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To obtain credit, read the article, correctly answer at least 70% of the questions in the Posttest, and complete the Evaluation.

CME Objective

After studying this article, you should be able to:

- Provide information to patients with resistant major depressive disorder about repetitive transcranial magnetic stimulation

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

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ABSTRACT

Objective: To evaluate the efficacy of repetitive transcranial magnetic stimulation (rTMS) in patients with major depressive disorder (MDD) and 2 or more prior antidepressant treatment failures (often referred to as treatment-resistant depression [TRD]). These patients are less likely to recover with medications alone and often consider nonpharmacologic treatments such as rTMS.

Data Sources: We searched MEDLINE, EMBASE, the Cochrane Library, PsycINFO, and the International Pharmaceutical Abstracts for studies comparing rTMS with a sham-controlled treatment in TRD patients ages 18 years or older.

Study Selection: We included 18 good- or fair-quality TRD studies published from January 1, 1980, through March 20, 2013.

Data Extraction: We abstracted relevant data, assessed each study's internal validity, and graded strength of evidence for change in depressive severity, response rates, and remission rates.

Results: rTMS was beneficial compared with sham for all outcomes. rTMS produced a greater decrease in depressive severity (high strength of evidence), averaging a clinically meaningful decrease on the Hamilton Depression Rating Scale (HDRS) of more than 4 points compared with sham (mean decrease = −4.53; 95% CI, −6.11 to −2.96). rTMS resulted in greater response rates (high strength of evidence); those receiving rTMS were more than 3 times as likely to respond as patients receiving sham (relative risk = 3.38; 95% CI, 2.24 to 5.10). Finally, rTMS was more likely to produce remission (moderate strength of evidence); patients receiving rTMS were more than 5 times as likely to achieve remission as those receiving sham (relative risk = 5.07; 95% CI, 2.50 to 10.30). Limited evidence and variable treatment parameters prevented conclusions about which specific treatment options are more effective than others. How long these benefits persist remains unclear.

Conclusions: For MDD patients with 2 or more antidepressant treatment failures, rTMS is a reasonable, effective consideration.

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Clinical Points

- The use of nonpharmacologic interventions in patients with treatment-resistant depression is a key clinical issue; clinicians and researchers are only beginning to identify the role of repetitive transcranial magnetic stimulation (rTMS) for this hard-to-treat population.
- Repetitive transcranial magnetic stimulation is a general class of treatments rather than a single entity, much as antidepressants represent a general approach encompassing a variety of compounds with a common therapeutic application but divergent mechanisms for achieving it.
- For patients with major depressive disorder with 2 or more antidepressant treatment failures, rTMS is a reasonable, effective consideration.

In any given year, between 13.1 million and 14.2 million US residents experience major depressive disorder (MDD).[1] Half seek help for this condition; only 1 in 5 of those seeking help receive adequate acute-phase treatment.[2] Even for patients receiving adequate treatment, only 30% (that is, 3% of patients with MDD) reach the treatment goal of remission.[3]

The remaining 70% of MDD patients will either respond without remission (about 20%) or not respond at all (50%).[3] Patients whose depressive disorder does not respond satisfactorily to appropriate therapy clearly have harder-to-treat depression.[4] In particular, patients with 2 or more failed attempts with adequate treatment are a common, challenging presentation to psychiatric and primary care clinics.[5] Expert consensus considers these patients to have treatment-resistant depression (TRD).[5–7]

Having 2 adequately dosed but unsuccessful treatment attempts in the same episode predicts a lower likelihood of remission with the next treatment.[5] Although the remission rate for depressed patients with a first or, if necessary, a second treatment attempt is approximately 30%, the likelihood of recovery with a subsequent medication treatment decreases to approximately 15%.[8] Patients with TRD incur the highest direct and indirect medical costs among those with MDD; these costs increase with the severity of the illness.[9]

Clinicians and patients need clear evidence to guide treatment decisions in TRD. The wide-ranging choices include both pharmacologic and nonpharmacologic interventions. Somatic treatments, which may involve use of a pharmacologic intervention or a device, are commonly considered for TRD patients. Given the decreasing efficacy of antidepressant medications following 2 unsuccessful treatments and their potentially serious side effects,[5,10] clinicians often look for alternative strategies for their TRD patients.

Repetitive transcranial magnetic stimulation (rTMS) is 1 possible option. Repetitive transcranial magnetic stimulation denotes a range of biologic, nonpharmacologic treatment devices that involve magnetic focal stimulation through the scalp. The current elicited by the electromagnetic coil stimulates nerve cells in the region of the brain involved in mood regulation and depression. The treatment may involve different types of coils, coil placements, and frequencies; the field has not yet agreed on one best rTMS method.[11] It can be delivered at either low or high frequency and administered in an office setting without anesthesia. Repetitive transcranial magnetic stimulation can be used as a primary treatment or as an augmentation strategy for an already existing antidepressant medication treatment and has been recommended as a consideration for use in acute-phase treatment by the American Psychiatric Association's *Practice Guideline* in MDD.[12] The US Food and Drug Administration (FDA) first approved a specific rTMS device in October 2008 "for the treatment of major depressive disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode."[13] In 2013, the FDA approved a second device for similar patients "who failed to achieve satisfactory improvement from previous anti-depressant medication treatment in the current episode,"[14] not limiting the approval to 1 prior episode failure.

The FDA approvals provide a mixed message about rTMS in TRD; they also reflect the evolving clinical research on rTMS, whose ideal methods for administration continue to be clarified. Repetitive transcranial magnetic stimulation is in many ways a "family" of treatments whose specifics are still being defined. Few insurers cover rTMS for depression in general, let alone TRD.[15] Nevertheless, many clinicians and TRD patients consider it a viable treatment option, and at least 1 advisory board recommends its use in TRD.[16] To provide an up-to-date synthesis of the available evidence, while acknowledging that rTMS is a general approach rather than a single entity, we report here on the efficacy of rTMS versus sham for patients with TRD.

METHOD

Data Sources and Searches

As part of a larger comparative effectiveness review on nonpharmacologic interventions for patients with TRD,[17] we reviewed evidence (from January 1, 1980, to November 18, 2010) addressing the efficacy of rTMS compared with sham control. This article updates our systematic searches for rTMS through March 20, 2013. We searched MEDLINE, EMBASE, the Cochrane Library, PsycINFO, and the International Pharmaceutical Abstracts. We used Medical Subject Headings (MeSH or MH) as search terms when available and key words when appropriate (Supplementary eTable 1). We combined terms for TRD, including the terms *refractory, resistant,* and *drug resistance.* We manually searched reference lists of relevant bibliographies, pertinent review articles, and letters to the editor and used SCOPUS to identify additional articles. Staff of the Agency for Healthcare Research and Quality (AHRQ)–supported Scientific Resource Center (SRC) contacted device manufacturers and invited them to submit dossiers, including citations, for review. In addition, the SRC conducted searches in clinical trial registries and

gray literature databases to detect unpublished studies (eg, meeting abstracts, white papers).[17]

Study Selection

Supplementary eTable 2 outlines study eligibility. We selected randomized controlled trials comparing rTMS with sham. Two independent reviewers assessed article abstracts for inclusion. All titles selected by at least 1 reviewer went on to full-text review by 2 independent reviewers. We applied a more detailed set of inclusion criteria at full-text review, requiring reasons for exclusion (eg, wrong design) and specifics on levels of treatment resistance.

Although we define TRD as 2 or more treatment failures, many trials involving populations with TRD did not use this definition when formulating their inclusion criteria. Some trials limited inclusion to individuals having 2 or more antidepressant treatment failures. Other trials provided analyses on depressed populations that combined subjects with 1 treatment failure and those with 2 or more treatment failures. Yet others reported on groups that most likely met our definition of TRD (eg, those described as "treatment resistant") but did not specify the number of treatment failures. A priori, we decided that excluding the latter 2 groups would not fairly reflect what was known about treatment for TRD populations.

Accordingly, we focused our synthesis on studies of patients who clearly met our definition of TRD: 2 or more prior antidepressant failures following adequate dose (as reported by the authors) and duration (at least 4 weeks). We called these tier 1 studies (Supplementary eTable 3). We also identified studies of patients with 1 or more antidepressant failures; we called these tier 2 studies. Trials that did not report the number of antidepressant failures but whose clinical context suggested a high probability of patients with 2 or more prior antidepressant failures are called tier 3 studies (eg, undefined treatment resistance).

The core patient population of interest was patients with MDD who met our definition of TRD. With support of a technical expert panel,[17] we also included studies in which the patient population included a "mix" of up to 20% of patients with bipolar disorder (ie, 80% or more of patients had only MDD), assuming that this small mix would not substantially alter outcomes seen with MDD-only populations.

Quality Assessment

We assessed the quality (internal validity or risk of bias) of all included studies using predefined criteria based on guidance in the AHRQ *Methods Guide for Comparative Effectiveness Reviews*[17] and the US Preventive Services Task Force definitions[18]; ratings can be good, fair, or poor. Two independent reviewers assigned quality ratings, resolving any disagreements by consensus discussion or by consulting with a third reviewer. In general terms, a "good" study met all criteria, has the least bias, and provides results considered to be valid. "Fair" studies presumably fulfilled all quality criteria but did not report their methods to an extent that answered all of our questions. A "poor" rating indicates significant bias.

Data Extraction

We used a structured, pilot-tested data abstraction form to ensure consistency of data abstraction.[17] Trained reviewers abstracted data on study design, baseline population characteristics, specifications of the intervention, and relevant outcome assessments for both efficacy and harms.

Data Synthesis and Analysis

Our analyses included only those studies assessed as fair or good quality, reported at least 1 key outcome (change in depressive severity, response, or remission), involved patients with a current major depressive episode, and were conducted within a TRD population aged 18 years or older.

