THE PRIMARY CARE COMPANION
FOR CNS DISORDERS

Supplementary Material

Article Title: Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in Adult and Youth Populations: A Systematic Literature Review and Meta-Analysis

Authors: Laura E. Leggett, MSc; Lesley J. J. Soril, MSc; Stephanie Coward, MSc; Diane L. Lorenzetti, MLS; Gail MacKean, MPA, PhD; and Fiona Clement, PhD

DOI Number: doi:10.4088/PCC.15r01807

List of Supplementary Material for the article

1. Table 1
2. Table 2
3. Table 3
4. Table 4
5. Table 5
6. Table 6
7. Table 7

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1: Characteristics of Studies Assessing the Efficacy of rTMS Versus Sham

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Avery[1] 1999 United States	**Patient Selection:** Patients were recruited through authors practice and other practitioners and were randomized to sham or active rTMS **Inclusion Criteria:** DSM-IV major depression or bipolar disorder (depressed phase), treatment resistant, right handed, 20 or more on Hamilton Depression Rating Scale **Exclusion Criteria: Patient Characteristics:** metal in body, cardiac pacemaker, implanted electronic device, history of head injury associated with loss of consciousness, brain surgery, epilepsy, labile or hypertensive blood pressure, other major psychiatric or medical illnesses, suicidal intent or plans **Patient Characteristics:** Four participants (all female) received active rTMS. Two participants (1 female, 1 male) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to two or more antidepressants	**Type of Control** Sham rTMS with stable dose of current ineffective medication for at least 6 weeks prior to start of trial, or medication free **Type of Comparator** active 10 Hz rTMS to left prefrontal cortex at 80% motor threshold for 10 sessions during 16 days	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory, Clinical Global Impression, Galveston Orientation and Amnesia Test, Rey Auditory Verbal Learning Test, Controlled Oral Word Association Test, Trail Making A and B, Stroop Color Word Test, WAIS-R Digit Span, Digit Symbol subtest **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, after 5th session, after 10th session, 1 week after completion of treatment, 2 weeks after completion of treatment **Type of Analysis:** Not reported
Avery[2] 2006 United States	**Patient Selection:** Patients were recruited through physician referral and advertisement between Jan. 2001- Feb. 2004, and were randomized by computer program. **Inclusion Criteria:** Age 21-65, current major depressive disorder as diagnosed by DSM-IV, treatment resistant, score of 17 or more on HAM-D **Exclusion Criteria:** Prior rTMS, bipolar disorder, failure of nine or more ECT treatments, substance abuse or addiction in past 2 years, antisocial or borderline personality disorder, psychosis, seizure disorder, closed head injury with loss of consciousness, brain surgery, major psychiatric or medical comorbidity **Patient Characteristics:** Thirty-five participants with a mean age of 44.3(10.3), 21 females and 14 males were randomized to the active group. Thirty-th68ree participants with a mean age of 44.2(9.7), 16 females and 17 males were randomized to the control group **Definition of Treatment Resistance:** Failure to respond to two or more antidepressants	**Type of Control** Sham rTMS with stable dose of current medication for 4 months or medication-free for 2 weeks **Type of Comparator** active 10 Hz rTMS to left DLPC at 110% motor threshold for 15 sessions over 4 weeks (2,400 total pulses)	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory, Re y Auditory Verbal Leaning Test, Digit Symbol Test and Digit Span, Mini-Mental State Examination, Stroop Test, Controlled Word Association Test, Galveston Orientation and Amnesia Test, Systematic Assessment for Treatment Emergent Effects (SAFTEE) **Follow-up time:** 5 weeks **Outcome ascertainment:** Baseline, visit 5, 10, 15 and 1 week after last session **Type of Analysis:** Intention-to-treat
Baeken[3] 2013 Belgium	**Patient Selection:** Participants were selects as part of a larger project looking at the influence of HF-rTMS on neurocognitive markers. All participants were included after screening by the Mini-international Neuropsychiatric Interview. Participants were randomized to receive active rTMS, followed by sham rTMS. **Inclusion Criteria:** right handed, unipolar depression diagnosis, treatment resistant **Exclusion Criteria:** history of epilepsy, neurosurgical interventions, pacemaker, metal or magnetic objects in the brain, Alcohol dependence, suicide attempts in prior 6 month **Patient Characteristics:** Twenty participants (13 females, 8 males), mean age 49.33(12.50) were included and received both sham and active rTMS in cross-over design. **Definition of Treatment Resistance: M**inimum of two unsuccessful treatment trials with serotonin reuptake inhibitors/ noradrenaline and/or serotonin reuptake inhibitors and one failed clinical trial with a tricyclic antidepressant	**Type of Control** sham rTMS on no medication **Type of Comparator** 20 HZ rTMS stimulation to the left dorsolateral prefrontal cortex at 110% motor threshold for 20 sessions during 4 days. Participants were on no mediation; total of 31,200 stimulations over 4 days	**Outcomes measured:** Hamilton Depression Rating Scale **Follow-up time:** Two weeks **Outcome ascertainment:** Baseline, after 1 week, and after 2 weeks **Type of Analysis:** Not reported
Bakim[4] 2012 Turkey	**Patient Selection:** Patient volunteers were recruited at 1 psychiatric outpatient clinic (no recruitment dates specified) and were randomized by computer program. **Inclusion Criteria:** Age 18-65, a diagnosis of unipolar major depression, recurrent or single episode and without psychotic features, treatment resistant depression, score of 18 or more on HAM-D or 20 on the MADRS, right-handedness **Exclusion Criteria:** comorbidity of any other Axis I disorder, including alcohol and substance use disorders, current or past history of epilepsy, head trauma, encephalitis, meningitis, or any other cerebrovascular disease, pregnancy, any pace-maker or medical pumps replaced in the body or a metal implant in the skull, any use of ECT, antipsychotics or anticonvulsants which may interfere with the excitability of cortical neurons and change the motor threshold, inability to read and understand the Turkish language. **Patient Characteristics:** Eleven participants with a mean age of 43.1 (8.2), 10 females and 1 male were randomized to high intensity rTMS. Twelve participants with a mean age of 44.41(10.22), 11 females and 1 male, were randomized to sham rTMS. **Definition of Treatment Resistance:** No response to adequate courses (at least 6 weeks) of at least two different classes of antidepressants used at optimal doses	**Type of Control** sham rTMS **Type of Comparator** 20 Hz rTMS to left DLPFC at 110% motor threshold for 20 trains of 40 pulses (24000 total treatment) once per day for 6 weeks	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline and every week **Type of Analysis:** Not reported
Bares[5] 2009 Czech Republic	**Patient Selection:** Patients were recruited from the Prague Psychiatric Centre between June 2005 and July 2008 due to lack of treatment response and were randomized using a permuted block design (Various outpatient clinics and psychiatric hospitals) **Inclusion Criteria:** 18-65 years old, Score of 20 or more on the Montgomery-Asberg Depression Rating Scale, and were determined to be treatment resistant **Exclusion Criteria:** Suicide risk, current psychiatric comorbidity on axis I, personality disorder, serious unstable medical illness, drug or alcohol abuse, risk of seizure, pregnancy or women who were nursing, previous treatment of fluoxetine, resistant to venlafaxine **Patient Characteristics:** Twenty-seven participants, mean age of 45.4(11.7) and 22 females, 5 males were randomized to the active rTMS group. Thirty-one participants with a mean age of 44.2(11.6), 24 females and 7 males, were randomized to receive sham rTMS and	**Type of Control** sham rTMS with 75mg of venalafaxine ER on days 1-5, increasing to 375mg by the end of the study **Type of Comparator** active 1 Hz rTMS to the right dorsolateral prefrontal cortex at 100% motor threshold for 20 sessions over 4 weeks (600 pulses per session)	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory short form, Clinical Global Impression **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, week 1, 2,3 and 4 **Type of Analysis:** Intention-to-treat

