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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**

1. [eTable 1](#) Treatment Resistant Depression Nonpharmacologic Interventions Database Search
2. [eTable 2](#) Study Outcomes and Eligibility
3. [eTable 3](#) Study Population Classification
4. [eTable 4](#) Summary of Findings on RCT vs Sham for Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 Studies
5. [eTable 5](#) Efficacy of rTMS Versus Sham: Tier 2
6. [eTable 6](#) Efficacy of rTMS Versus Sham: Tier 3
7. [eFigure 1](#) Relative Risk Meta-Analysis of Response Rates Comparing rTMS With Sham: Tiers 1 & 2, All Populations
8. [eFigure 2](#) Relative Risk Meta-Analysis of Remission Rates Comparing rTMS With Sham: Tiers 1 & 2, All Populations

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SUPPLEMENTARY MATERIALS

**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 <b>Depression articles limited to English, Human, and Adults, with no editorials, letters, case reports or case-control studies.</b>	<b>46002</b>
#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 <b>48 Psychotherapy/CBT/Depression articles limited to the "refractory" terms.</b>	<b>48</b>
#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] <b>These are the terms used for RCTs.</b>	392864
#17	Search #14 AND #16 <b>There are 203 RCTs about Depression and ECT.</b>	203
#18	Search "Longitudinal Studies"[Mesh] OR "Comparative Study "[Publication Type]) OR "Cohort Studies"[Mesh] OR "observational studies"[tw]	1992678
#19	Search #14 AND #18 <b>There are 361 "observational studies" about Depression and ECT.</b>	361

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

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

**Supplementary eTable 3. Study population classification**

Tier 1	Patients with $\geq 2$ failures of adequate antidepressant treatment
Tier 2	Patients with $\geq 1$ 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**

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

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

<sup>(1)</sup>Strength of evidence is based on guidance provided in the AHRQ *Methods Guide for Comparative Effectiveness Reviews*(18).

<sup>(2)</sup>Good and fair designations relate to quality ratings for each study.



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

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

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

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

Abbreviations: DLPFC, dorsolateral prefrontal cortex; ; HAM-D<sub>17</sub>, 17-item Hamilton Depression Scale; HAM-D<sub>21</sub>, 21-item Hamilton Depression Scale; HAM-D<sub>25</sub>, 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.

<sup>a</sup>Study required failure in the current episode.

<sup>b</sup>Study did not require failure in the current episode.

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

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

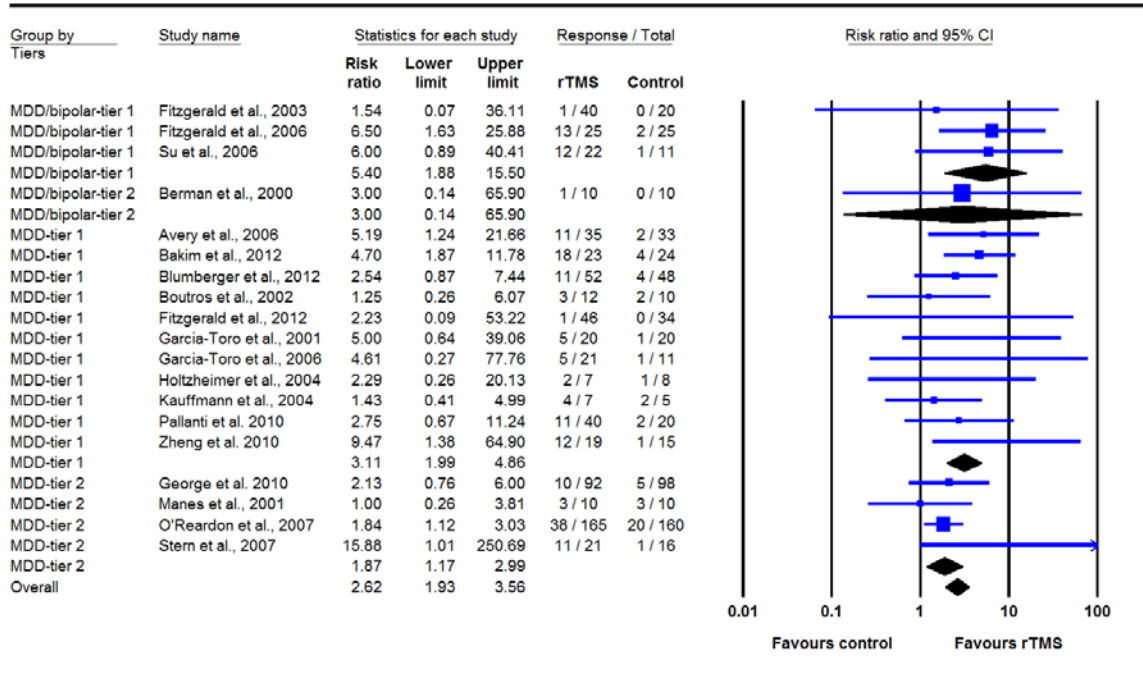
Author, Year	Intervention	Failed Trials	Baseline Depression	Change in Severity	Response	Remission
Duration	Sample Size	Mean (SD)	Mean (SD)	Mean (SD)	N (%)	N (%)
Quality		Bipolar diagnosis (%)				
George et al., 1997(45) <sup>a*</sup>	rTMS (n = 12)	Overall: 13.4	HAM-D <sub>21</sub>	HAM-D <sub>21</sub>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