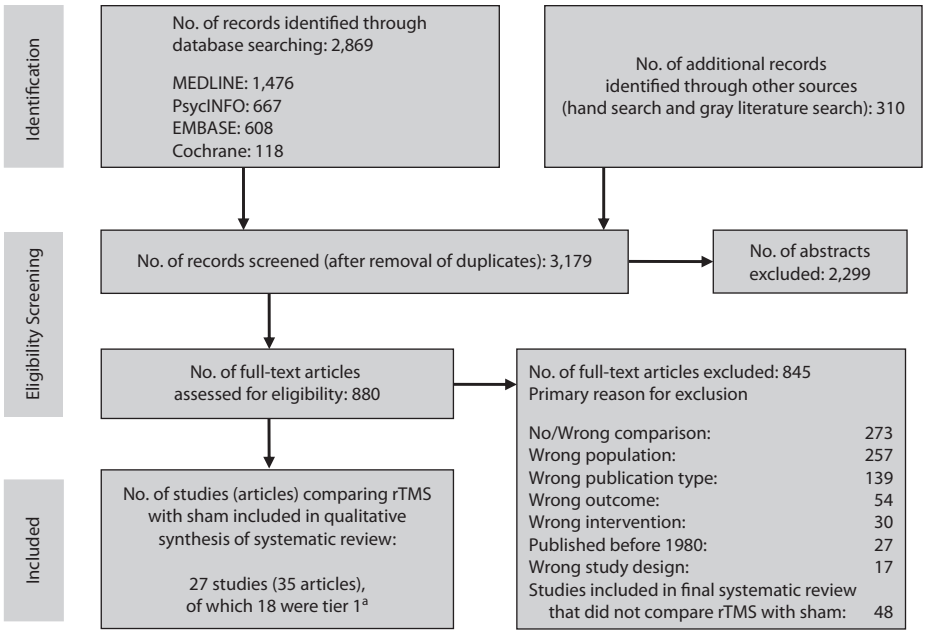
Our efficacy outcome measure of choice was the Hamilton Depression Rating Scale (HDRS).[19] If a study included a measure other than the HDRS (eg, Montgomery-Asberg Depression Rating Scale [MADRS], Beck Depression Inventory, or Quick Inventory of Depressive Symptomatology), we abstracted those data. We calculated change in depressive severity using the baseline and endpoint data when trials did not present that information. When possible, we used the number of patients randomized rather than only those included in the analysis to show the percentage achieving response (≥ 50% in depressive severity) or remission (as indicated by a score on a validated depressive tool, eg, ≤ 7 on the HDRS) to reflect a true intention-to-treat analysis.

If we found 3 or more studies with similar study populations, treatment interventions, and outcome assessments, we conducted quantitative analyses. We first pooled results for our tier 1 TRD studies. We then ran combined and stratified analyses by tiers to assess how treatment effects differed by tiers. For efficacy, we used 3 outcome measures:

1. The weighted mean difference of changes on the HDRS, which estimates the actual differences between intervention and sham in effect sizes.
2. The relative risk of being a responder (≥ 50% improvement from baseline) on the HDRS or the MADRS at study endpoint.
3. The relative risk of achieving remission on the HDRS or MADRS at study endpoint. The HDRS definition was ≤ 7 for the 17-item version and ≤ 10 for the 21-item version. For the MADRS, the remission definition was a score of ≤ 8. If a trial used a slightly different definition for remission, we noted this difference in the study's summary table and included the information in our analyses when, in the authors' judgment, it did not substantially differ from the above definitions.

For each meta-analysis, we conducted tests of heterogeneity (I^2 index and Cochran Q test) and applied both a random- and a fixed-effects model. To explore reasons for

Figure 1. PRISMA Flow Diagram



[a]The updated literature search added 3 studies (all tier 1).
Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

heterogeneity, we used metaregressions. We report the results from random effects models because, in all meta-analyses, the results from random- and fixed-effects models were very similar. If the relative risk was statistically significant, we calculated the number needed to treat (NNT) from the pooled relative risk when variations in baseline risks were small. We assessed publication bias using funnel plots, Egger regression intercept, and Kendall *S* statistic. Given the small number of trials in some of our meta-analyses, these tests have low sensitivity to detect publication bias.[20]

We evaluated the strength of evidence (SOE) based on the initial AHRQ guidance for grading SOE.[21] Although we provide additional evidence (tiers 2 and 3) for evaluating the outcomes in a TRD population (tier 1), our SOE grades consider tier 1 evidence only.

RESULTS

For our full review, we identified 3,179 citations through database and hand searching (Figure 1). For this article on rTMS interventions versus sham control, we included 35 published articles reporting on 27 trials involving all 3 tiers. For tier 1, we identified 18 trials of either good or fair quality: 13 MDD-only[22–34] and 5 MDD/bipolar mix studies.[35–39] Table 1 lists their characteristics, sorted first by diagnostic population involved (MDD-only or MDD/bipolar mix) and then by treatment strategy (whether rTMS is used as part of an augmentation strategy, a switch strategy, or a mixture of the 2). Data addressing the 3 primary outcomes are provided in the last 3 columns.

Of these 18 tier 1 trials, we rated 3 as good quality.[32,36,37] Sample sizes ranged from 12 to 74 subjects; study duration ranged from 1 week to 6 weeks (mean = 2.67). Nearly three-fourths of the 18 trials (13 studies) used an augmentation strategy[22–29,35–39]; others (all MDD only) used a switch (1 study)[31] or a mixed strategy (4 studies).[30,32–34] No study gave information for all 3 outcomes, so the total number of trials providing data for any 1 outcome was fewer than 18.

Seven of these 18 trials reported the mean number of antidepressant treatment failures (range, 3.2–6.5); the remaining 10 trials either did not provide information beyond their eligibility requirement for ≥ 2 antidepressant treatment failures or reported only that all patients had had at least 2 failures. Six trials required failure to be in the current episode (rather than lifetime), 5 with MDD only[22,24,27,30,33] and 1 with MDD/bipolar mix.[35] Of the 18 trials, all but 1 gave information on baseline depressive severity (HDRS or MADRS): severe to very severe in 15 trials and moderate in 1 trial. Key treatment parameters, including stimulus intensity, pulse frequency, and stimulus duration, differed across the intervention trials.

Efficacy of rTMS Versus Sham for Acute-Phase Treatment of TRD (tier 1)

Results from MDD-only and from MDD/bipolar mix studies were in the same direction and of similar magnitude. Results from combining these 2 populations did not substantially differ from MDD-only results, suggesting that combining these 2 populations was reasonable. Therefore, we report findings based on the combined data.

We excluded 1 trial[39] from our meta-analyses because an extensive, supportive social intervention for all treatment groups distinguished it from all other trials. This additional cointervention may have diminished the comparative efficacy of rTMS and sham stimulation, and it introduced

Table 1. Efficacy of rTMS Versus Sham: Tier 1 Trials

Study, Duration, Quality	Intervention Sample Size	Failed Trials, Mean (SD)	Baseline Depression, Mean (SD)	Change in Severity, Mean (SD)	Response, N (%)	Remission, N (%)
Population: MDD only; treatment strategy: augmentation						
Bakim, 2012[22,a] 6 wk Fair	rTMS 1 (n = 12) 80% MT at 20 Hz, 30 sessions rTMS 2 (n = 11) 110% MT at 20 Hz, 30 sessions Sham (n = 12)	NR	$HDRS_{17}$ rTMS 1: 23.08 (3.63) rTMS 2: 24.09 (2.77) Sham: 25.58 (3.82)	$HDRS_{17}$ rTMS 1: −12.91 (NR), $P < .01$ rTMS 2: −12.45 (NR), $P < .01$ Sham: −6.08 (NR), $P < .01$ rTMS 1 vs sham, $P = .03$ rTMS 2 vs sham, $P = .04$ rTMS 1 vs rTMS 2, $P = .86$	$HDRS_{17}$ rTMS 1: 10 (83.3) rTMS 2: 8 (72.7) Sham: 2 (16.7), $P < .01$ rTMS 1vs sham, $P < .01$ rTMS 2 vs sham, $P = .01$ rTMS 1vs. rTMS 2, $P = .64$	$HDRS_{17}$ rTMS 1: 3 (25) rTMS 2: 6 (54) Sham: 1 (8.3), $P = .04$ rTMS 1 vs sham, $P = .59$ rTMS 2 vs sham, $P = .03$ rTMS 1 vs rTMS 2, $P = .21$
Boutros et al, 2002[23,b] 2 wk Fair	rTMS (n = 12) High frequency, 10 sessions Sham (n = 9)	NR	$HDRS_{25}$ rTMS: 34.4 (10.1) Sham: 31.7 (4.9)	$HDRS_{25}$ rTMS: −11.75 Sham: −6.22 P = NS	$HDRS_{25}$ Response 1 rTMS: 7 (58.3) Sham: 2 (22.2), P = NR Response 2 rTMS: 3 (25.0) Sham: 2 (22.2), P = NR	NR
Garcia-Toro et al, 2001[24,a] 2 wk Fair	rTMS (n = 20) High frequency, 10 sessions Sham (n = 20)	NR	$HDRS_{21}$ rTMS: 27.11 (6.65) Sham: 25.6 (4.92)	$HDRS_{21}$ rTMS: −7.05 (5.66) Sham: −1.77 (3.78) $P = .003$	$HDRS_{21}$ rTMS: 5 (25) Sham: 1 (5), P = NR	NR
Garcia-Toro et al, 2006[25,b] 2 wk Fair	rTMS 1 (n = 10) High frequency plus low frequency, 10 sessions rTMS 2 (n = 10) Same as above, but with individually assessed location Sham (n = 10)	NR	$HDRS_{21}$ rTMS 1: 27.30 (4.97) rTMS 2: 25.00 (4.14) Sham: 25.10 (7.28)	$HDRS_{21}$ rTMS 1: −7.2 rTMS 2: −6.9 Sham: −1.5 rTMS 1 and rTMS 2 vs Sham $P = .048$	$HDRS_{21}$ rTMS 1: 2 (20.0) rTMS 2: 2 (20.0) Sham: 0 (0) P = NR	NR
Kauffmann et al, 2004[26,b] 2 wk Fair	rTMS (n = 7) Low frequency, 10 sessions Sham (n = 5)	NR	$HDRS_{21}$ rTMS: 21.86 (2.31) Sham: 18.20 (2.20)	$HDRS_{21}$ rTMS: −10.57 Sham: −6.31 P = NS	$HDRS_{21}$ rTMS: 4 (57) Sham: 2 (40) P = NR	$HDRS_{21}$ rTMS: 4 (57) Sham: 1 (20) P = NR
Padberg et al, 1999[27,a] Fair	rTMS 1 (n = 6) High frequency, 5 sessions rTMS 2 (n = 6) Low frequency, 0.3 Hz, left-DLPFC, 5 sessions Sham (n = 6)	rTMS 1: 4.0 (2.2) rTMS 2: 3.2 (0.8) Sham: 3.2 (1.2)	$HDRS_{21}$ rTMS 1: 30.2 (9.5) rTMS 2: 26.7 (9.4) Sham: 22.2 (8.8)	$HDRS_{21}$ rTMS 1: −1.7 rTMS 2: −5.2 Sham: −1.3 P = NS	NR	NR
Pallanti et al, 2010[28,b] 3 wk Fair	rTMS 1 (n = 20) Low then high frequency, 15 sessions rTMS 2 (n = 20) Low frequency, 15 sessions Sham (n = 20)	rTMS 1: 5.90 (1.48) rTMS 2: 6.50 (1.48) Sham: 5.95 (1.67)	$HDRS_{17}$ rTMS 1: 28.75 (6.01) rTMS 2: 27.95 (5.89) Sham: 29.05 (3.54)	NR	$HDRS_{17}$ rTMS 1: 4 (20) rTMS 2: 7 (35) Sham: 2 (10), P = NR NNT (95% CI) rTMS 1 vs sham 10.00 (3.13 to −8.39) rTMS 2 vs sham 4.00 (2.01 to 328.11)	rTMS 1: 2 (10) rTMS 2: 6 (30) Sham: 1 (5) $P = .064$ NNT (95% CI) rTMS 1 vs sham 20.00 (4.71 to −8.89) rTMS 2 vs sham 4.00 (2.12 to 36.23)