	venlafaxine ER **Definition of Treatment Resistance:** Failure to respond to at least one antidepressant treatment		
Berman[6] 2000 United States	**Patient Selection:** Patients were selected who met the inclusion criteria, and were randomized to receive sham or active rTMS **Inclusion Criteria:** Age 18-70, met DSM-IV criteria for major depressive episode, treatment resistant, no diagnosis of substance or alcohol abuse, no history of neurologic illness **Exclusion Criteria:** Pregnancy, EEG abnormality suggestive of epileptic predisposition, significant unstable medical illness **Patient Characteristics:** Twenty participants with a mean age of 44.3, 6 females and 14 males were included, Three sham discontinued due to lack of response **Definition of Treatment Resistance:** Failed at least one pharmacologic trial during current or previous episode	**Type of Control** sham rTMS with no antidepressants, neuroleptics or benzodiazepines for one week prior to starting sham procedure **Type of Comparator** active 20 Hz rTMS to the left dorsolateral prefrontal cortex, delivered at 80% motor threshold for 10 consecutive weekdays	**Outcomes measured:** Hamilton Depression Rating Scale, side effects checklist, Beck Depression Inventory, Hamilton Anxiety Scale **Follow-up time:** Two weeks **Outcome ascertainment:** Baseline, each day for 10 consecutive weekdays **Type of Analysis:** Intention-to-treat
Blumberger[7] 2012 Canada	**Patient Selection:** Patient volunteers recruited from 3 outpatient clinics from Jan 2006 to Jan 2009 and were randomized using a computer-generated list. **Inclusion Criteria:** Age 18-85, DSM-IV diagnosis of MDD without psychotic features based on the Structured Clinical Interview for DSM-IV, treatment resistant depression, score of greater than 21on HAM-D, receiving stable doses of psychotropic medications for at least four weeks prior to randomization, capable to consent as assessed based on their ability to provide a spontaneous narrative description of the key elements of the study using the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), currently an outpatient. **Exclusion Criteria:** DSM-IV substance dependence in the last 6 months (excluding nicotine) or DSM-IV substance abuse in the last month, mMet DSM-IV criteria for borderline personality disorder or antisocial personality disorder based on the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II), Bipolar I, II or NOS, had a significant unstable medical or neurologic illness or a history of seizures, acutely suicidal, pregnant, metal implants in the cranium, had a known diagnosis of dementia or a current MMSE score less than 26, had received benzodiazepines (dose equivalent > lorazepam 2 mg/day), monoamine oxidase inhibitors, or buproprion during the previous four weeks, received prior treatment with rTMS for any indication **Patient Characteristics:** Twenty-six patients with a mean age of 58.0 (12.5), 14 females, 12 males were randomized to unilateral rTMS. Twenty patients with a mean age of 45.8 (13.4), 14 females, 6 males were randomized to sham rTMS. **Definition of Treatment Resistance:** Failed to achieve a clinical response, or did not tolerate, at least two separate trials of antidepressants from different classes at sufficient dose for at least 6 weeks according to Stage II criteria outline by Thase and Rush	**Type of Control** sham rTMS with coil angled at 90 degrees off the scalp **Type of Comparator** 10 Hz rTMS to HFL 100% motor threshold for 29 trains of 50 pulses (1450 total treatment) 5 days per week for 3 weeks	**Outcomes measured:** Hamilton Depression Rating Scale, Repeatable Battery for the assessment of Neuropsychological Status, Hopkins Verbal Learning Test (Revised), Brief Visual Memory Test (Revised), Grooved Peg Board test **Follow-up time:** 6 weeks **Outcome ascertainment:** baseline and every 5 treatments **Type of Analysis:** Modified IIT
Bortolomasi[8] 2007 Italy	**Patient Selection:** Patients who met the inclusion criteria were selected and randomized to receive sham or active rTMS **Inclusion Criteria:** Right handed, no history of brain trauma or seizure, normal neurological examination, treatment resistant, DSM-IV criteria for major depression **Exclusion Criteria:** Those with pacemakers, mobile metal implants, or implanted medical pumps **Patient Characteristics:** Twelve participants, ranging from 45-56 years old (7 females and 5 males) were randomized to receive active rTMS. Seven participants, four females and three males, ranging from 44-53 years old were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Not reported	**Type of Control** sham rTMS with unchanged medication (including tricyclic or serotonin reuptake inhibitors) **Type of Comparator** active 20 Hz rTMS, at 90% motor threshold (800 stimuli per day) targeting the left prefrontal area was given for five sessions per week over 4 weeks. Medication was unchanged during treatment (including tricyclic or serotonin reuptake inhibitors).	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory **Follow-up time:**12 weeks **Outcome ascertainment:** Baseline, 1, 4, and 12 weeks **Type of Analysis:** Per protocol
Boutros[9] 2002 United States	**Patient Selection:** Outpatients meeting the inclusion criteria were randomized using a computer generated sequence **Inclusion Criteria:** Diagnosis of major depression, Treatment resistance, score of at least 20 on Ham-D scale **Exclusion Criteria:** Suicidal ideations, prominent psychotic symptoms, history of neurological disorder, history of drug abuse within the past 3 months **Patient Characteristics:** Twelve participants, with a mean age of 49.5 (8) were randomized to receive active rTMS. Nine participants with a mean age of 52(7) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failed two prior medication trials judged to be of adequate dose and duration, or unwilling to try medication	**Type of Control** sham rTMS with unchanged medication for 2 weeks prior to rTMS and during treatment **Type of Comparator** active 20 Hz rTMS to the left prefrontal cortex for 10 consecutive weekdays (800 stimuli per session) at 80% motor threshold	**Outcomes measured:** Hamilton Depression Rating Scale **Follow-up time:** Five months **Outcome ascertainment:** Baseline and days 3,5,6,8 and 10 **Type of Analysis:** Not reported
Bretlau[10] 2008 Denmark	**Patient Selection:** Participants were recruited between April 2003 and December 2005, by general practitioners. **Inclusion Criteria:** Age 18-75, meet DSM-IV criteria for current major depressive disorder, treatment resistant **Exclusion Criteria:** organic brain disorder, substance abuse, severe anxiety disorder, personality disorder, history of epilepsy, metal implants in head or neck, pacemaker, suicidal ideation (score of more than 2 on the suicide item of Ham-D), those receiving antipsychotics, current episode has lasted longer than 24 months, risk factors deterring escitalopram treatment, pregnancy **Patient Characteristics:** Twenty-two participants, with a mean age of 53.1 (10.1), 7 males and 15 females, were randomized to receive active rTMS. Twenty-three participants, with a mean age of 57.8(10.0), 10 males and 13 females, were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failed to respond to at least one adequate antidepressant treatment during current episode	**Type of Control** sham rTMS combined with 20mg escitalopram/day, but no other medication. **Type of Comparator** active 8 Hz rTMS to the left dorsolateral prefrontal cortex delivered at 90% motor threshold for 15 consecutive workdays (3 weeks) for a total of 19,200 pulses. Active rTMS was combined with 20mg escitalopram/day.	**Outcomes measured:** Hamilton Depression Rating Scale, Bech-Rafaelsen Melancholia Scale, UKU Scale, Major Depression Inventory **Follow-up time:**12 weeks **Outcome ascertainment:** Baseline, and 2,3,5,8 and 12 weeks **Type of Analysis:** Not reported
Chen[11] 2013 China	**Patient Selection:** Patients were recruited between January 1, 2008 and October 31, 2008 from one hospital in Taiwan, and randomized. **Inclusion Criteria:** Treatment resistant depression, score of greater than 18 on Ham-D, able to be in hospital during treatment, diagnosis of major depressive disorder by DSM-IV criteria **Exclusion Criteria:** High risk of suicide, head injury, epilepsy, implanted pacemaker **Patient Characteristics:** Ten participants, with an average age of 44.1 (4.4), 3 males and 7 females, were randomized to receive active rTMS. Ten participants, with an average age of 47.3(3.5), 6 males and 4 females, were randomized to receive sham rTMS.	**Type of Control** sham rTMS remaining on consistent antidepressant therapy **Type of Comparator** active 20Hz rTMS to the left dorsolateral prefrontal cortex delivered at 90% motor threshold for 10 sessions completed during 4 weeks	**Outcomes measured:** Beck Depression Inventory II, 17-item Hamilton Depression Rating Scale, Brief Psychotic Rating Scale, Young Mania Rating Scale **Follow-up time:** One month after completion of treatment **Outcome ascertainment:** Baseline, after 5th treatment, after 10th treatment, and one month after completing treatment.

