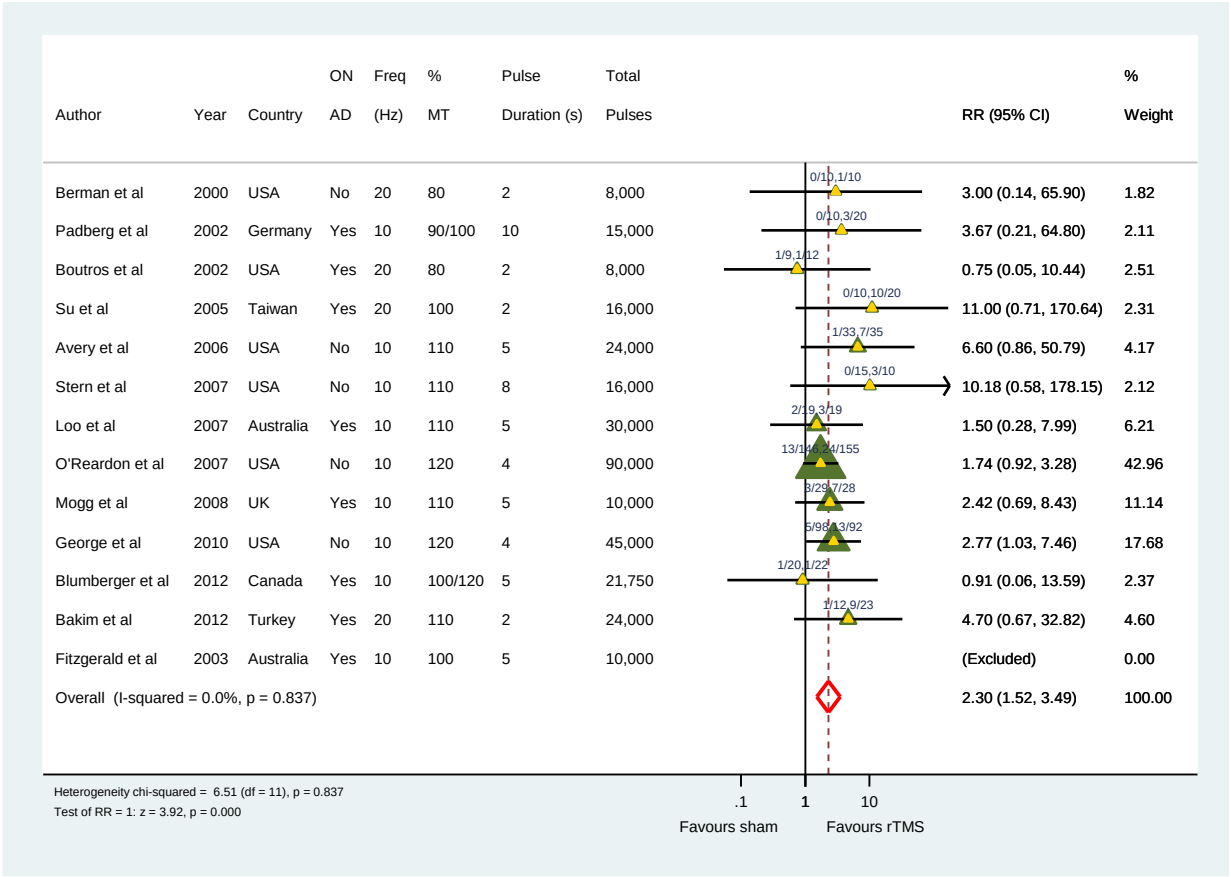


Figure A3: Remission Rate of rTMS Versus Sham

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; RR, risk ratio; rTMS, repetitive transcranial magnetic stimulation.