(continued)

Table 1 (continued). Efficacy of rTMS Versus Sham: Tier 1 Trials

Study, Duration, Quality	Intervention Sample Size	Failed Trials, Mean (SD)	Baseline Depression, Mean (SD)	Change in Severity, Mean (SD)	Response, N (%)	Remission, N (%)
Population: MDD only; treatment strategy: augmentation						
Zheng et al, 2010[29,b] 4 wk Fair	rTMS (n = 19) High frequency, 20 sessions Sham (n = 15)	NR	$HDRS_{17}$ rTMS: 24.6 (2.9) Sham: 24.6 (2.8)	$HDRS_{17}$ rTMS: −11.1 Sham: −1.7 *P* = NR	$HDRS_{17}$ rTMS: 12 (63.2) Sham: 1 (6.7) *P* = NR	NR
Population: MDD only; treatment strategy: mixed						
Blumberger, 2012[30,a] 3 wk Fair	rTMS 1 (n = 28) Bilateral, low frequency right, high frequency left rTMS, 15 sessions rTMS 2 (n = 24) Unilateral, high frequency left rTMS, 15 sessions Sham rTMS (n = 22)	NR	$HDRS_{17}$ rTMS 1: 25.1 (3.8) rTMS 2: 26.0 (3.3) Sham: 25.2 (2.8)	$HDRS_{17}$ rTMS 1: −9.8 (NR) rTMS 2: −6.4 (NR) Sham: −7.4 (NR) *P* = NR	$HDRS_{17}$ rTMS 1: 10 (38.5) rTMS 2: 1 (4.5) Sham: 2 (10) *P* = .006 rTMS 1 vs rTMS 2, *P* = .003 rTMS 1 vs sham, *P* = .022 rTMS 2 vs sham, *P* = 1.00	$HDRS_{17}$ rTMS 1: 9 (34.6) rTMS 2: 1 (4.5) Sham: 1 (5) *P* = .005 rTMS 1 vs rTMS 2, *P* = .002 rTMS 1 vs sham, *P* = .028 rTMS 2 vs sham, *P* = .48
Avery et al, 2006[32,b] 4 wk Good	rTMS (n = 35) High frequency, 15 sessions over 4 wk Sham (n = 33)	rTMS: 3.2 (2.44) Sham: 3.3 (1.72)	$HDRS_{17}$ rTMS: 23.5 (3.9) Sham: 23.5 (2.9)	$HDRS_{17}$ rTMS: −7.8 (7.8) Sham: −3.7 (6.3) *P* = .002	$HDRS_{17}$ rTMS: 11 (31.4) Sham: 2 (6.1) *P* = .008	$HDRS_{17}$ rTMS: 7 (20) Sham: 1 (3) *P* = .033
Fitzgerald, 2012[33,a] 3 wk Fair	rTMS 1 (n = 22) Bilateral: low frequency right side; high frequency left side, 15 sessions rTMS 2 (n = 24) Unilateral: high frequency left side, 15 sessions Sham (n = 17)	rTMS 1: 4.7 (3.1) rTMS 2: 5.5 (3.7) Sham: 4.9 (2.6)	$HDRS_{17}$ rTMS 1: 24.3 (3.6) rTMS 2: 23.7 (3.8) Sham: 22.9 (2.1)	$HDRS_{17}$ rTMS 1: −2.1 (NR) rTMS 2:−4.1 (NR) Sham: −0.2 (NR) rTMS 2 vs sham, *P* = .02 rTMS 1 vs sham, *P* = NS rTMS 1 vs rTMS 2, *P* = NS	$HDRS_{17}$ rTMS 1: 1 (4.54) rTMS 2: 0 (0) Sham: 0 (0) *P* = NR	NR
Pascual-Leone et al, 1996[34,b] Crossover trial, 1 wk Fair	rTMS (n = 17) High frequency, 5 sessions Sham (n = 17)	NR	NR	NR, *P* < .0005	NR	NR
Population: MDD only; treatment strategy: switch						
Holtzheimer et al, 2004[31,b] 2 wk Fair	rTMS (n = 7) High frequency rTMS, 10 sessions Sham rTMS (n = 8)	NR	$HDRS_{17}$ rTMS: 22.7 (5.3) Sham: 20.8 (6.3)	$HDRS_{17}$ rTMS: −8.1 Sham: −5.5 *P* = NS	$HDRS_{17}$ rTMS: 2 (28.6) Sham: 1 (14.3) *P* = NR	NR
Population: MDD and ≤ 20% bipolar disorder; treatment strategy: augmentation						
Bocchio-Chiavetto et al, 2008[35,a] Crossover: 1wk Fair	rTMS (n = 36) Low-frequency rTMS (n = 18), 5 sessions, or high frequency rTMS (n = 18), 5 sessions Sham (n = 15)	2.89 (NR)	$HDRS_{21}$ rTMS: 23.19 (5.12) Sham: 24.53 (4.79)	$HDRS_{21}$ rTMS: −5.69 Sham: −3.40 *P* = NR	NR	NR

(continued)

Table 1 (continued). Efficacy of rTMS Versus Sham: Tier 1 Trials

Study, Duration, Quality	Intervention Sample Size	Failed Trials, Mean (SD)	Baseline Depression, Mean (SD)	Change in Severity, Mean (SD)	Response, N (%)	Remission, N (%)
Population: MDD and ≤ 20% bipolar disorder; treatment strategy: augmentation						
Fitzgerald et al, 2003[36,b] 2 wk Good	rTMS 1 (n = 20) High frequency, 10 sessions rTMS 2 (n = 20) Low frequency, 10 sessions Sham (n = 20)	5.68 (3.40)	MADRS rTMS 1: 36.05 (7.55) rTMS 2: 37.70 (8.36) Sham: 35.75 (8.14)	MADRS rTMS 1: −5.25 rTMS 2: −5.5 Sham: −0.35 rTMS 1 vs sham, rTMS 2 vs sham, $P < .005$	MADRS Response 1 rTMS 1: 8 (40) rTMS 2: 7 (35) Sham: 2 (10), $P = .07$ Response 2, n (%) rTMS 1: 0 (0) rTMS 2: 1 (5) Sham: 0 (0), P = NR	NR
Fitzgerald et al, 2006[37,b] 6 wk Good	rTMS (n = 25) High-frequency rTMS up to 30 sessions plus low-frequency rTMS up to 30 sessions Sham (n = 25)	rTMS: 5.6 (3.1) Sham: 6.2 (3.0)	$HDRS_{17}$ rTMS: 22.5 (7.4) Sham: 19.8 (4.4)	$HDRS_{17}$ rTMS: −10.2 Sham: 1.1 $P < .001$	$HDRS_{17}$ rTMS: 13 (52) Sham: 2 (8) $P = .001$	$HDRS_{17}$ rTMS: 10 (40) Sham: 0 (0) $P = .001$
Su et al, 2005[38,b] 2 wk Fair	rTMS 1 (n = 11) High frequency (20 Hz), 10 sessions rTMS 2 (n = 11) High frequency (5 Hz), 10 sessions Sham (n = 11)	NR	$HDRS_{21}$ rTMS 1: 23.2 (7.5) rTMS 2: 26.5 (5.2) Sham: 22.7 (4.7)	$HDRS_{21}$ rTMS 1: −13.4 (4.9) rTMS 2: −14.2 (6.0) Sham: −3.7 (9.3) $P < .01$	$HDRS_{21}$ rTMS 1: 6 (60.0) rTMS 2: 6 (60.0) Sham: 1 (10.0) $P = .01$	$HDRS_{21}$ rTMS 1: 5 (50) rTMS 2: 5 (50) Sham: 0 (0) P = NR
Triggs et al, 2010[39,b] 2 wk Fair	rTMS 1 (n = 18) High frequency, 10 sessions rTMS 2 (n = 16) High frequency to the right prefrontal cortex, 10 sessions Sham 1 (n = 7), sham to left Sham 2 (n = 7), sham to right	NR	$HDRS_{24}$ rTMS 1: 28.2 (6.0) rTMS 2: 27.2 (4.8) Sham 1: 27.7 (3.5) Sham 2: 27.3 (2.7)	$HDRS_{24}$ rTMS 1: −8.4 rTMS 2: −13.5 Sham 1: −5.7 Sham 2: −13.9 $P = .14$	$HDRS_{24}$ rTMS 1: 4 (22.2) rTMS 2: 5 (31.3) Sham 1: 2 (28.6) Sham 2: 4 (57.1) P = NR	NR

[a]Study required failure in the current episode. [b]Study did not require failure in the current episode.