	Definition of Treatment Resistance: No response to two different antidepressants over a period of 6 weeks each		**Type of Analysis:** Not reported
Fitzgerald[12] 2003 Australia	**Patient Selection:** Patients were recruited from 2 outpatient clinics and psychiatrists between Oct 2000 and Sept 2002 and were randomized via sealed envelopes. **Inclusion Criteria:** Not reported **Exclusion Criteria:** Significant medical illness, neurologic disorders or other Axis I psychiatric disorders **Patient Characteristics:** Twenty patients with a mean age of 49.15 (14.243), 11 females and 9 males were randomized to sham rTMS. Twenty patients with a mean age of 42.2 (9.8), 8 females and 12 males were randomized to high frequency left sided rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 courses of antidepressants medications for at least 6 weeks	**Type of Control** sham rTMS **Type of Comparator** 10 Hz rTMS to HFL 100% motor threshold for 20 trains (1000 stimuli per treatment) 5 days per week for 2 weeks	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, Brief Psychiatric Rating Scale, CORE rating of psychomotor disturbance, Clinical Global Impression, Personal Semantic Memory Schedule, Autobiographical Wechsler Adult Intelligence Scale, Tower of London, Controlled Oral Word Association Test **Follow-up time:** 4 weeks **Outcome ascertainment:** baseline, 2 weeks, 4 weeks **Type of Analysis:** Not reported
Fitzgerald[13] 2006 Australia	**Patient Selection:** Patients were recruited from an outpatient department of a regional mental health department, or by referral by psychiatrist, between January 2003 and September 2004, and randomized to sham or active rTMS using a single random-number sequence **Inclusion Criteria:** Diagnosis of major depressive episode or bipolar I disorder based, treatment resistant, >20 on MADRS **Exclusion Criteria:** Significant medial illness, neurological disorder, another axis I psychiatric disorder **Patient Characteristics:** Twenty-five participants, mean age 46.8(10.7), 10 males and 15 females were randomized to receive active rTMS. Twenty-five participants, mean age 43.7(10.2), 9 males and 16 females were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least two trials of antidepressant medication for at least 6 weeks using a standard effective dose	**Type of Control** sham rTMS with no change in medication 4 weeks prior to or during the trial **Type of Comparator** active 1 Hz rTMS stimulation to the right dorsolateral prefrontal cortex delivered at 110% motor threshold followed by 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex delivered at 100% motor threshold. Participants had no change in medication 4 weeks prior to or during the trial	**Outcomes measured:** MADRS, Hamilton Depression Rating Scale, Beck Depression Inventory, Brief Psychiatric Rating Scale, CORE Rating of Psychomotor Disturbances, Global Assessment of Functioning Scale, Clinical Global Impression **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, week 2,3,4,5, and 6 **Type of Analysis:** Intention-to-treat
Fitzgerald[14] 2012 Australia	**Patient Selection:** Patients were recruited from Jan 2008-Nov 2010 and were randomized (method not specified). **Inclusion Criteria:** Hamilton Depression Rating Scale score > 15 **Exclusion Criteria: bipolar disorder,** significant currently active medical illness, current neurological disease, contraindication to rTMS **Patient Characteristics:** Twenty-four patients with a mean age of 43.4 (12.7.1),15 females and 9 males were randomized to unilateral left high frequency rTMS. Seventeen patients with a mean age of 44.9(15.7), 8 females and 12 males were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 courses of antidepressants medications for at least 6 weeks in the current episode	**Type of Control** sham rTMS **Type of Comparator:** 10 Hz 120% motor threshold for 30 trains for 3 weeks	**Outcomes measured:** Hamilton Depression Rating Scale , Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, CORE rating of psychomotor disturbance, State-Trait Anxiety Inventory, Depressive Personality Disorders Inventory, Wechsler Test of Adult Reading, Rey Auditory Verbal Learning Test, Brief Visual Spatial Memory Test, Digit Span, Trail Making Test A & B, Stroop and COWAT phonemic Fluency **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, 3 weeks, 6 weeks **Type of Analysis:** Not reported
Garcia-Toro[15] 2001 Spain	**Patient Selection:** Not reported **Inclusion Criteria:** Age 18 or older, DSM-IV diagnosis of unipolar major depression, treatment resistant, right-handed **Exclusion Criteria:** History of seizures or neurosurgery, serious or uncontrolled medial illness, pacemaker or hearing aid, pregnancy, women of childbearing potential lacking effective contraceptive, high suicidal risk **Patient Characteristics:** Seventeen participants (10 males, 7 females) with a mean age of 51.5(15.9) received active rTMS. Eighteen participants (10 males, 8 females) with a mean age of 50(11) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least two antidepressant medications at the maximum dose tolerated for a least 6 weeks during the current episode	**Type of Control** sham rTMS with patients taking stable doses of antidepressants for the six weeks prior to trial **Type of Comparator** active 20 Hz rTMS stimulation to the left Dorsolateral Prefrontal Cortex, delivered at 90% motor threshold for ten consecutive workdays. Stable dose of antidepressants for six weeks prior to trial.	**Outcomes measured:** Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Clinical Global Impression, Beck Depression Inventory **Follow-up time:** Four weeks **Outcome ascertainment:** Baseline, week 1, 2 and 4 **Type of Analysis:** Not reported
Garcia-Toro[16] 2006 Spain	**Patient Selection:** Not reported. Randomization occurred using sealed envelopes. **Inclusion Criteria:** Age > 18, unipolar major depression **Exclusion Criteria:** high suicidal risk **Patient Characteristics:** Ten patients with a mean age of 48.5 (13.3), 4 females and 6 males received rTMS. Ten patients with a mean age of 47.20(11.8), 7 females and 3 males received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 trials of antidepressants medications	**Type of Control** sham rTMS **Type of Comparator** Alternating 1 Hz at 110% motor threshold for 30 trains with 20 Hz at 110% motor threshold for 30 trains	**Outcomes measured:** Hamilton Depression Rating Scale, Clinical Global Impression **Follow-up time:** 10 sessions **Outcome ascertainment:** Baseline, 1 week, 2 weeks, 4 weeks **Type of Analysis:** Not reported
George[17] 2010 United States	**Patient Selection:** Patients were recruited between October 15, 2004 and March 31, 2009 using advertisement and referral. **Inclusion Criteria:** age 18-70, free of anti-depressant medication, DSM-IV diagnosis of major depressive disorder, current episode lasting less than 5 years, score of 20 or more on Ham-D, stable during 2 weeks free of medication, treatment resistance **Exclusion Criteria:** Other axis I disorders, fail to respond to electroconvulsive therapy, pervious treatment with rTMS or vagus nerve stimulation, family history of seizure disorder, neurologic disorder, ferromagnetic material in body or near head, pregnancy, taking medication which lowers seizure threshold, positive urine test for cocaine, marijuana, PCP or opiates **Patient Characteristics:** Ninety-two participants (34 male, 58 female) with a mean age of 47.7(10.6) received active rTMS. Ninety-eight participants (48 male, 50 female) with a mean age of 46.5(12.3) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to 1-4 antidepressants, or intolerant to 3 or more.	**Type of Control** sham rTMS with no medication **Type of Comparator** active 10 Hz rTMS stimulation to the left prefrontal cortex delivered using 110-120% motor threshold over three weeks for 15 total sessions, with no medication (3000 pulses per session)	**Outcomes measured:** Ham-D, Montgomery-Asperg Depression Rating Scale, Clinical Global Impression Severity of Illness Scale, Inventory of Depressive Symptoms **Follow-up time:** Three weeks **Outcome ascertainment:** Baseline, 3 weeks **Type of Analysis:** Intention-to-treat