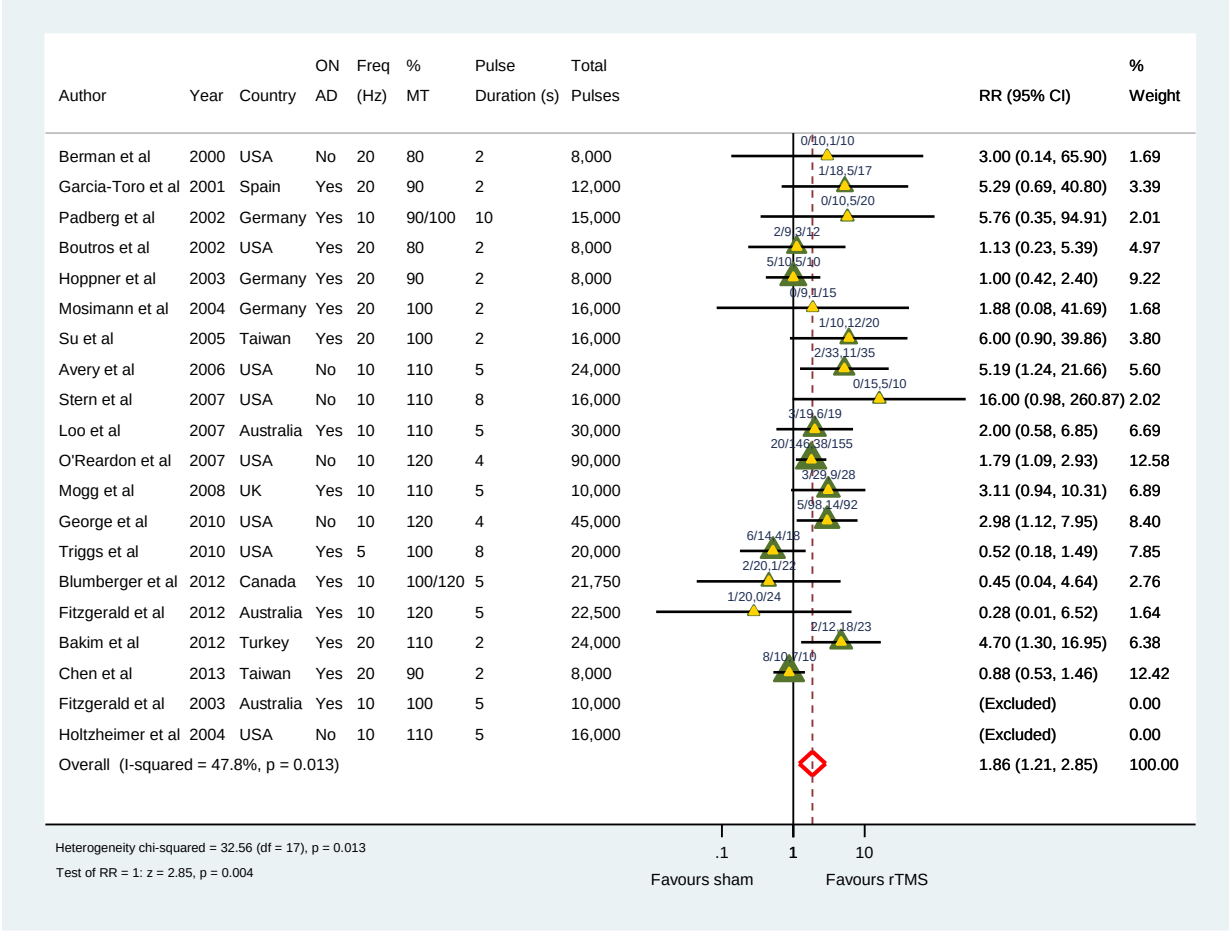


Figure A4: Response Rate of rTMS Versus Sham

Abbreviations: CI, confidence interval; df, degrees of freedom; Freq, frequency; MT, motor threshold; On AD, using antidepressant during rTMS or sham treatment; RR, risk ratio; rTMS, repetitive transcranial magnetic stimulation; WMD, weighted mean difference.

Appendix 5: Forest Plots for All Studies, Including Those With Intensive Protocols: rTMS Versus ECT