Abbreviations: DLPFC = dorsolateral prefrontal cortex, HDR_{17} = 17-item Hamilton Depression Rating Scale, $HDRS_{21}$ = 21-item Hamilton Depression Rating Scale, $HDRS_{24}$ = 24-item Hamilton Depression Rating Scale, $HDRS_{25}$ = 25-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MT = motor threshold, NNT = number needed to treat, NR = not reported, NS = not significant, rTMS = repetitive transcranial magnetic stimulation.

considerable heterogeneity to the analyses.

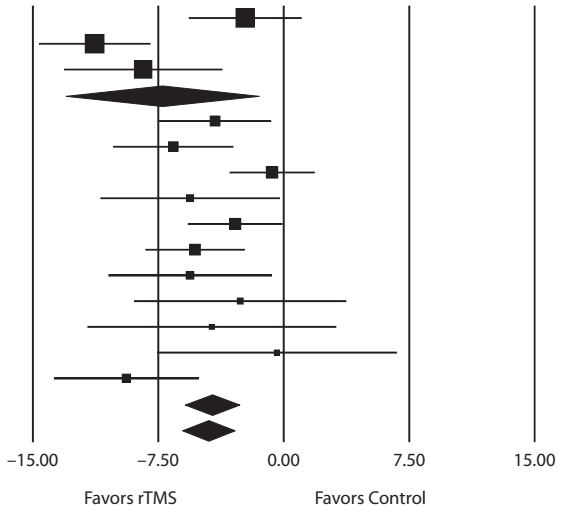
We made strength of evidence assessments for 3 outcomes: change in depressive severity, response rates, and remission rates. For changes in depressive severity, 17 trials of 1 to 6 weeks' duration (N = 686) provided a high strength of evidence that rTMS produces a greater decrease in depressive severity than sham (Supplementary eTable 4).[22–27,29–39] In the meta-analysis of 14 tier 1 trials (N = 564), rTMS produced a decrease in HDRS depressive severity of more than 4 points relative to sham (decrease in HDRS: −4.53; 95% CI, −6.11 to −2.96) (Figure 2).

For response rates, 15 rTMS trials of 2 to 6 weeks' duration (N = 643) provided a high strength of evidence that rTMS is more likely than sham to produce a response.[22–26,28–33,36–39] The raw mean response rate was 29% for intervention patients and 8% for control patients. A meta-analysis of 14 tier 1 studies (N = 605) showed that patients receiving rTMS were more than 3 times as likely to achieve a depressive response as patients receiving sham intervention (pooled relative risk for response = 3.38; 95% CI, 2.24 to 5.10) (Figure 3). Given that response rates in the control groups varied widely (most likely because of many small studies), we conservatively calculated the NNT for the mean response rate in the sham groups in the 5 largest trials (sample size from 63 to 87); this control response rate averaged 5% (lower than the overall mean sham rate of 8%). For a population with a control response rate of 5% and study duration between 2 and 6 weeks, the NNT to achieve 1 additional response is 9 (95% CI, 5 to 16). By comparison, if the true control response rate were 10%, the NNT would be 5 (95% CI, 2 to 8).

For remission rates, 7 tier 1 rTMS trials (N = 332) provided moderate strength of evidence that rTMS produces greater remission rates than sham.[22,26,28,30,32,37,38] The raw mean remission rate was 30% for intervention patients and 6% for sham

Figure 2. Mean Difference Meta-Analysis of Changes in Depressive Severity Comparing rTMS and Sham: Tier 1 Trials[a]

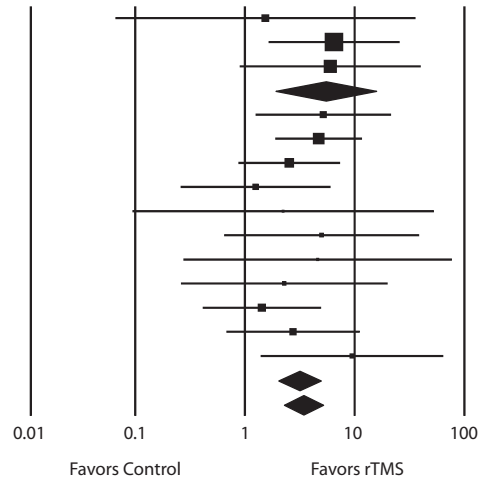
Group by Tier	Study	Difference in Means	Lower Limit	Upper Limit
MDD/bipolar-tier 1	Bocchio-Chiavetto et al, 2008[35]	−2.30	−5.70	1.10
MDD/bipolar-tier 1	Fitzgerald et al, 2006[37]	−11.30	−14.67	−7.93
MDD/bipolar-tier 1	Su et al, 2005[38]	−8.40	−13.16	−3.64
MDD/bipolar-tier 1		−7.30	−13.07	−1.53
MDD-tier 1	Avery et al, 2006[32]	−4.10	−7.48	−0.72
MDD-tier 1	Bakim et al, 2012[22]	−6.60	−10.22	−2.98
MDD-tier 1	Blumberger et al, 2012[30]	−0.70	−3.28	1.88
MDD-tier 1	Boutros et al, 2002[23]	−5.60	−11.00	−0.20
MDD-tier 1	Fitzgerald et al, 2012[33]	−2.90	−5.77	−0.03
MDD-tier 1	Garcia Toro et al, 2001[24]	−5.30	−8.30	−2.30
MDD-tier 1	Garcia Toro et al, 2006[25]	−5.60	−10.52	−0.68
MDD-tier 1	Holtzheimer et al, 2004[31]	−2.60	−8.98	3.78
MDD-tier 1	Kauffmann et al, 2004[26]	−4.30	−11.77	3.17
MDD-tier 1	Padberg et al, 1999[27]	−0.40	−7.59	6.79
MDD-tier 1	Zheng et al, 2010[29]	−9.40	−13.77	−5.03
MDD-tier 1		−4.31	−5.95	−2.68
Overall		−4.53	−6.11	−2.96



[a]Random-effects meta-analysis, $I^2 = 65\%$.
Abbreviations: MDD = major depressive disorder, rTMS = repetitive transcranial magnetic stimulation.

Figure 3. Relative Risk Meta-Analysis of Response Rates Comparing rTMS and Sham: Tier 1 Trials[a]

Group by Tier	Study	Risk Ratio	Lower Limit	Upper Limit	Response/Total, n/n rTMS	Response/Total, n/n Control
MDD/bipolar-tier 1	Fitzgerald et al, 2003[36]	1.54	0.07	36.11	1/40	0/20
MDD/bipolar-tier 1	Fitzgerald et al, 2006[37]	6.50	1.63	25.88	13/25	2/25
MDD/bipolar-tier 1	Su et al, 2005[38]	6.00	0.89	40.41	12/22	1/11
MDD/bipolar-tier 1		5.40	1.88	15.50		
MDD-tier 1	Avery et al, 2006[32]	5.19	1.24	21.66	11/35	2/33
MDD-tier 1	Bakim et al, 2012[22]	4.70	1.87	11.78	18/23	4/24
MDD-tier 1	Blumberger et al, 2012[30]	2.54	0.87	7.44	11/52	4/48
MDD-tier 1	Boutros et al, 2002[23]	1.25	0.26	6.07	3/12	2/10
MDD-tier 1	Fitzgerald et al, 2012[33]	2.23	0.09	53.22	1/46	0/34
MDD-tier 1	Garcia Toro et al, 2001[24]	5.00	0.64	39.06	5/20	1/20
MDD-tier 1	Garcia Toro et al, 2006[25]	4.61	0.27	77.76	5/21	1/11
MDD-tier 1	Holtzheimer et al, 2004[31]	2.29	0.26	20.13	2/7	1/8
MDD-tier 1	Kauffmann et al, 2004[26]	1.43	0.41	4.99	4/7	2/5
MDD-tier 1	Pallanti et al, 2010[28]	2.75	0.67	11.24	11/40	2/20
MDD-tier 1	Zheng et al, 2010[29]	9.47	1.38	64.90	12/19	1/15
MDD-tier 1		3.11	1.99	4.86		
Overall		3.38	2.24	5.10		



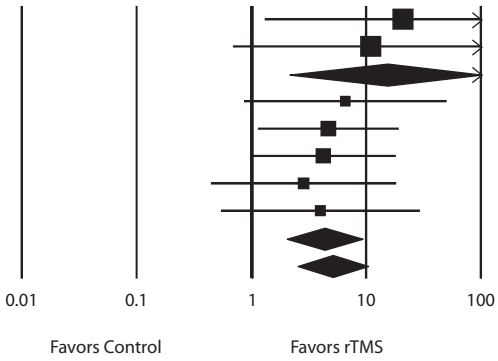
[a]Random-effects meta-analysis, $I^2 = 0\%$.
Abbreviations: MDD = major depressive disorder, rTMS = repetitive transcranial magnetic stimulation.

patients. Meta-analysis (all trials lasting between 2 and 6 weeks) showed that patients receiving rTMS were more than 5 times as likely to achieve remission as patients receiving sham control (pooled relative risk for remission = 5.07; 95% CI, 2.50 to 10.30) (Figure 4). In this population with a 6% spontaneous remission rate, the NNT would be 5 (95% CI, 2 to 11).

We considered how key clinical variables might affect our findings, but various data limitations prevented any firm conclusions. Given the small number and great variability of the tier 1 trials, we were unable to detect clear differences by treatment characteristics (ie, pharmacotherapy strategy, rTMS pulse frequency, stimulus intensity, stimulus duration, or treatment duration). Because nearly all patients were severely depressed, we could not detect any differences by severity of depression. Comparing effect sizes and CIs in the 3 studies that required TRD in the current episode with the effect sizes in trials that included patients with lifetime TRD suggested no differences; the small number of studies, however, prevented us from conducting a formal statistical test of no difference.