Hernandez-Ribas[18] 2013 Spain	**Patient Selection:** Participants were recruited from the Mood Disorders Unit of the Bellvitge University Hospital. **Inclusion Criteria:** Right handed, non-psychotic major depressive or bipolar disorder, treatment resistant, stable dose of antidepressants during treatment and 6 weeks prior, DSM-IVcriteria for major depressive episode **Exclusion Criteria:** history of other axis I diagnosis, history of neurological condition, serious medical condition, abnormal MRI, presence of any factor preventing MRI acquisition **Patient Characteristics:** Ten participants (8 females and 2 males), mean age 42.6(5.56) were randomized to receive active rTMS. Eleven participants (8 females, 2 males), mean age 46.31(7.34) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least one trial of adequate antidepressant	**Type of Control** sham rTMS with participants on stable dose of medications for at least 6 weeks prior to and during trial **Type of Comparator** 15 Hz rTMS stimulation to the left dorsolateral prefrontal cortex delivered using 100% motor threshold for 15 sessions over 3 weeks. Participants on stable dose of medication for at least 6 weeks prior to and during trial.	**Outcomes measured:** Hamilton Rating Scale **Follow-up time:** three weeks **Outcome ascertainment:** Baseline, week 1, 2 and 3 **Type of Analysis:** Not reported
Holtzheimer[19] 2004 United States	**Patient Selection:** Participants were recruited by physician referral, referral from centers doing ECT, and media advertisements between January 1998 and December 1999 **Inclusion Criteria:** Age 21-65, right handed, meet DSM-IV criteria for major depressive episode due to major depressive disorder, no major psychiatric or medical comorbidity, treatment resistant, score of at least 18 on Ham-D scale, not on medication **Exclusion Criteria:** History of bipolar disorder, failure to respond to electroconvulsive therapy, history of substance abuse, psychosis, pregnancy **Patient Characteristics:** Seven participants (4 females, 3males), mean age 40.4(8.5) received active rTMS. Eight participants (3 females, 5 males), mean age 45.4(4.9) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least two adequate trials of antidepressants	**Type of Control** sham rTMS on no medication **Type of Comparator** 10 Hz rTMS stimulations to the left dorsolateral prefrontal cortex delivered using 110% motor threshold for 10 sessions over two weeks (1600 pulses per day)	**Outcomes measured:** Beck Depression Inventory, Hamilton Depression Rating Scale **Follow-up time:** Three weeks **Outcome ascertainment:** Baseline, week 1, 2 and 1 week after final session **Type of Analysis:** Intention-to-treat
Jorge[20] 2004 United States	**Patient Selection:** Participants were recruited, at the University of Iowa Adult Psychiatry Outpatient Clinic, the University of Iowa Outpatient Cardiology Clinic and through newspaper advertisement **Inclusion Criteria:** Diagnosis of hemispheric, brainstem or cerebellar stroke, DSM-IV diagnosis of depression due to stroke, treatment resistant **Exclusion Criteria:** severe systemic disease, ongoing neoplasia, neurodegenerative disorder, clinical evidence of dementia, aphasic patients with language comprehension deficits, suicidal risk, prominent psychotic features, bipolar course, substance abuse during past 12 months, history of seizure, major head trauma, idiopathic epilepsy, metal in head or neck, cardiac pacemaker, implanted defibrillator, intracardiac lines, cortical lesions of the left frontal cortex **Patient Characteristics:** Ten participants (4 females, 6 males), mean age 63.1(8.1) received active rTMS. Ten participants (5 females, 5 males), mean age 66.5(12.2) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least two adequate trials of antidepressants	**Type of Control** sham rTMS with no medication **Type of Comparator** 10 Hz rTMS stimulation to the left prefrontal cortex delivered using 110% motor threshold for 10 sessions over three weeks with no medication	**Outcomes measured:** Hamilton Depression Rating Scale, premorbid intelligence quotients, Stroop Test, Trail Making Test A and B, Controlled Oral Word Association Test, Rey Auditory Verbal Learning Test, Benton Visual Retention Test, Boston Naming Test, Token Test, Sentence Repetition Subtest of the Multilingual Aphasia Examination, Wechsler Adult Intelligence Scale-III, Line Bisection Test, Mini Mental State Examination **Follow-up time:** Three weeks **Outcome ascertainment:** Baseline, 3 weeks **Type of Analysis:** Not reported
Jorge[21] 2008 United States	**Patient Selection:** Participants were recruited from the Department of Psychiatry at the University of Iowa hospitals, the Department of Psychiatry at the Iowa City Veterans Affairs Medical Center, and through advertising **Inclusion Criteria:** Age 50 or older, history of subcortical stroke, at least three cardiovascular risk factors (arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, smoking), major depression as diagnosed by DSM-IV criteria, treatment resistance **Exclusion Criteria:** Severe heart or respiratory failure, renal or hepatic failure, occurrence of ongoing neoplastic process, neurodegenerative disorder, clinical evidence of dementia, suicide risk, prominent psychotic features, substance abuse within the prior two years, prior induced seizures, major head trauma, history of epilepsy, metal in head or neck, cardiac pacemaker, implanted defibrillator, medication pump **Patient Characteristics:** Fifteen participants (6 females, 9 males), mean age 62.9(7.2) received active rTMS. Fifteen participants (8 females, 7 males), mean age 66.1(11) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least one adequate trial of antidepressant	**Type of Control** sham rTMS **Type of Comparator** 10 Hz rTMS stimulation to the left dorsolateral prefrontal delivered at 110% motor threshold for 10 sessions over a 10 day period	**Outcomes measured:** Hamilton Depression Rating Scale, Rey Auditory Verbal Learning Test, Stroop Colour and Word Test, Trail Making Tests A and B, Controlled Oral Word Association Test, Functional Independence Measure, Mini Mental State Examination **Follow-up time:** 3 weeks **Outcome ascertainment:** Baseline, week 2, week 3 **Type of Analysis:** Intention-to-treat
Kauffmann[22] 2004 United States	**Patient Selection:** Unknown, randomized **Inclusion Criteria:** Over 18 years old, met DSM-IV criteria for major depression, treatment resistant **Exclusion Criteria:** Pre-existing neurological and/or cardiac diseases **Patient Selection:** Twelve patents with mean age of 51.7 (17.2), 11 females and 1 male, randomly assigned to receive active or sham rTMS, 7 in active group and 5 in sham group **Definition of Treatment Resistance:** Failure to respond to at least two antidepressants given for 8 weeks at adequate dosages	**Type of Control** Sham rTMS (same as comparator but 45 degree angle from the skull) with previous medication regimen **Type of Comparator** tangential to the skull, 1Hz, 0.1ms pulse duration, field intensity 10% above motor threshold, 10 treatments over 2 weeks. Participants could continue on previous medication regimen during rTMS treatment.	**Outcomes measured:** Hamilton Depression Scale, SCL-90 **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, 1 week and after last session (2 weeks) **Type of Analysis:** Not Reported
Lisanby[23] 2009 United States	**Patient Selection:** Patients were recruited from twenty-three sites in the United States, Australia, and Canada, between January 2004 and August 2005, and were randomized **Inclusion Criteria:** DSM-IV diagnostic criteria for unipolar, nonpsychotic major depressive disorder, treatment resistant depression, medication free outpatient, age 18-70, Clinical Global Impression score at least 4, HAMD17 score at least 20 **Exclusion Criteria:** Risk factors for seizures **Patient Selection:** 164 participants who were treatment resistant were randomized to receive active rTMS. Sixty-seven participants (42 females), mean age 47(11.3) were randomized to receive active rTMS. Seventy participants (32 females), mean age 45.3(10.6) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to more than 1 adequate antidepressant trial	**Type of Control** Sham rTMS with medication free **Type of Comparator** 10 HZ rTMS to the left dorsolateral prefrontal cortex using 120% motor threshold, 4s in duration with 26s interval (40 pulses for each pulse train), 75 pulse trains, 3000 pulses	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Hamilton Depression Scale, ATHF, IDS-SR, Clinical Global Impression **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, week 2, 4, 6, participants unblinded at 4 weeks **Type of Analysis:** Intention-to-treat

Loo[24] 1999 United States	**Patient Selection:** Unknown **Inclusion Criteria:** DSM-IV major depressive episode, treatment resistant depression, ≥25 on the Montgomery-Asberg Depression Rating Scale **Exclusion Criteria:** major physical or neurological abnormalities, treated with ECT during this depressive episode **Patient Selection:** 18 patients (9 male, 9 female), mean age real rTMS 45.7 (14.7) and for sham age 50.9(14.7). Nine participants, mean age 45.7(14.7) received active rTMS. Nine participants, mean age 50.9(14.7) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Not reported	**Type of Control** Sham with or without continued antidepressants **Type of Comparator** 10Hz rTMS delivered at 110% motor threshold, 30 train of 5 seconds, 30 seconds apart; for 10 sessions over 2 weeks	**Outcomes measured:** Hamilton Depression Scale, Montgomery-Asberg Depression Rating Scale, CPRE scale, self-rated Beck Depression Inventory, AUSSI scale, Mini-Mental State examination, digit span, simple and complex reaction time, Luria hand sequences, visual paired associates learning, verbal fluency, Tower of London, Rey Auditory Verbal Learning Test, Autobiographical Memory interview **Follow-up time:** 2 weeks (4 weeks of real rTMS for those that were in Sham if they choose, or those in real could choose to continue for another 2 weeks) 1 month follow up **Outcome ascertainment:** Baseline, week 2 **Type of Analysis:** Intention-to-treat
Loo[25] 2003 Australia	**Patient Selection:** Unknown **Inclusion Criteria:** DSM-IV major depressive episode, less than 2 years long, treatment resistant depression, ≥25 on the Montgomery-Asberg Depression Rating Scale **Exclusion Criteria:** physical or neurological disease, treated with ECT during current episode **Patient Selection:** Nine participants, (6 female, 3 male), mean age 54.9(18.03) received active rTMS. Ten participants (6 female, 4 male), mean age 48.4(10.88) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 1 adequate trial of antidepressants	**Type of Control** Sham with or without continued antidepressants (either tapered or remained in the ineffective antidepressants) **Type of Comparator** 15Hz rTMS delivered at 90% motor threshold for 24 sessions over 3 weeks.	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, CARE, Beck Depression Inventory, Hamilton Depression Scale, AUSSI, Mini-mental State examinations, Rey Auditory Verbal learning Test, Tower of London, Controlled Oral Word Association Test, Expanded Paired Associate Test, visual learning **Follow-up time:** Seven weeks **Outcome ascertainment:** Baseline, week 3, 1 post-treatment **Type of Analysis:** Intention-to-treat
Loo[26] 2007 Australia	**Patient Selection:** Outpatients referred by psychiatrists or general practitioners **Inclusion Criteria:** DSM-IV diagnosis of major depressive episode, less than 2 years in length, ≥25 on the Montgomery-Asberg Depression Rating Scale, treatment resistant depression **Exclusion Criteria:** Axis 1 disorders, neurological illness, epilepsy, severe medical illness, implanted electronic devices, suicidal, or psychotic, patients that had failed more than 2 classes of antidepressants **Patient Selection:** Thirty-eight subjects randomly assigned (19 active, 21 sham). Nineteen participants (10 females, 9 males), mean age 49.8 (2.5) received active rTMS. Twenty-one participants (8 females, 11 males) mean age 45.7(15.0) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 1 adequate trial of antidepressants	**Type of Control** Sham with or without continued antidepressants (on medications that they had failed to respond to) **Type of Comparator** 10 Hz rTMS to the left dorsolateral prefrontal cortex delivered at 110% motor threshold, 5 second duration, 30 trains, 25 seconds between trains, for 2 times a day, separated by 2 hours over a period of 2 weeks	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Hamilton Depression Scale, CORE, Beck Depression Inventory, AUSSI, Rey auditory verbal learning test, Trail making test A and B, Wechsler Adult Intelligence Scale digit span, Controlled Oral Word Association Test. **Follow-up time:** 6 months post-rTMS **Outcome ascertainment:** Baseline, weekly, 1 month, and 6 month follow-up. Blind broken at 2 weeks. **Type of Analysis: I**ntention-to-treat
Manes[27] 2001 United States	**Patient Selection:** Outpatients in Iowa City recruited through advertisement **Inclusion Criteria:** Major or minor depression as diagnosed by DSM-IV, treatment resistant, Caucasian, older than 50 years old **Exclusion Criteria:** Not reported **Patient Selection:** Ten participants (5 females, 5 males), mean age 60.35(3.4) received active rTMS. Ten participants (5 females, 5 males), mean age 60.9(2) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least one 4 week trial of the highest tolerated dose of antidepressant medication.	**Type of Control** Sham without medication **Type of Comparator** 20Hz rTMS delivered at 80% motor threshold, for 2 seconds x 20 trains, 1 minute between trains; for 5 days	**Outcomes measured:** Hamilton Depression Scale, Mini-Mental State Exam, **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, daily, 1 week after last treatment **Type of Analysis:** Not reported
Mantovani[28] 2013 United States	**Patient Selection:** Brain behaviour clinic and the Anxiety Disorders Clinic of New York State Psychiatric Institute/Columbia University between January 2008 and December 2010 **Inclusion Criteria:** 18-65 years old, diagnosis of panic disorder and major depressive disorder confirmed with DSM-IV, lasting at least a month, treatment resistant, if patient is on medication must be stable for at least 4 weeks or psychotherapy for 3 months **Exclusion Criteria:** had acute suicide risk, history of bipolar disorder, psychotic disorder, substance abuse within the past year, neurological disorders, increase risk of seizure, implanted devised, metal in brain, unstable medical conditions, pregnant or breast feeding, prior rTMS **Patient Selection:** Twelve participants (8 female, 4 male), mean age 40.2(10) received active rTMS. Thirteen participants (5 female, 8 male), mean age 39.8(13.3) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least one adequate antidepressant trial	**Type of Control** Sham remaining on medication **Type of Comparator** 1 Hz rTMS to the right dorsolateral prefrontal cortex, delivered at 100% motor threshold in 30 min train (1800 pulses per day) 5 days a week for 4 weeks	**Outcomes measured:** PDSS and PDSS self-report, Hamilton Depression Rating Scale, HARS-14, Beck Depression Inventory-II, ZUNG-self-administered scale, Clinical Global Impression, PGI, Self-reported social adaptation scale **Follow-up time:** 6 months **Outcome ascertainment:** Baseline, weeks 2, 4, 6 months post-treatment **Type of Analysis:** Not reported
McDonald[29] 2006 United States	**Patient Selection:** Patients were recruited from the community (no dates specified). Randomization method was not specified. **Inclusion Criteria:** Hamilton Depression Rating Scale > 20 **Exclusion Criteria:** evidence of dementia on neuropsychological testing or meeting SCID criteria for Organic Brain Syndrome, Organic Mood Disorder, Substance Dependence within the last 6 months, a diagnosis of a significant central neurological disorders, pregnancy, the presence of cardiac pacemakers, cochlear implants, or other intracranial implants with the exception of dental fillings, presence of psychiatric symptoms of significant severity, requirement of continued treatment with antidepressant medications, acute, unstable medical conditions, previous TMS. **Patient Characteristics:** Twelve participants (7 males, 5 females), mean age 54 (SD not reported), were randomized to receive sham rTMS. Twenty-five patients with a mean age of 49.0 (SD not reported),18 females and 7 males received left-sided high frequency then right-sided low frequency rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 3 trials of antidepressants medications during the current episode	**Left-sided high frequency/right-sided low frequency:** 10Hz to the left DLPFC at 110% motor threshold for 20 trains (1000 pulses) followed by 1 Hz to the right DLPFC 110% motor threshold for 20 trains (600 pulses) for 5 days/week for 2 weeks	**Outcomes measured:** Hamilton Depression Rating Scale, Clinical Global Impression, Beck Depression Inventory, Brief Psychiatric Rating Scale **Follow-up time:** 3 months **Outcome ascertainment:** Baseline, week 2, month 1, month 2, month 3 **Type of Analysis:** Intention-to-treat