Abbreviations: DLPFC, dorsolateral prefrontal cortex; ; HAM-D<sub>17</sub>, 17-item Hamilton Depression Scale; HAM-D<sub>21</sub>, 21-item Hamilton Depression Scale; HAM-D<sub>25</sub>, 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.

<sup>a</sup>Study required failure in the current episode.

<sup>b</sup>Study did not require failure in the current episode.

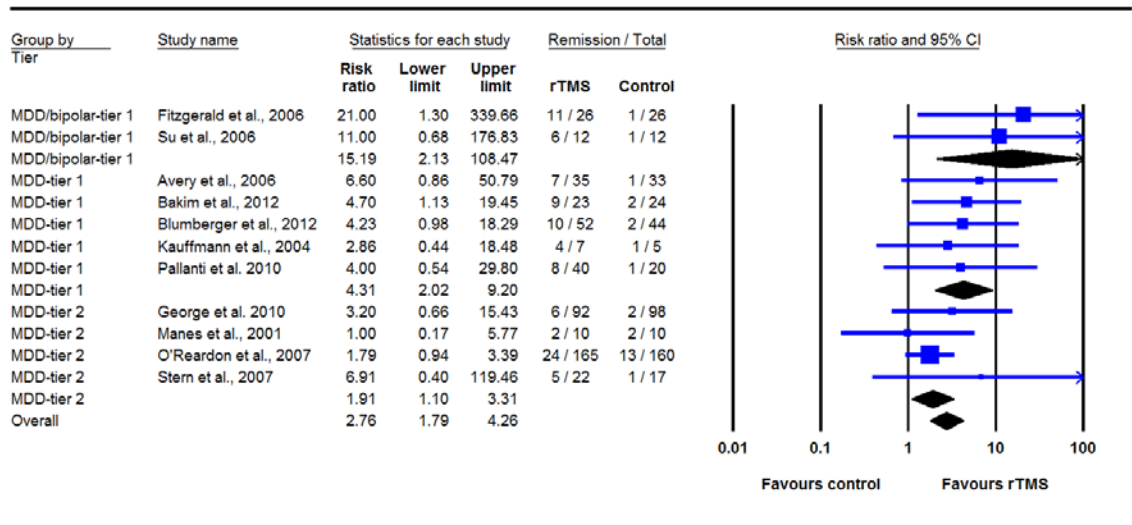
**Supplementary eFigure 1. Relative risk meta-analysis of response rates comparing rTMS with sham: Tiers 1 & 2, all populations\***



Random effects meta-analysis; I-squared 0%

\*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\***



Random effects meta-analysis; I-squared 0%

\*no Tier 3 studies reported remission rates