Figure 4. Relative Risk Meta-Analysis of Remission Rates Comparing rTMS and Sham: Tier 1 Trials[a]

Group by Tier	Study	Statistics for Each Study: Risk Ratio	Lower Limit	Upper Limit	Remission/Total, n/n: rTMS	Control
MDD/bipolar-tier 1	Fitzgerald et al, 2006[37]	21.00	1.30	339.66	11/26	1/26
MDD/bipolar-tier 1	Su et al, 2005[38]	11.00	0.68	176.83	6/12	1/12
MDD/bipolar-tier 1		15.19	2.13	108.47		
MDD-tier 1	Avery et al, 2006[32]	6.60	0.86	50.79	7/35	1/33
MDD-tier 1	Bakim et al, 2012[22]	4.70	1.13	19.45	9/23	2/24
MDD-tier 1	Blumberger et al, 2012[30]	4.23	0.98	18.29	10/52	2/44
MDD-tier 1	Kauffmann et al, 2004[26]	2.86	0.44	18.48	4/7	1/5
MDD-tier 1	Pallanti et al, 2010[28]	4.00	0.54	29.80	8/40	1/20
MDD-tier 1		4.31	2.02	9.20		
Overall		5.07	2.50	10.30		



[a]Random-effects meta-analysis, $I^2 = 0\%$.
Abbreviations: MDD = major depressive disorder, rTMS = repetitive transcranial magnetic stimulation.

We assessed whether date of publication affected the size of the treatment effect. We found a statistically significant decrease in treatment effect of 0.45 HDRS points with each subsequent year of publication over a 17-year period ($P < .0001$).

Figures 2, 3, and 4 also allow comparison of the MDD-only groups with the MDD/bipolar mix groups. Point estimates for MDD/bipolar mix patients tended to be higher than those for MDD-only. However, the CIs overlapped, suggesting no clear difference between effect sizes in these 2 sets of patient populations. Combining the 2 populations did not affect the directionality of estimates or substantially influence the magnitude of estimates; the combined results were consistent with our findings for the separate tier 1 syntheses.

Efficacy of rTMS Versus Sham for Acute-Phase Treatment of TRD (all tiers)

We assessed whether our findings differed if we included studies from all 3 tiers. Adding tier 2 provided 6 additional trials (Supplementary eTable 5); 4 were MDD-only studies (reported in 5 articles)[40–44] and 2 were MDD/bipolar mix studies.[45,46] Adding tier 3 gave 3 more trials; these were MDD/bipolar mix populations reporting only change in depressive severity[47–49] (Supplementary eTable 6).

Combining data from all 3 tiers produced results consistent with those from tier 1 alone but yielded more conservative point estimates and narrower CIs. The weighted mean difference in HDRS depressive severity was −4.81 (95% CI, −6.11 to −3.52). Because sample sizes of individual studies were small and responses to sham procedures varied in the small control groups, heterogeneity was high ($I^2 = 78\%$), and our estimates are uncertain with respect to the magnitude of changes on the HDRS.

Considering the additional studies reduced the intervention response rate slightly (to 26% from 29%) and increased the control response rate slightly (to 9% from 8%), the pooled relative risk indicated that patients receiving rTMS were more than twice as likely to respond than those receiving sham (pooled relative risk = 2.62; 95% CI, 1.93 to 3.56) (Supplementary eFigure 1); for a population with a control response rate of 9%, the NNT is 8 (95% CI, 5 to 13).

Remission rates also favored rTMS. Adding in the tier 2 and tier 3 trials decreased the intervention remission rate from 30% to 21%; the control remission rate remained at 6%. The pooled relative risk for remission was 2.76 (95% CI, 1.79 to 4.26) (Supplementary eFigure 2), which translates to a NNT of 10 (95% CI, 5 to 21) for a population with a control remission rate of 6%.

DISCUSSION

Repetitive transcranial magnetic stimulation was beneficial relative to patients receiving a sham procedure for all 3 outcomes—severity of depressive symptoms, response rate, and remission rate. For depressive severity (high strength of evidence), rTMS averaged a decrease in depressive severity measured by the HDRS of more than 4 points relative to sham control; this change meets the minimum threshold of the 3-point HDRS difference that is considered clinically meaningful.[50] Response rates (which averaged 29%) were greater with rTMS than with sham (high strength of evidence); those receiving rTMS were more than 3 times as likely to respond. The NNT ranged between 9 (assuming a spontaneous response rate of 5%) and 5 (assuming a spontaneous response rate of 10%); as a comparison, the NNT for atypical antipsychotics in TRD is approximately 9.[51] Finally, rTMS was also more likely to produce remission than sham (moderate strength of evidence); patients receiving rTMS had an average remission rate of 30% and were more than 5 times as likely to achieve remission. These response and remission rates are consistent with, if slightly more conservative than, rates seen with pharmacologic antidepressants following 2 antidepressant failures (38%–39% and 22%–27%, respectively).[17] Further,

the clinically meaningful benefit persists even when the stringent inclusion criteria requiring MDD and 2 treatment failures are relaxed.

A recent systematic review that considered the role of rTMS in TRD reported NNTs for remission similar to ours (an NNT of 5, assuming a spontaneous remission rate of 6%): 6 for a sample with a 9% spontaneous response rate, and 7 for a sample with a 6% spontaneous remission rate.[52] Our analyses added 6 tier 1 studies published since then and applied a stricter and more current definition of TRD (2 or more failed antidepressants of adequate dose and duration, not just 1 or more failed antidepressant trials). Our approach thus represents treatment strategies more reflective of current practice. Furthermore, we could distinguish between study populations with MDD only and those with samples of at least 80% MDD patients and no more than 20% bipolar patients. Combining these 2 groups did not substantially affect our overall results, although in each case the MDD-only group had more precise and conservative estimates of benefit.

Our results also extend results from recent systematic reviews that have underscored the efficacy of rTMS as a general treatment for MDD (not just TRD). Compared with placebo, the response and remission rates for low-frequency rTMS were, respectively, 38.2% versus 15.1% ($P = .007$) and 34.6% versus 9.7% ($P < .001$)[53]; for high frequency rTMS, the rates were, respectively, 29.3% versus 10.4% ($P < .0001$) and 18.6% versus 5% ($P < .0001$)[11]; and for bilateral rTMS, they were 24.7% versus 6.8% ($P < .0001$) and 19% versus 2.6% ($P < .006$).[54] Our results mirror these earlier findings, considering all tiers for response rates (26%) and remission rates (21%). Each of these 3 reviews had produced NNTs between 5 and 7; these estimates are consistent with our NNT of 7 for response (all tiers) but slightly more beneficial than our NNT of 10 for remission (all tiers). Taken together, these findings suggest benefit for populations that have been stringently defined as TRD and for those including patients likely to have TRD.

Accordingly, our analyses add to the evidence base supporting benefit for rTMS as a general class of treatments for patients with TRD. Initial FDA approval for rTMS involved a specific treatment device with an indication for patients who have not responded to 1 adequate trial of antidepressant medication. The evidence for the regulatory approval involved a secondary data analysis of a trial of patients with nonpsychotic MDD; the number of prior treatment failures was the strongest predictor for positive response to acute treatment with TMS.[55] In that analysis using change in MADRS as the primary outcome, patients with 1 adequate antidepressant trial (N = 164) had a significantly greater change from baseline depressive severity than the sham group, whereas those who failed 2 to 4 adequate trials (N = 137) could not be distinguished from the sham group.

In contrast, our analyses of rTMS trials involving a variety of treatment parameters for patients having failed 2 or more antidepressant trials showed an rTMS benefit in depressive severity (N = 564, 14 trials in meta-analysis) averaging more than 4 points (a clinically meaningful difference). Moreover, benefits for rTMS versus sham were greater for both rates of response (N = 605, 14 studies) and remission (N = 332, 7 studies). These findings are more in line with information supplied for the second rTMS device for MDD with FDA approval, which did not restrict the indication to patients having failed a single treatment.[14]

Decisions to use an effective intervention must always be weighed by considerations of harms. Patients tend to tolerate rTMS well.[56,57] The greatest concern focuses on the increased risk of seizures with rTMS[58]; the risk of seizure in individuals with no prior history of seizure disorder may not be greater than that associated with oral antidepressant treatment; the incidence is approximately 0.01% among people with no prior history.[59] Our earlier work has shown low or insufficient evidence addressing this issue.[17]

The available data had some limitations. The adequacy of sham controls in earlier rTMS studies has been a persistent concern. In earlier studies, patients were likely to be able to distinguish between the sham and intervention arms and hence might favor rTMS.[44,60] Such an effect might bias results in favor of rTMS in TRD studies. Consequently, more recent trials have made greater efforts to ensure high-quality sham procedures; this improvement is reflected in our findings of a statistically significant decrease in treatment effect of 0.45 HDRS points per year.

Even with this decrease, however, more recent trials remained strongly positive for rTMS benefit. Our response and remission relative risks (3.38 and 5.07, respectively) were consistent with the 3 most recent trial results (ranging from 2.23 to 4.70 and from 4.23 to 4.70, respectively); they were also similar to results from the George et al clinical trial,[44] a tier 2 MDD-only study with most likely the best sham control to date (4.6 and 4.2, respectively). Finally, a recent meta-analysis[61] of the blinding integrity of sham-controlled rTMS trials for MDD found that commonly used sham methods appear to be adequate for concealing treatment allocation.

In addition, treatment lengths ranged from 1 to 6 weeks (mean = 2.67). Given the few tier 1 trials, we were unable to detect clear differences by rTMS frequency. However, the 4 trials with the 2 longest treatment periods (4 weeks[29,32] or 6 weeks[22,37]) each had response and remission relative risks (ranging from 4.70 to 9.47 and from 4.70 to 21.0, respectively) that exceeded our meta-analytic results. This finding suggests that our results may underestimate rTMS effects. Further, the average number of sessions in our sample (12.75) is equivalent to the 12 to 13 sessions considered standard by other reviews.[11,53,54]

Ideally, all studies we meta-analyzed would have used the 17-item HDRS version; however, 7 did not. Sensitivity analyses including only the 17-item versions did not change our estimates.