Moller[30] 2006 Iceland	**Patient Selection:** Participants were referred by psychiatrists from Landspitali-University Hospital, and randomized by coin toss **Inclusion Criteria:** Treatment resistant, diagnosis of depressive disorder based on ICD 10, had not received rTMS before, met published safety criteria for rTMS treatment **Exclusion Criteria:** Not reported **Patient Selection:** 10 patients (6 women and 4 men), average age 54 (14), randomized to 7 in active and 3 sham **Definition of Treatment Resistance:** Determined by referral psychiatrists	**Type of Control** Sham with sustained medication **Type of Comparator** 10Hz rTMS to the left prefrontal cortex, for 5 seconds x 40 trains, 25 seconds between trains; every day for 5 days with 4 weeks washout in between	**Outcomes measured:** Hamilton Depression Rating Scale, P_{300} **Follow-up time:** 4-6 weeks **Outcome ascertainment:** Baseline, 1 week after treatment **Type of Analysis:** Not Reported
Moser[31] 2002 United States	**Patient Selection:** Not reported **Inclusion Criteria:** Treatment resistant depression, 48-78 years **Exclusion Criteria:** Not reported **Patient Selection:** Nine participants, mean age 61.22[10.3] were randomized to receive active rTMS. Ten participants, mean age 60.9[10.2] were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Not reported	**Type of Control** Sham without medication **Type of Comparator** 20Hz rTMS to the left dorsolateral prefrontal cortex, delivered at 80% motor threshold, 2 second trains x20, 1min between trains; 5 sessions over 5 days	**Outcomes measured:** Hamilton Depression Rating Scale, Trail making Test A and B, Stroop Test, Controlled oral word association, Boston naming test, Rey Auditory Verbal Learning Test, Judgment of Line Orientation **Follow-up time:** 5 days **Outcome ascertainment:** Baseline, 5 days **Type of Analysis:** Not reported
Mosimann[32] 2004 United States	**Patient Selection:** Referred by general practitioners or psychiatrists **Inclusion Criteria:** 40-90 years old, diagnosis of treatment resistant depression according to DSM-IV and ICD-10 **Exclusion Criteria:** head injury, epilepsy, comorbid unstable medical or neurological illness, no birth control (women), **Patient Selection:** Forty-two patients referred, 18 excluded before patient randomization. Fifteen participants (5 female, 10 male), mean age 60 (13.4) received active rTMS. Nine participants (5 female, 4 male), mean age 64.4(13) received sham rTMS **Definition of Treatment Resistance:** Failure to respond to at least two adequate antidepressant trials during current depressive episode.	**Type of Control** Sham with antidepressant medication (remaining stable) **Type of Comparator** 20 Hz rTMS to the left dorsolateral prefrontal cortex delivered at 100% motor threshold in 2 second trains with 28 seconds between trains (1600 pulses), for 10 daily sessions over 2 weeks (5 per week)	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory, National Institute of Mental Health Scale, Visual analogue scale, Mini-mental State exam, Verbal learning task, Stroop test, Trail-Making Tests A and B, word fluency test **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, week 2 **Type of Analysis:** Not reported
O'Reardon[33] 2007 United States	**Patient Selection:** Participants were recruited from twenty-three sites in United States, Australia, Canada, from January 2004 to August 2005 **Inclusion Criteria:** Medication free outpatient, age 18-70, DSM-IV diagnosis of Major Depressive Disorder, <3 year length of current episode, ≥4 Clinical Global Impression, ≥20 Hamilton Depression Rating Scale, symptom stability for 1 week, treatment resistant depression **Exclusion Criteria:** psychosis, bipolar disorder, obsessive compulsive disorder, posttraumatic stress disorder, eating disorder, no response to ECT, prior treatment with TMS, pregnant, personal or family history of seizures, neurologic disorder or medication that alters seizure threshold, ferromagnetic material in close proximity to head **Patient Selection:** 155 participants (86 females, 69 males), mean age 47.9(11) were randomized to receive active rTMS. 146 participants (74 females, 72 males), mean age 48.7(10.6) were randomized to receive sham rTMS **Definition of Treatment Resistance:** Failure to respond to 1-4 adequate trials of antidepressants	**Type of Control** Sham with no antidepressants **Type of Comparator** rTMS to the left dorsolateral prefrontal cortex delivered at 120% motor threshold, 10pulses a second, 4 seconds on at 26 second intervals; 6 weeks with 5 sessions per week (1 daily)	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Hamilton Depression Rating Scale, Clinical Global Impression **Follow-up time:** 10 weeks **Outcome ascertainment:** Baseline, week 2, 4, and 6 **Type of Analysis:** Intention-to-treat
Padberg[34] 1999 Germany	**Patient Selection:** Right-handed patients from the Department of Psychiatry, Ludwig-Maximilian University Munich participated in the study. **Inclusion Criteria:** Patients who met the DSM-IV criteria for Major Depressive Disorder (single episode in three, recurrent depression in 15). **Exclusion Criteria:** Patients with organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps were excluded. **Patient Characteristics:** Eighteen patients (12 received rTMS) were included. Six patients were randomized to the sham rTMS group, 4 males and 2 females were, with a mean age of 63.5(15.8). Six patients were randomized to the high-frequency rTMS group, 2 women and 4 men, with a mean age of 63.5 ± 15.8 years. **Definition of Treatment Resistance:** Received at least two, 4-week trials of adequate antidepressant treatment, including one tricyclic antidepressant, without a therapeutic response.	**Type of Control** sham rTMS **Type of Comparator** Fast rTMS at 10 Hz administered as 5 trains of 5s duration (≥30 s intertrain interval). Stimulation was applied at 90% of MT, using 250 stimuli per day for 5 successive days from Monday (day 1) to Friday (day 5).	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Adjective Mood (Bf-Sr/Bf-S9) and Depression (D-SrD-S9) Scales, Verbal Learning Task. **Follow-up time:** 5 days **Outcome ascertainment:** Baseline and after the last rTMS treatment (day 5) **Type of Analysis:** Not reported
Padberg[35] 2002 Germany	**Patient Selection:** Patients from the Department of Psychiatry, Ludwig-Maximilian University Munich participated in the study. **Inclusion Criteria:** Patients who met the DSM-IV criteria for Major Depressive Disorder (single episode in three, recurrent depression in 15). **Exclusion Criteria:** Patients with organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps were excluded. **Patient Characteristics:** Thirty-one patients (20 received rTMS) were included. Ten patients were randomized to the sham rTMS group, 8 females and 2 males, with a mean age of 52.7(5.7) years. Ten patients were randomized to the high-stimulation intensity group, 6 women and 4 men, with a mean age of 62.1 ± 4.6 years. **Definition of Treatment Resistance:** At least two antidepressant trials of adequate duration and dosage without significant clinical improvement.	**Type of Control** sham rTMS **Type of Comparator** 100% stimulation intensity related to MT (1500 stimuli/day, 10 Hz, 10 s, 15 trains, 30 s intertrain-interval). Patients underwent 10 afternoon sessions of rTMS at the left DLPFC within two weeks.	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Clinical Global Impression, VAS and brief questionnaires to document side effects, tolerability, and rTMS-induced sensations. **Follow-up time:** 14 days **Outcome ascertainment:** Before treatment (baseline), and at day 7 and day 14 of the study. **Type of Analysis:** Not reported