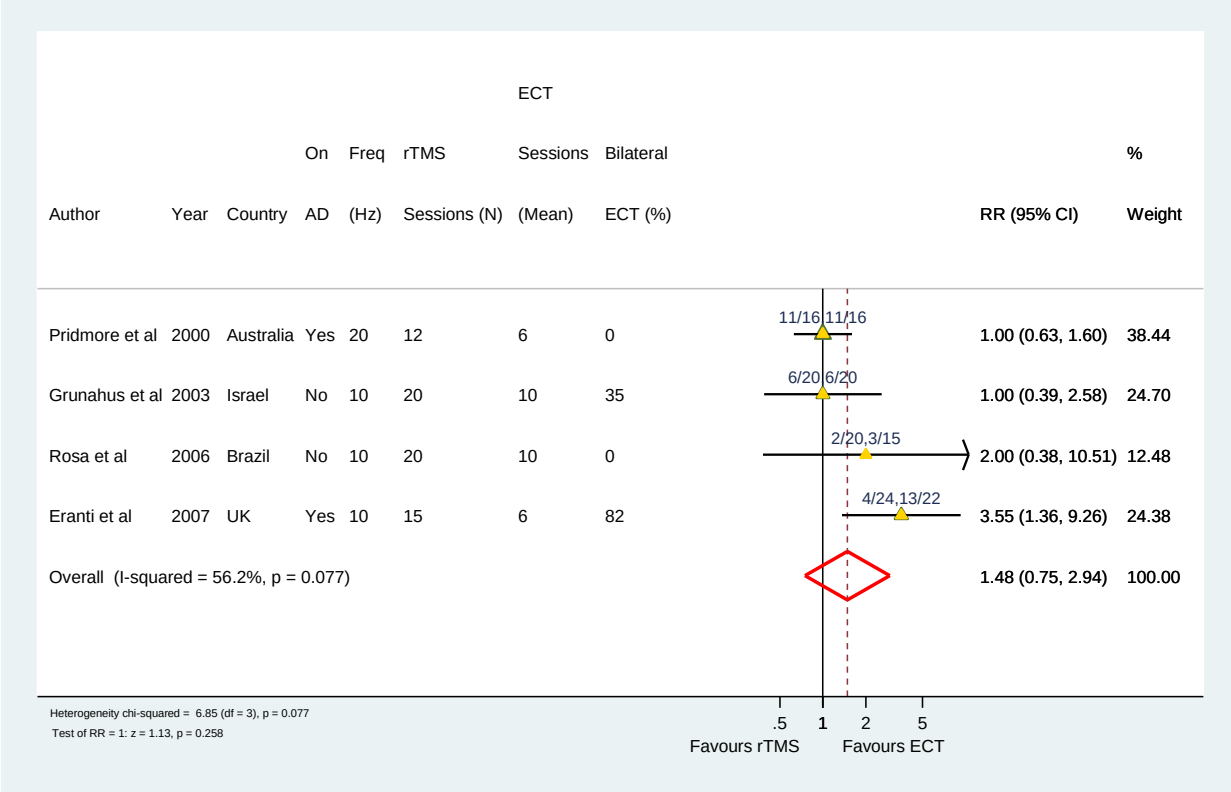


Figure A5: Remission Rate of rTMS Versus ECT

Abbreviations: CI confidence interval; df, degrees of freedom; ECT, electroconvulsive therapy; Freq, frequency; On AD, using antidepressant during rTMS or sham treatment; RR, risk ratio; rTMS, repetitive transcranial magnetic stimulation.

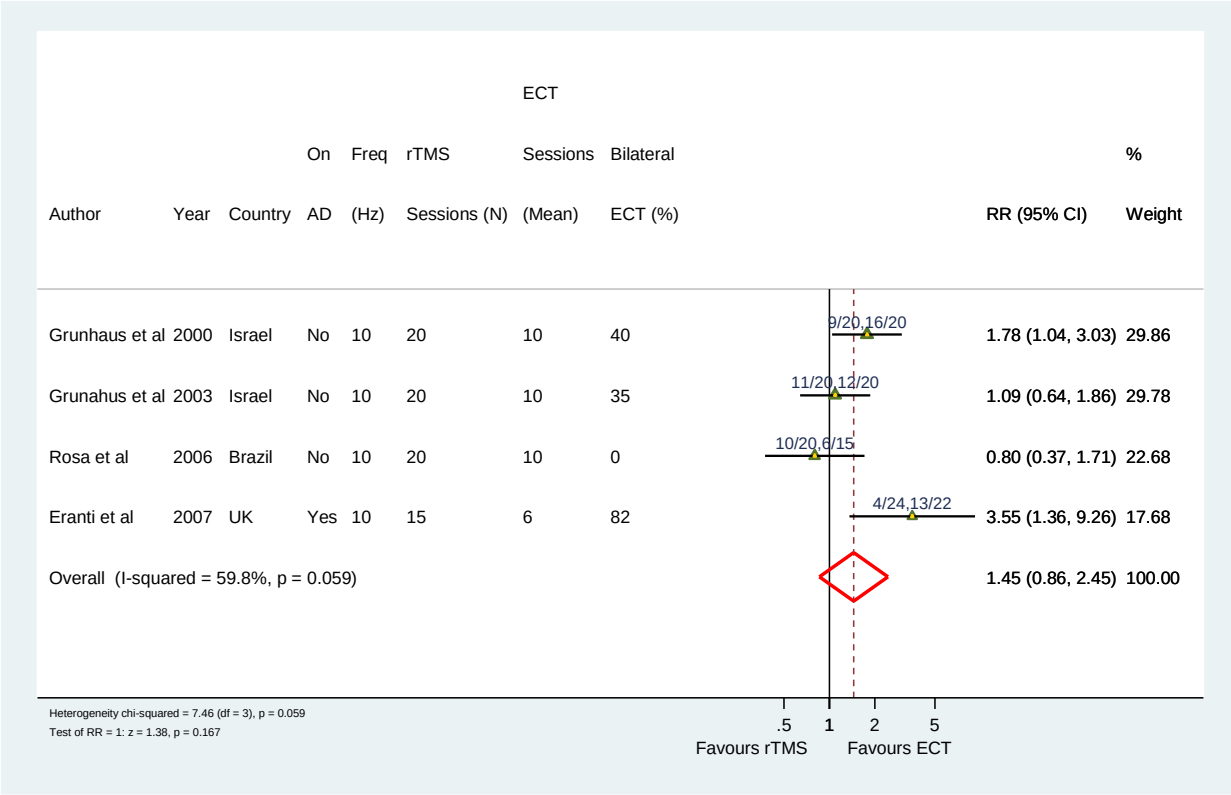


Figure A6: Response Rate of rTMS Versus ECT

Abbreviations: CI confidence interval; df, degrees of freedom; ECT, electroconvulsive therapy; Freq, frequency; On AD, using antidepressant during rTMS or sham treatment; RR, risk ratio; rTMS, repetitive transcranial magnetic stimulation.

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

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About Health Quality Ontario

About the Ontario Health Technology Advisory Committee (OHTAC)

How to Obtain OHTAC Recommendation Reports

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