Also, given the limited amount of relevant data in tier 1 trials, we could not explore how other potential effect modifiers such as pharmacotherapy strategy, severity of

depression, and treatment resistance in the current episode (vs in previous episodes) might affect outcomes.

Publication bias is a concern for any systematic review. Although we conducted comprehensive searches of the gray literature, we cannot determine conclusively whether we missed any relevant unpublished studies. Statistical tests and funnel plots did not indicate publication bias in our meta-analyses. However, we acknowledge that the power and reliability of such tests are low. To assess the potential impact of publication bias on the results of our meta-analyses, we conducted fail-safe n tests. Findings showed that for all of our meta-analyses it would require more than 20 unpublished studies to change statistically significant findings to nonstatistically significant results.

We uncovered no information about maintenance therapy following completion of rTMS treatment for TRD. No studies assessed outcome beyond a week following the final session of rTMS (or sham) treatment, so no data were available to assess the persistence of the positive effect in this population.

Finally, our results reflect an assessment of the degree to which, *in general*, rTMS interventions can offer benefit to patients with TRD. Repetitive transcranial magnetic stimulation is an emerging field; in its current stage of development, it is best understood as a general class of treatments whose most effective elements are still being actively researched. The limited number of studies to date prevented us from performing subgroup analyses to determine how specific treatment parameters affect outcomes for different types of TRD patients. Accordingly, our results indicate an overall effect for the general class of rTMS interventions and represent an important first step toward defining the role of rTMS in TRD.

CONCLUSIONS AND FUTURE DIRECTIONS

The use of nonpharmacologic interventions in TRD patients is a key clinical issue; clinicians and researchers are only beginning to identify the role of rTMS for this hard-to-treat population. For MDD patients with 2 or more antidepressant treatment failures, rTMS is a reasonable, effective consideration. Further research to clarify rTMS use in TRD patients should reflect improved trial designs and, thus, help to clarify which key treatment parameters may be relevant to TRD. In particular, investigators need to apply a consistent definition of TRD; carefully delineate the number of adequate pharmacologic failures in the *current depressive episode*; clarify standard parameters of optimal treatment, including stimulus intensity, pulse frequency, stimulus duration, and length of treatment; and specify whether rTMS is used as augmentation or as a switch strategy. Comparative effectiveness designs, which could involve direct comparisons of varying rTMS parameters and of rTMS with other TRD treatments (eg, electroconvulsive therapy or combination medications) would help identify these optimal parameters. Longer trials or follow-up periods will help to clarify whether treatment response is maintained over a period longer than just a few weeks.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, while the US Food and Drug Administration has approved Neurostar "for the treatment of major depressive disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode," findings in this article relate to rTMS devices (including Neurostar) for patients with 2 or more prior antidepressant failures.
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Role of the sponsor: The AHRQ participated in formulating the key questions and reviewed and commented on planned methods for the larger comparative effectiveness review. The AHRQ had no role in study selection, quality ratings, strength of evidence grades, or interpretation and synthesis of the evidence, although AHRQ staff reviewed interim and final evidence reports and oversaw distribution of these for external peer review by outside experts. The authors of this report are responsible for its content.
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1. In the studies in this meta-analysis, patients whose major depressive disorder (MDD) was deemed treatment-resistant if they had had 2 or more failed antidepressant trials, despite adequate dose and duration, received repetitive transcranial magnetic stimulation (rTMS) either alone or as augmentation. In this pooled population, depressive severity per the Hamilton Depression Rating Scale (HDRS) scores ___.

a. Decreased by a clinically meaningful amount

b. Decreased slightly but not meaningfully

c. Increased by nearly 4 points

d. Did not change

2. The mean remission rate among patients receiving rTMS across all of the studies in the meta-analysis ___.

a. Was the same as the remission rate for those receiving sham treatment

b. Was more than 5 times greater than the remission rate for those receiving sham treatment

c. Was less than the remission rate for those receiving sham treatment

3. The greatest safety concern about rTMS is the risk of seizures. Among people without a history of seizures, the incidence with rTMS is approximately 0.01%.

a. True

b. False

4. Your patient, Ms A, has had an episode of severe MDD for 18 weeks; she has not had any unusual life circumstances. She sought treatment after 6 weeks, and you have tried 2 antidepressants from different classes, titrated up to high doses, for 6 weeks each. She had some response to the second agent and also started psychotherapy 4 weeks ago. However, her HDRS score still indicates severe depression. What information should you give her about rTMS?

a. Studies have shown efficacy of rTMS in patients with treatment-resistant depression, but only in mild to moderate, not severe, MDD

b. rTMS seems to be no more effective for MDD than sham treatment, and we should consider other alternatives

c. If you might want to try rTMS, let's first check into costs and insurance coverage for the types that are available

d. Research has now clarified the ideal parameters of rTMS treatment, including stimulus intensity, pulse frequency, and number of sessions

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Supplementary Material

Article Title: Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis

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List of Supplementary Material for the article

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Supplementary eTable 1.

Treatment Resistant Depression Nonpharmacologic Interventions Database Search

TRD Search 06.23.09

Search	Most Recent Queries	Result
#1	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh]	110342
#2	Search #1 Limits: Entrez Date from 1980/01/01, Humans, English, All Adult: 19+ years	56274
#3	Search #2 Limits: Editorial, Letter, Case Reports	7200
#5	Search "Case Control Studies"[Mesh]	421177
#6	Search #2 AND #5	3156
#7	Search #3 OR #6	10272
#8	Search #2 NOT #7	**46002**
	Depression articles limited to English, Human, and Adults, with no editorials, letters, case reports or case-control studies.	
#9	Search "Socioenvironmental Therapy"[Mesh] OR "interpersonal psychotherapy"[tw] OR "ipt"[tw] OR "psychotherapy"[mesh] OR "Cognitive Therapy"[Mesh] OR "cognitive behavioral therapy"[tw] OR "cbt"[tw]	123383
#10	Search #8 AND #9	2910
#11	Search "Drug Resistance"[Mesh] OR refractory[tw] OR resistant[tw]	379438
#12	Search #10 AND #11	**48**
	48 Psychotherapy/CBT/Depression articles limited to the "refractory" terms.	
#13	Search "Electroconvulsive Therapy"[Mesh] OR "ect"[tw] OR "electroconvulsive therapy"[tw]	10514
#14	Search #8 AND #13	1112
#16	Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh] **These are the terms used for RCTs.**	392864
#17	Search #14 AND #16	203
	There are 203 RCTs about Depression and ECT.	
#18	Search "Longitudinal Studies"[Mesh] OR "Comparative Study "[Publication Type]) OR "Cohort Studies"[Mesh] OR "observational studies"[tw]	1992678
#19	Search #14 AND #18	361
	There are 361 "observational studies" about Depression and ECT.	

#20	Search #17 OR #19	**447**
	Combining the RCTs and Observational studies for the ECT literature here.	
#21	Search "Transcranial Magnetic Stimulation"[Mesh] OR "(r)tms"[tw]	2864
#22	Search #8 AND #21	**141**
	141 TMS articles.	
#23	Search "Vagus Nerve Stimulation"[Mesh] OR "vagus nerve stimulation"[tw]	808
#24	Search #8 AND #23	**37**
	37 VNS articles.	
#25	Search #12 OR #20 OR #22 OR #24	**649**
	Combining all results for the main search here: Psychotherapy, ECT, TMS, and VNS.	
	Final number of records after duplicates removed	**630**

A search with analogous terms was performed in the following databases:

EMBASE = **269 (159 after duplicates removed)**
PsycINFO= **422 (296 after duplicates removed)**
Cochrane = 6 (no duplicates found)
EndNote file for the main search = 1346 (1074 after duplicates removed)

TRD Update Search 11.18.2010

Search	Most Recent Queries	Result
#1	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh]	120871
#2	Search ((#1) AND "2009/04/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	9152
#3	Search #2 Limits: Editorial, Letter, Case Reports	909
#4	Search "Case Control Studies"[Mesh]	476252
#5	Search #2 AND #4	558
#6	Search #3 OR #5	1460
#7	Search #2 NOT #6	7692
#8	Search "Socioenvironmental Therapy"[Mesh] OR "interpersonal psychotherapy"[tw] OR "ipt"[tw] OR "psychotherapy"[mesh] OR "Cognitive Therapy"[Mesh] OR "cognitive behavioral therapy"[tw] OR "cbt"[tw]	131504
#9	Search #7 AND #8	758

#10	Search "Drug Resistance"[Mesh] OR refractory[tw] OR resistant[tw]	414955
#11	Search #9 AND #10	25
#12	Search "Electroconvulsive Therapy"[Mesh] OR "ect"[tw] OR "electroconvulsive therapy"[tw]	11003
#13	Search #2 AND #12	149
#14	Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh]	431969
#15	Search #13 AND #14	21
#16	Search "Longitudinal Studies"[Mesh] OR "Comparative Study "[Publication Type]) OR "Cohort Studies"[Mesh] OR "observational studies"[tw]	2109685
#17	Search #13 AND #16	27
#18	Search #15 OR #17	37
#19	Search "Transcranial Magnetic Stimulation"[Mesh] OR "(r)tms"[tw]	3733
#20	Search #2 AND #19	78
#21	Search "Vagus Nerve Stimulation"[Mesh] OR "vagus nerve stimulation"[tw]	988
#22	Search #2 AND #21	18
#23	Search #22 OR #20 OR #18 OR #11	143
#24	Search #23 Limits: Humans, English, All Adult: 19+ years Sort by: PublicationDate	77
#25	Search #23	143

A search with analogous terms was performed in the following databases:

PubMed 76 (77 before duplicates removed)

EMBASE 80 (187 before duplicates removed)

PsycINFO 170 (211 before duplicates removed)

The Cochrane Library 26 (27 before duplicates removed)

EndNote file for the Update Search = 352 (before being added to main database and duplicates removed)

TRD Update Search

20 March 2013

PubMed:

Search	Query	Items found
#1	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh]	139331
#2	Search (#1) AND ("2011/01/01"[Date - Entrez] : "3000"[Date - Entrez])	13415
#3	Search (#1) AND ("2011/01/01"[Date - Entrez] : "3000"[Date - Entrez]) Filters: Humans	12815