Paillère Martinot[36] 2010 France	**Patient Selection:** Patients were recruited by senior psychiatrists from consecutive admissions at five university psychiatry departments. **Inclusion Criteria:** Patients with a DSM-IV-R diagnosis of major depressive disorder. **Exclusion Criteria:** Age >65 yr, alcohol or substance dependence in the past 6 months, electroconvulsive therapy (ECT) treatment in the past 6 months, any present medical condition, history of epileptic seizures, history of neurological disorders or substantial brain damage, and contraindication to magnetic fields, according to established safety criteria. **Patient Characteristics:** Fifty patients (34 received rTMS) entered the study. Twenty patients were randomized to the standard rTMS group, 11 females and 9 males, with a mean age: 48.19 ± 7.77 years. Fourteen patients were randomized to the sham rTMS group, 10 females and 6 males, with a mean age of 46.57(10.27) years. **Definition of Treatment Resistance:** At least two trials of antidepressants of different classes given at adequate doses (>150 mg/d in an equivalent dose of imipramine) and duration (at least 4 wk for each drug).	**Type of Control:** Sham with stable doses of prior medication for at least 2 weeks **Type of Comparator:** rTMS target location was based on motor cortex location. Twenty trains of 8 s with 60-s inter-train intervals were administered with stimulus frequency at 10 Hz and intensity at 90% of MT, resulting in a total of 1600 pulses over 20 min. rTMS was administered on 10 consecutive working days, providing a total of 16000 impulses. While on a stable dose of prior medications	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Hamilton Depression Rating Scale, and the Clinical Global Impression of Illness – Severity (CGI-S). **Follow-up time:** 10 days **Outcome ascertainment:** Baseline and the last day of treatment (Day 10). **Type of Analysis:** Intent-to-treat
Pascual-Leone[37] 1996 Spain	**Patient Selection:** Participants consisted of 17 right-handed patients either admitted to hospital or treated in an outpatient setting. **Inclusion Criteria:** Patients who met the diagnostic criteria for major depression psychotic subtype (DSM-III-R); met published safety criteria for rTMS; and gave their informed consent to the study. **Exclusion Criteria:** History of brain surgery or epilepsy; abnormal neurological and general physical examinations; concurrent serious medical illnesses requiring long-term treatment; previously received TMS. **Patient Characteristics:** Seventeen patients entered into the multiple cross-over study. None had bipolar affective disorder, but all had a history of relapsing unipolar major depression. Nine patients had previously received electroconvulsive treatment to which they had responded with significant benefit for several months. **Definition of Treatment Resistance:** At least three episodes of depression that had been resistant to multiple medications, despite combinations and high dosage.	**Type of Control:** Sham with or without antidepressant usage **Type of Comparator:** rTMS to the left DLPFC applied at different scalp positions. Five courses of rTMS were administered, each consisting of five sessions over 5 (consecutive) days. Each session consisted of 20 trains of 10 s duration separated by 1 min pauses. Stimulation was applied at 10 Hz frequency at 90% intensity of the patient's motor threshold.	**Outcomes measured:** Hamilton Depression Rating Scale and Beck's Questionnaire for patient self-rated mood. **Follow-up time:** 5 months **Outcome ascertainment:** Baseline and weekly throughout the study (i.e. at the end of weeks 1-20 of the study). **Type of Analysis:** Not reported
Peng[38] 2012 China	**Patient Selection:** Inpatient and outpatient units at Institute of Mental Health at Sexond Xiangya Hospital of Central South University **Inclusion Criteria:** Treatment resistant, met DSM-IV for major depressive episode, naïve to rTMS **Exclusion Criteria:** psychiatric axis 1 and 2 disorders, epileptic seizures, any neurological disorder, metal implants, other clinically relevant abnormalities **Patient Selection:** Seventeen participants (7 females, 10 males), mean age 27.4(6.145) were randomized to receive active rTMS. Thirteen participants (4 females, 9 males), mean age 26.380(3.452) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 different antidepressants given for 4 weeks each at the maximum recommended dose	**Type of Control** Sham with 10mg/day escitalopram **Type of Comparator** 15 Hz rTMS to the left dorsolateral prefrontal cortex at 110% motor threshold, 4 second duration of 50 trains, (3000 stimulations a day); 4 weeks with 20 sessions (5 per week). In addition to active rTMS, participants took 10mg/day escitalopram.	**Outcomes measured:** Beck Depression Inventory, Hamilton Depression Rating Scale **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, week 4 **Type of Analysis:** Not reported
Rossini[39] 2005 Italy	**Patient Selection:** Participants consisted of right-handed patients, consecutively admitted to the mood disorders center of the Department of Psychiatry (San Raffaele Hospital, Milan, Italy). **Inclusion Criteria:** Patients suffering from a severe (HAM-D score of 26 or higher) and drug-resistant major depressive episode without psychotic features established on the basis of unstructured clinical interviews and medical records according to DSM-IV criteria and following the best estimate procedure. **Exclusion Criteria:** Age younger than 18 years and older than 75 years, history of seizures or neurological illnesses, severe medical conditions that could interfere with the clinical evaluation, pregnancy, mental retardation, and Edinburgh Handedness Inventory score below +70, and patients bearing pacemakers, mobile metal implants, implanted medical pumps or metal clips placed inside the skull. **Patient Characteristics:** Fifty-two out of 54 patients enrolled, completed the entire study protocol. Eighteen patients were randomized to the high-intensity rTMS group, 12 females and 6 males, with a mean age of 57.4 ± 8.7 years. Seventeen patients (11 females, 6 males) with a mean age of 56.3(12.6) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** A lack of improvement to at least two different treatments with antidepressants, at adequate dosage and duration, administered during the current episode.	**Type of Control:** Sham with stable medication **Type of Comparator:** rTMS stimulation intensity of 100% of MT, frequency 15 Hz and duration of the train of stimulations 2 s. The inter-train interval was 28 s, and every subject received 20 trains of pulses per session. Patients underwent 10 sessions of stimulation over a 2-week period (Monday to Friday).	**Outcomes measured:** Hamilton Depression Rating Scale, Clinical Global Impression (Severity and Improvement) **Follow-up time:** 5 weeks **Outcome ascertainment:** Baseline (with the exception of CGI-I) and weekly thereafter for 5 weeks. **Type of Analysis:** Not reported
Speer[40] 2009 United States	**Patient Selection:** Not reported **Inclusion Criteria:** Highly treatment-resistant depressed patients meeting DSM-IV criteria for either bipolar illness or unipolar major depression. **Exclusion Criteria:** Not reported **Patient Characteristics:** Twenty-two patients with either bipolar illness (n=9) or unipolar major depression (n=13) were included in the multiple cross-over study and 19 of these patients received both high- and low-frequency active rTMS. **Definition of Treatment Resistance:** Not reported	**Type of Control:** sham rTMS **Type of Comparator:** 20 Hz stimulation was administered with 2s on an d 28 s off, 40 times, for a total of 1600 stimulations per 20-minute session. Stimulation was applied over the left PFC at 100% of MT. Patients were first randomized to receive 10 daily sessions (five times/week) of a) high- or low-frequency active rTMS, or b) sham rTMS. Those receiving active rTMS were then crossed over to the opposite frequency in the second two weeks to evaluate response within individuals. Those receiving sham rTMS first were then exposed to both of the other rTMS frequencies for two weeks. After patients were exposed to both active	**Outcomes measured:** Hamilton Depression Rating Scale (28-item expanded version). **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline and the end of weeks 1, 2, 3 and 4. **Type of Analysis:** Not reported

		frequencies, they were allowed to enter a continuation phase (at the rTMS frequency to which they had responded the best) for treatment confirmation and optimization.	
Speer[41] 2013 United States	**Patient Selection:** Participants were recruited from treatment resistant inpatients and outpatients. **Inclusion Criteria:** Patients diagnosed by SCID interview meeting DSM-IV criteria for major depressive episode that were treatment resistant. **Exclusion Criteria:** A history of seizure disorders or other major comorbid medical problems or psychiatric diagnoses, and not previously undergone ECT. **Patient Characteristics:** Twenty-four patients (16 received rTMS) presented with unipolar (n=15) or bipolar (n=9) depression were included. Eight patients were randomized to the sham rTMS group, 3 females and 5 males, with a mean age of 44.9(9.1) years. Eight patients were randomized to the high-frequency rTMS group, 5 females and 3 males, with a mean age of 41.3 ± 14.5 years. **Definition of Treatment Resistance:** Failed at least two previous antidepressant trials.	**Type of Control:** Sham **Type of Comparator:** 20 Hz stimulation was administered with 2s on and 28 s off, 40 times, for a total of 1600 stimulations/20 min session. Patients received 15 daily sessions of rTMS (five times/week) over the left PFC at 110% of MT.	**Outcomes measured:** Hamilton Depression Rating Scale (28-item expanded version). **Follow-up time:** 7 weeks: 3 weeks randomized, blind trial and 4 weeks of open treatment continuation. **Outcome ascertainment:** Baseline and weekly thereafter for 7 weeks. **Type of Analysis:** Not reported
Stern[42] 2007 United States	**Patient Selection:** Participants were outpatients who had been referred for ECT having failed an adequate course of antidepressant medication. **Inclusion Criteria:** Patients were right-handed, between the ages of 21 and 80, met the SCID and DSM-IV criteria for a major depressive episode (score of 20 on the HAM-D), had no psychotic features, no other Axis I were naïve to TMS, and not participated in previous research studies on TMS and depression. **Exclusion Criteria:** A history of any psychotic disorder, including schizophrenia or schizoaffective disorder; bipolar disorder; obsessive compulsive disorder; personality disorder; substance abuse (except nicotine) within past year; current acute or chronic medical condition requiring treatment with psychoactive medication; a history of epilepsy or unprovoked seizures or other neurological disorder; abnormal neurological examination; family history of medication-resistant epilepsy; prior brain surgery; metal in the head; an implanted medical device; pregnancy; or unable to tolerate the medication withdrawal (14-day washout period). **Patient Characteristics:** Sixty patients (30 received rTMS) with unipolar disorder were included. Fifteen patients were randomized to the sham rTMS group, 9 females and 6 males, with a mean age of 53.3(9) years. Ten patients were randomized to the left-sided high-frequency rTMS group, 6 females and 4 males, with a mean age of 53.2 ± 12 years. **Definition of Treatment Resistance:** Not reported	**Type of Control:** Sham without medication **Type of comparator:** Left-sided DLPFC rTMS at a frequency of 10 Hz, 20 train per session (8s train and 52s intertrain interval), duration of 1200s per session, and stimuli provided at 110% MT. Patients received rTMS treatment for 10 days.	**Outcomes measured:** Hamilton Depression Rating Scale (21-item). **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 4 weeks. **Type of Analysis:** Not reported
Su[43] 2005 China	**Patient Selection:** Not reported **Inclusion Criteria:** Patients who met the DSM-IV criteria for a major depressive episode or bipolar disorder (based on the Mini-International Psychiatric Interview), were treatment resistant. **Exclusion Criteria:** A history of epilepsy, history of physical or neurological abnormalities, an implanted pacemaker, showed any signs of substantial risk of suicide during the trial, or previously had major head trauma or displayed any psychotic symptoms, not previously had rTMS treatment or ECT. **Patient Characteristics:** Thirty patients (22 received rTMS) were included. Ten patients were randomized to the sham rTMS group, 7 females and 3 males, with a mean age of 42.6(11.0) years. Ten patients were randomized to the high-frequency rTMS group, 7 females and 3 males, with a mean age of 43.6 ± 12.0 years. **Definition of Treatment Resistance:** Failed to respond to at least two adequate trials of antidepressant medications (a minimum of 6 weeks of treatment with a dosage adequate for treatment of depression in the majority of patients) prior to rTMS treatment.	**Type of Control:** Sham **Type of Comparator:** 20 Hz stimulation to the left DLPFC, in 40 2-second trains over 20 mins for 10 weekdays (total= 16,000 pulses) at 100% MT.	**Outcomes measured:** Hamilton Depression Rating Scale (21-item), Clinical Global Impression – Severity, Beck Depression Inventory. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 2 weeks. **Type of Analysis:** Not reported
Triggs[44] 2010 United States	**Patient Selection:** Participants were recruited through psychiatrists in private practice, referrals from tertiary care center clinics, and newspaper advertisements. **Inclusion Criteria:** Between 18 and 75 years of age, medically-resistant major depression according to DSM-IV criteria and verified by the SCID, and score of 18 or higher and a score of at least 3 on item number 1 of the 24-item HAM-D in two separate screening sessions. **Exclusion Criteria:** A lifetime history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar illness, alcohol or drug abuse within the past year; a positive urine drug test; axis II diagnosis of Cluster A (paranoid, schizoid, or schizotypal) or Cluster B (antisocial, borderline, histrionic, or narcissistic) personality disorder or mental retardation; use of medications that may lower seizure threshold (e.g. metronidazole) if the particular medication could not be stopped or altered without affecting the patient's medical care; history of neurological illness, epilepsy or seizure disorder, intracranial tumor, or major head trauma leading to loss of consciousness of any duration; evidence of central nervous system disease based on baseline complete neurological examination, EEG and contrast-enhanced computerized tomography or magnetic resonance imaging of the brain; history of implanted pacemaker or medication pump, metal plate in skull, or metal objects in the eye or skull; need for rapid clinical response due to conditions such as inanition, psychosis, or suicidality (defined as suicide attempt during the current major depressive episode or having a specific plan for committing suicide); a medical condition that was not well controlled, such as diabetes or hypertension, or concomitant medical or nutritional problems necessitating hospitalization; use of anticonvulsant mood stabilizers (e.g. carbamazepine, valproic acid); or inability to personally grant informed consent.	**Type of Control:** Sham with medication **Type of Comparator:** Left rTMS at 100% to the DLPFC at 100% of MT at a rate of 5 Hz. Each daily treatment consisted of 2000 stimuli divided into 50 trains of 40 stimuli. Participants received 10 daily weekday sessions of either rTMS or sham rTMS over a 2-week period.	**Outcomes measured:** Hamilton Depression Rating Scale (24-item), Beck Depression Inventory, State Trait Anxiety Inventory **Follow-up time:** 3 months **Outcome ascertainment:** Baseline (3 separate occasions during the 2-week period prior to rTMS), weekly during the 2-week rTMS treatment period, and 1 week, 1-month and 3-months following completion of rTMS. **Type of Analysis:** Not reported

	Patient Characteristics: Seven patients were randomized to the sham rTMS group, 4 females and 3 males, with a mean age of 46.6(20.2) years. Eighteen patients were randomized to the left-sided rTMS group, 14 females and 4 males, with a mean age of 46.7 ± 15.3 years. **Definition of Treatment Resistance:** Failed historically to respond to at least two separate trials (minimum duration 4 weeks) of therapeutic dosages of antidepressant medication (including at least one SSRI) or were intolerant of at least three different antidepressant medications (including at least one SSRI).		
Zheng[45] 2010 China	**Patient Selection:** Unknown **Inclusion Criteria:** Treatment Resistant, DSM-IV diagnosis of major depressive episode, Age 18-37 years, naïve to rTMS **Exclusion Criteria:** axis-I or axis-II disorders, epileptic seizure or other neurologic disorder, metal implants, clinically relevant abnormalities, drug of alcohol abuse **Patient Characteristics:** 34 subjects randomized to 19 active with 12 males and 7 females(mean age 26.9[6.2]), and 15 sham with 10 males and 5 females (mean age 26.7[4.3]) **Definition of Treatment Resistance:** Failure to respond to more than 2 antidepressants given at an adequate dosage for no longer than 4 weeks	**Type of Control** Sham taking escitalopram 10mg per day, not discontinuing antidepressants **Type of Comparator** 15 Hz 110% motor threshold, over the dorsolateral prefrontal cortex, 20 sessions over 4 weeks (3000 stimuli/day) taking escitalopram 10mg per day, not discontinuing antidepressants	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, week 4 **Type of Analysis:** Not reported

DLPFC Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **rTMS** Repetitive Transcranial Magnetic Stimulation; **SD** Standard Deviation; **SSRI** Selective Serotonin Reuptake Inhibitor