#4	Search (#1) AND ("2011/01/01"[Date - Entrez] : "3000"[Date - Entrez]) Filters: Humans; English	11832
#5	Search (#1) AND ("2011/01/01"[Date - Entrez] : "3000"[Date - Entrez]) Filters: Humans; English; Adult: 19+ years	8337
#6	Search "Transcranial Magnetic Stimulation"[Mesh] OR "rTMS"[tiab]	6014
#7	Search (#5) AND #6	61
#8	Search "Electroconvulsive Therapy"[Mesh] OR "ECT"[tiab] OR "electroconvulsive therapy"[tiab]	12042
#9	Search (#5) AND #8	138
#10	Search "Vagus Nerve Stimulation"[Mesh] OR "vagus nerve stimulation"[tiab] OR "VNS"[tiab]	1710
#11	Search (#5) AND #10	7
#12	Search (#7) AND #9	8
#13	Search (#7) AND #11	0
#14	Search (#9) AND #11	2
#15	Search ((#7) OR #9) OR #11	196

PubMed (rTMS):

Search	Query	Items found
#1	Search "Transcranial Magnetic Stimulation"[Mesh] OR "rTMS"[tiab]	6014
#2	Search (#1) AND ("2011/01/01"[Date - Entrez] : "3000"[Date - Entrez])	1464
#3	Search (#1) AND ("2011/01/01"[Date - Entrez] : "3000"[Date - Entrez]) Filters: Humans	1212
#4	Search (#1) AND ("2011/01/01"[Date - Entrez] : "3000"[Date - Entrez]) Filters: Humans; English	1165
#5	Search (#1) AND ("2011/01/01"[Date - Entrez] : "3000"[Date - Entrez]) Filters: Humans; English; Adult: 19+ years	874
#6	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh]	139331
#7	Search (#5) AND #6	61

Cochrane Library

Search	Query	Items found
#1	"Depression"[Mesh] OR "Depressive Disorder"[Mesh], from 2011	2286
#2	"Transcranial Magnetic Stimulation"[Mesh] or "rTMS"[tiab]	1074
#3	(#1 AND #2)	41
#4	"Electroconvulsive Therapy"[Mesh] OR "electroconvulsive therapy"[tiab]	783
#5	(#1 AND #4)	30
#6	"Vagus Nerve Stimulation"[Mesh] OR "vagus nerve"[tiab]	403
#7	(#1 AND #6)	10
#8	(#3 OR #5 OR #7)	77
#9	"Humans"[Mesh] AND "Adult"[Mesh]	244469
#10	(#8 AND #9)	43
#11	"tinnitus"[ti]	979
#12	(#10 AND NOT #11)	35

PsycINFO:

Search	Query	Items Found
S1	DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Treatment Resistant Depression"	(82355)
S2	DE "Electroconvulsive Shock Therapy"	(4808)
S3	(S1 and S2)	(1853)
S4	DE "Transcranial Magnetic Stimulation"	(3229)
S5	S1 AND S4	(509)
S6	(DE "Deep Brain Stimulation" OR DE "Electrical Stimulation") AND (DE "Vagus Nerve")	(142)
S7	"vagus nerve stimulation"	(415)

S8	S6 OR S7	(449)
S9	S1 AND S8	(165)
S10	S3 OR S5 OR S9	(2402)
S11	S10	(130)

Embase:

Search	Query	Items Found
#1	'major depression'/exp	28832
#2	'electroconvulsive therapy'/exp	16457
#3	'vagus nerve stimulation'/exp	6456
#4	'transcranial magnetic stimulation'/exp	10378
#5	#2 OR #3 OR #4	32260
#6	#1 AND #5	1973
#7	#6 AND [english]/lim AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND ([embase]/lim OR [embase classic]/lim) AND [2011-2013]/py	187

Supplementary eTable 2. Study Outcomes and Eligibility

Outcomes	Study Eligibility Criteria (Inclusion and Exclusion Criteria)
Outcomes • Change in depressive severity • Response • Remission **Measurement Scales** • Hamilton Rating Scale for Depression Scale (HAM-D) • Montgomery-Åsberg Depression Rating Scale (MADRS) • Beck Depression Inventory (BDI) • Quick Inventory of Depressive Symptomatology (QIDS) • Clinical Global Impression (CGI) • Other relevant scales if none of the above is reported (e.g., Patient Health Questionnaire [PHQ-9])	**Study design** RCTs of rTMS vs. placebo or sham Good- or fair-quality meta-analyses **Minimum study duration** Any duration **Sample size** No minimum **Treatment Resistant Depression** • Defined as MDD that has not recovered following two or more adequate antidepressant medication treatments

Supplementary eTable 3. Study population classification

Tier 1	Patients with ≥ 2 failures of adequate antidepressant treatment
Tier 2	Patients with ≥ 1 failure of adequate antidepressant treatment
Tier 3	Patients referred for ECT or undefined treatment resistance

Supplementary eTable 4. Summary of findings on RCT vs. sham for adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 studies

Comparison	Outcome	Number of Subjects; Studies	Strength of Evidence[1]	Findings[2]
rTMS vs. sham	Change in depressive severity	686; 17	High	9 trials (3 good, 6 fair): rTMS had a significantly greater decrease in depressive severity than sham. 4 fair trials: rTMS had nonsignificantly greater decrease in depressive severity than sham. 3 fair trials: rTMS had greater decrease than sham but significance NR. 1 fair trial: rTMS did not significantly differ from sham.
rTMS vs. sham	Response rate	643; 15	High	6 trials (3 good, 3 fair): rTMS had a significantly higher response rate than sham. 1 fair trial: rTMS had a nonsignificantly higher response rate than sham. 7 fair trials: rTMS had a higher response rate than sham, but significance NR. 1 fair trial: rTMS did not clearly differ from sham, but significance NR.
rTMS vs. sham	Remission rate	332; 7	Moderate	3 trials (2 good, 1 fair): rTMS had significantly greater remission rate than sham. 2 fair trials: rTMS had a greater remission rate than sham but significance NR. 2 fair trials: rTMS had a nonsignificantly higher remission rate than sham.

NR, not reported; rTMS, repetitive transcranial magnetic stimulation; vs., versus.

[1]Strength of evidence is based on guidance provided in the AHRQ *Methods Guide for Comparative EffectivenessReviews(18)*.
[2]Good and fair designations relate to quality ratings for each study.

Supplementary eTable 5. Efficacy of rTMS versus Sham: Tier 2

Author, Year **Duration** **Quality**	**Intervention** **Sample Size**	**Failed Trials** Mean (SD)	**Baseline Depression** Mean (SD)	**Change in Severity** Mean (SD)	**Response** N (%)	**Remission** N (%)
Population: MDD only; Treatment strategy: Augment						
None						
Population : MDD Only ; Treatment strategy : Mixed						
None						
Population: MDD Only; Treatment Strategy: Switch						
George et al., 2010(41)[b] Up to 6 weeks, mITT Good	rTMS (n = 92) High frequency, 15 sessions Sham (n = 98) *mITT (N randomized = 199)	Current/lifetime rTMS: 1.62/3.34 Sham: 1.41/3.28	HAM-D_{24} rTMS: 26.3 (5.0) Sham: 26.5 (4.8)	HAM-D_{24} At 3 weeks Change, mean (SD) rTMS**: -4.7 Sham**: -3.1 **observed rTMS n = 83 Sham n = 91 95% CI effect estimate (adjusted) -4.23 to 0.10, P = 0.06	HAM-D_{24} rTMS*: 14 (15.2) Sham*: 5 (5.1) OR, 4.6 (95% CI, 1.47-14.42)	HAM-D_{24} rTMS*: 13 (14.1) Sham*: 5 (5.1) OR, 4.18 (95% CI, 1.32-13.24)
Manes et al., 2001(37) and Moser et al., 2002(38)[b] 1 week, all reported patients included in analysis Fair	rTMS (n = 10) High frequency, 5 sessions Sham (n = 10)	rTMS: 4 (2.3) Sham: 4 (1.2)	HAM-D (NR) rTMS: 22.7 (5.2) Sham: 22.7 (7.1)	HAM-D (NR) rTMS: -9 Sham: -6.5 P >0.66	HAM-D (NR) rTMS: 3 (30) Sham: 3 (30) P = NS	HAM-D (NR) rTMS: 2 (20) Sham: 2 (20) P = NS

Author, Year **Duration** **Quality**	**Intervention** **Sample Size**	**Failed Trials** Mean (SD)	**Baseline Depression** Mean (SD)	**Change in Severity** Mean (SD)	**Response** N (%)	**Remission** N (%)
Stern et al., 2007(39)[a] 2 weeks, all reported patients included in analysis Fair	rTMS -1(n = 10) High frequency,10 sessions rTMS -2(n = 10) Low frequency (1 Hz), Left-DLPFC, 10 sessions rTMS-3 (n = 10) Low frequency, 10 sessions Sham (n = 15)	NR	HAM-D_{21} rTMS-1: 27.8 (3.2) rTMS-2: 27.6 (3.9) rTMS-3: 27.9 (3.8) Sham: 27.4 (2.9)	HAM-D_{21} rTMS-1: -12.7 rTMS-2: 0.0 rTMS-3: -12.1 Sham: -0.7 rTMS-1 > rTMS-2 + sham and rTMS > rTMS-2 + sham, P < 0.0005	HAM-D_{21} rTMS-1: 5 (50) rTMS-2: 0 (0) rTMS-3: 5 (50) Sham: 0 (0) P = NR	HAM-D_{21} rTMS-1: 3 (30) rTMS -2: 0 (0) rTMS -3: 1 (10) Sham: 0 (0) P = NR
O'Reardon, 2007(40)[b] 6 weeks; at week 4, patients not responding left study with LOCF, mITT Good	rTMS (n = 165) High frequency, up to 30 sessions Sham (n = 160)	rTMS: 1.6 Sham: 1.6	HAM-D_{17} rTMS: 22.6 (3.3) Sham: 22.9 (3.5)	HAM-D_{17} rTMS*:-5.5 Sham*:-3.3 P = 0.005 *Results based on rTMS: n = 155 Sham: n = 146	HAM-D_{17} rTMS: 38 (24.5) Sham: 20 (13.7) P < 0.05	HAM-D_{17} rTMS: 24 (15.5) Sham: 13 (8.9) P = 0.065
Population: MDD and ≤ 20 percent bipolar disorder; Treatment strategy: Augment						
None						
Population: MDD and ≤ 20 percent bipolar disorder; Treatment strategy: Mixed						
Bretlau et al., 2008(43)[a] 3 weeks, mITT Fair	rTMS (n = 25) High frequency, 15 sessions over 3 weeks Sham (n = 24) 20 mg escitalopram	2.89 (NR)	HAM-D_{21} rTMS: 23.19 (5.12) Sham: 24.53 (4.79)	HAM-D_{21} rTMS: -5.69 Sham: -3.40 *P* = NR	NR	NR
Population: MDD and ≤ 20 percent bipolar disorder; Treatment strategy: Switch						

Author, Year **Duration** **Quality**	**Intervention** **Sample Size**	**Failed Trials** Mean (SD)	**Baseline Depression** Mean (SD)	**Change in Severity** Mean (SD)	**Response** N (%)	**Remission** N (%)
Berman et al., 2000(42)[b] 2 weeks Fair	rTMS (n = 10) High frequency, 10 sessions Sham (n = 10)	rTMS: 5 Sham: 3.5 (plus 1 failed augmentation medication each)	$HAM\text{-}D_{25}$ rTMS: 37.1 Sham: 37.3	$HAM\text{-}D_{25}$ rTMS: -14.0 (3.7) Sham: -0.2 (4.1) P < 0.01 *adjusted mean decreases based on best fit slopes	rTMS: 1 (10) Sham: 0 (0) P = 0.09	NR

Abbreviations: DLPFC, dorsolateral prefrontal cortex; ; $HAM\text{-}D_{17}$, 17-item Hamilton Depression Scale; $HAM\text{-}D_{21}$, 21-item Hamilton Depression Scale; $HAM\text{-}D_{25}$, 25-item Hamilton Depression Scale; Hz, hertz; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; mg/d, milligram per day; MT, motor threshold; n, number; NR, not reported; NS, not significant; *P*, p-value; pts, patients; pps, pulses per session; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; txt(s), treatment(s); vs., versus.

[a]Study required failure in the current episode.

[b]Study did not require failure in the current episode.

Supplementary eTable 6. Efficacy of rTMS versus Sham: Tier 3

Author, Year **Duration** **Quality**	**Intervention** **Sample Size**	**Failed Trials** Mean (SD) **Bipolar diagnosis (%)**	**Baseline Depression** Mean (SD)	**Change in Severity** Mean (SD)	**Response** N (%)	**Remission** N (%)
Population: MDD and ≤ 20 percent bipolar disorder; Treatment strategy: Augment						
Bortolomasi et al., 2006(44)[b] 1 week, all reported patients included in analysis Tier 3—"drug resistance" not defined Fair	rTMS (n = 12) High frequency, 5 sessions Sham (n = 7)	NR Bipolar: rTMS: 16.7% Shame: 14.3%	HAM-D_{24} rTMS: 25.17 Sham: NR	HAM-D_{24} rTMS: -13.84 Sham: NR P = data NR but text states not significant	NR	NR
Moller, 2006(46)[b] Crossover, within 1 week of completing 1 week of txt Tier 3—TRD stated but not defined Fair	rTMS (n = 10) High frequency, 5 sessions Sham (n = 10)	NR Bipolar: Overall: 20%	HAM-D_{17} Median (range) rTMS: 20 (13-37) Sham: 16 (7-31)	Change (median) rTMS: -7 Sham: -1 P = 0.075	NR	NR
Population : MDD and ≤ 20 percent bipolar disorder; Treatment strategy : Mixed						
None						

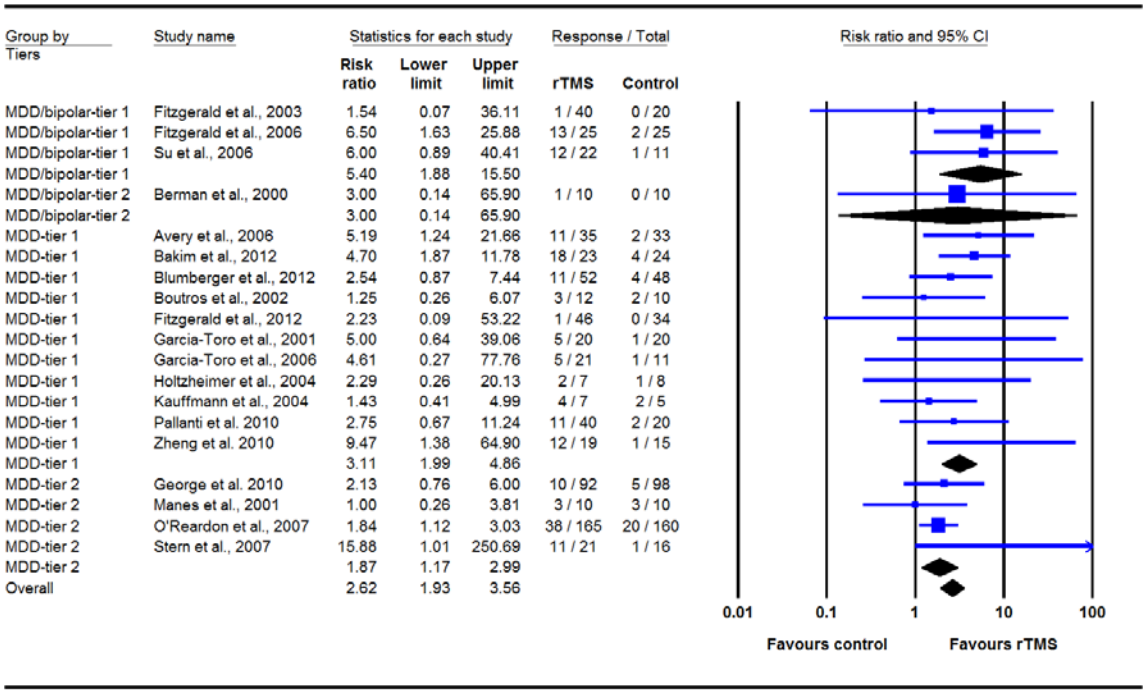
Author, Year **Duration** **Quality**	**Intervention** **Sample Size**	**Failed Trials** Mean (SD) **Bipolar diagnosis (%)**	**Baseline Depression** Mean (SD)	**Change in Severity** Mean (SD)	**Response** N (%)	**Remission** N (%)
George et al., 1997(45)[a]* Crossover design, 2 weeks *all patients had 1+ implied current episode failures Fair	rTMS (n = 12) High frequency, 10 sessions Sham (n = 12) Patients discontinued their (failed) ADs with the exception of 3 patients who were partial responders	Overall: 13.4 Bipolar Overall: 8.3%	HAM-D_{21} Overall: 28.5 (4.2)	HAM-D_{21} rTMS: -5.25 Sham: +3.33 P < 0.03	NR	NR

Abbreviations: DLPFC, dorsolateral prefrontal cortex; ; HAM-D_{17}, 17-item Hamilton Depression Scale; HAM-D_{21}, 21-item Hamilton Depression Scale; HAM-D_{25}, 25-item Hamilton Depression Scale; Hz, hertz; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; mg/d, milligram per day; MT, motor threshold; n, number; NR, not reported; NS, not significant; *P*, p-value; pts, patients; pps, pulses per session; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; txt(s), treatment(s); vs., versus.

[a]Study required failure in the current episode.

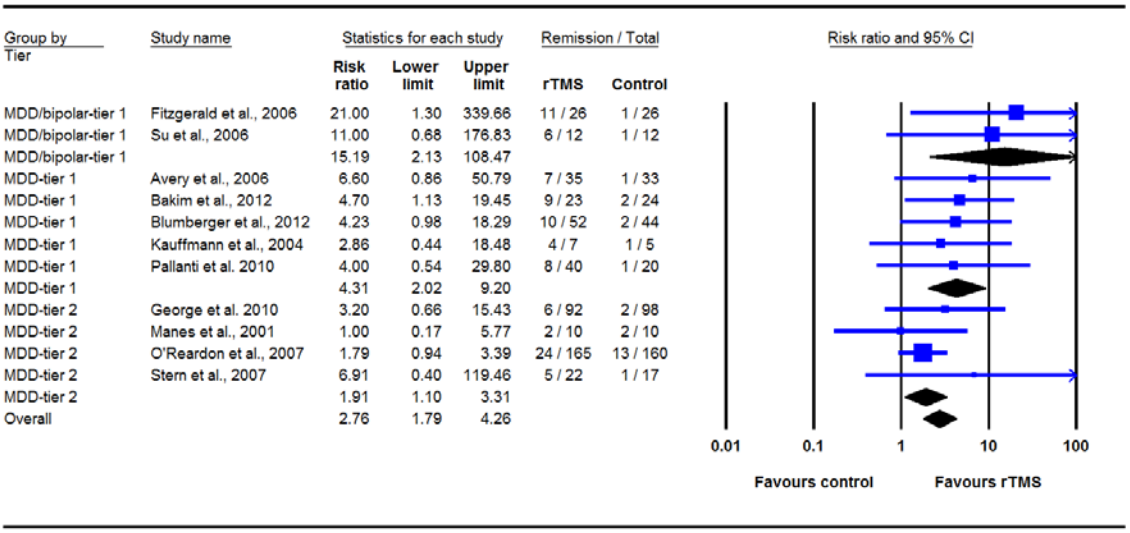
[b]Study did not require failure in the current episode.

Supplementary eFigure 1. Relative risk meta-analysis of response rates comparing rTMS with sham: Tiers 1 & 2, all populations*



*no Tier 3 studies reported response rates

Supplementary eFigure 2. Relative risk meta-analysis of remission rates comparing rTMS with sham: Tiers 1 & 2, all populations*



*no Tier 3 studies reported remission rates