Reference List

1. Avery DH, Claypoole K, Robinson L et al. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *J Nerv Ment Dis* 1999;187(2):114-117.
2. Avery DH, Holtzheimer PE, Fawaz W et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry* 2006;59(2):187-194.
3. Baeken C, Vanderhasselt MA, Remue J et al. Intensive HF-rTMS treatment in refractory medication-resistant unipolar depressed patients. *J Affect Disord* 2013;151(2):625-631.
4. Bakim B, Uzun UE, Karamustafalioglu O et al. The combination of antidepressant drug therapy and high-frequency repetitive transcranial magnetic stimulation in medication-resistant depression. *Klin Psikofarmakol Bul* 2012;22(3):244-253.
5. Bares M, Kopecek M, Novak T et al. Low frequency (1-Hz), right prefrontal repetitive transcranial magnetic stimulation (rTMS) compared with venlafaxine ER in the treatment of resistant depression: a double-blind, single-centre, randomized study. *J Affect Disord* 2009;118(1-3):94-100.
6. Berman RM, Narasimhan M, Sanacora G et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol Psychiatry* 2000;47(4):332-337.
7. Blumberger DM, Mulsant BH, Fitzgerald PB et al. A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *World J Biol Psychiatry* 2012;13(6):423-435.
8. Bortolomasi M, Minelli A, Fuggetta G et al. Long-lasting effects of high frequency repetitive transcranial magnetic stimulation in major depressed patients. *Psychiatry Res* 2007;150(2):181-186.
9. Boutros NN, Gueorguieva R, Hoffman RE, Oren DA, Feingold A, Berman RM. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. *Psychiatry Res* 2002;113(3):245-254.
10. Bretlau LG, Lunde M, Lindberg L, Unden M, Dissing S, Bech P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry* 2008;41(2):41-47.
11. Chen SJ, Chang CH, Tsai HC, Chen ST, Lin CC. Superior antidepressant effect occurring 1 month after rTMS: add-on rTMS for subjects with medication-resistant depression. *Neuropsychiatr dis treat* 2013;9:397-401.
12. Fitzgerald PB, Brown TL, Marston NAU, Daskalakis ZJ, de Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 2003;60(10):1002-1008.
13. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 2006;163(1):88-94.
14. Fitzgerald PB, Hoy KE, Herring SE et al. A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. *J Affect Disord* 2012;139(2):193-198.
15. Garcia-Toro M, Pascual-Leone A, Romera M et al. Prefrontal repetitive transcranial magnetic stimulation as add on treatment in depression. *J Neurol Neurosurg Psychiatry* 2001;71(4):546-548.
16. Garcia-Toro M, Salva J, Daumal J et al. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. *Psychiatry Res* 2006;146(1):53-57.

17. George MS, Lisanby SH, Avery D et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010;67(5):507-516.
18. Hernandez-Ribas R, Deus J, Pujol J et al. Identifying brain imaging correlates of clinical response to repetitive transcranial magnetic stimulation (rTMS) in major depression. *Brain Stimul* 2013;6(1):54-61.
19. Holtzheimer PE, Russo J, Claypoole KH, Roy-Byrne P, Avery DH. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. *Depress Anxiety* 2004;19(1):24-30.
20. Jorge RE, Robinson RG, Tateno A et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. *Biol Psychiatry* 2004;55(4):398-405.
21. Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry* 2008;65(3):268-276.
22. Kauffmann CD, Cheema MA, Miller BE. Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: A double-blind, placebo-controlled study. *Depress Anxiety* 2004;19(1):59-62.
23. Lisanby SH, Husain MM, Rosenquist PB et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology* 2009;34(2):522-534.
24. Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *Am J Psychiatry* 1999;156(6):946-948.
25. Loo CK, Mitchell PB, Croker VM et al. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. *Psychol Med* 2003;33(1):33-40.
26. Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. *Psychol Med* 2007;37(3):341-349.
27. Manes F, Jorge R, Morcuende M, Yamada T, Paradiso S, Robinson RG. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *Int Psychogeriatr* 2001;13(2):225-231.
28. Mantovani A, Aly M, Dagan Y, Allart A, Lisanby SH. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. *J Affect Disord* 2013;144(1-2):153-159.
29. McDonald WM, Easley K, Byrd EH et al. Combination rapid transcranial magnetic stimulation in treatment refractory depression. *Neuropsychiatr dis treat* 2006;2(1):85-94.
30. Moller AL, Hjaltason O, Ivarsson O, Stefansson SB. The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P(300) event-related potential. *Nord J Psychiatry* 2006;60(4):282-285.
31. Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG. Improved executive functioning following repetitive transcranial magnetic stimulation. *Neurology* 2002;58(8):1288-1290.
32. Mosimann UP, Schmitt W, Greenberg BD et al. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Res* 2004;126(2):123-133.
33. O'Reardon JP, Solvason HB, Janicak PG et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007;62(11):1208-1216.
34. Padberg F, Zwanzger P, Thoma H et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 1999;88(3):163-171.
35. Padberg F, Zwanzger P, Keck ME et al. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology* 2002;27(4):638-645.
36. Paillere Martinot ML, Galinowski A, Ringuenet D et al. Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: a [(18)F]-fluorodeoxyglucose PET and MRI study. *Int J Neuropsychopharmcol* 2010;13(1):45-59.
37. Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 1996;348(9022):233-237.
38. Peng H, Zheng H, Li L et al. High-frequency rTMS treatment increases white matter FA in the left middle frontal gyrus in young patients with treatment-resistant depression. *J Affect Disord* 2012;136(3):249-257.
39. Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res* 2005;137(1-2):1-10.
40. Speer AM, Benson BE, Kimbrell TK et al. Opposite effects of high and low frequency rTMS on mood in depressed patients: relationship to baseline cerebral activity on PET. *J Affect Disord* 2009;115(3):386-394.

41. Speer AM, Wassermann EM, Benson BE, Herscovitch P, Post RM. Antidepressant efficacy of high and low frequency rtms at 110% of motor threshold versus sham stimulation over left prefrontal cortex. *Brain Stimul* 2013;No.
42. Stern WM, Tormos JM, Press DZ, Pearlman C, Pascual-Leone A. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. *J Neuropsychiatry Clin Neurosci* 2007;19(2):179-186.
43. Su TP, Huang CC, Wei IH. Add-on rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *J Clin Psychiatry* 2005;66(7):930-937.
44. Triggs WJ, Ricciuti N, Ward HE et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. *Psychiatry Res* 2010;178(3):467-474.
45. Zheng H, Zhang L, Li L et al. High-frequency rTMS treatment increases left prefrontal myo-inositol in young patients with treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2010;34(7):1189-1195.

Supplementary Table 2: Characteristics of Studies Assessing Efficacy of High Frequency rTMS Versus Low Frequency rTMS

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Eche[1] 2012 France	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** MADRS score > 20 despite prescription of an anti-depressant for at least 12 weeks. **Exclusion Criteria:** History of personal or family seizures, neurological or neurosurgical antecedent, inner ear prosthesis, pace-maker, and anticonvulsive medication. **Patient Characteristics:** Eight patients with mean age of 46.1 (16.3), 6 females and 2 males were randomized to low frequency. Six patients with a mean age of 50.8 (9.4), 2 females and 4 males were randomized to high frequency. **Definition of Treatment Resistance:** Stage 1 of treatment-resistant depression.	**Low:** 1 HZ rTMS to right DLPFC 100% MT for 2 trains of 120 pulses once per day for 2-4 weeks. **High:** 10 HZ rTMS to left DLPFC 100% MT for 40 trains of 2000 pulses once per day for 2-4 weeks.	**Outcomes measured:** MADRS **Follow-up time:** 20 sessions (between 2-4 weeks) **Outcome ascertainment:** Baseline and every 5 sessions **Type of Analysis:** NR
Fitzgerald[2] 2003 Australia	**Patient Selection:** Patients were recruited from 2 outpatient clinics and by psychiatrist referral between October 2000 and September 2002 and were randomized via sealed envelopes. **Inclusion Criteria:** NR **Exclusion Criteria:** Significant medical illness, neurologic disorders or other Axis I psychiatric disorders. **Patient Characteristics:** Twenty patients with a mean age of 45.5 (11.49), 7 females and 13 males were randomized to low frequency right-sided rTMS. Twenty patients with a mean age of 42.2 (9.8), 8 females and 12 males were randomized to high frequency left-sided rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks.	**Low:** 1 Hz rTMS to right DLPFC 100% MT for 5 trains (300 stimuli per treatment) 5 days per week for 2 weeks. **High:** 10 Hz rTMS to left DLPFC 100% MT for 20 trains (1000 stimuli per treatment) 5 days per week for 2 weeks.	**Outcomes measured:** MADRS, BDI, BPRS, CORE rating of psychomotor disturbance, CGI, Personal Semantic Memory Schedule, Autobiographical Wechsler Adult Intelligence Scale, Tower of London, Controlled Oral Word Association Test **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, 4 weeks **Type of Analysis:** NR
Fitzgerald[3] 2006 Australia	**Patient Selection:** Patients were recruited from 3 hospitals between May 2004 and January 2006 and were randomized using computer generated sequences. **Inclusion Criteria:** HAMD score > 16 **Exclusion Criteria:** Significant medical illness, neurologic disorders, contraindications to rTMS, DSM-IV diagnosis of alcohol or substance dependence. **Patient Characteristics:** Sixty-seven patients with a mean age of 50.5 (13.8), 45 females and 22 males were randomized to low frequency rTMS. Sixty-three patients with a mean age of 48.1 (14.0), 38 females and 25 males were randomized to high frequency rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Low:** 1 Hz rTMS to right DLPFC 110% MT for 1 train (900 stimuli per treatment) 5 days per week for 2 weeks. **High:** 2 Hz rTMS to right DLPFC 110% MT for 1 train (1800 stimuli per treatment) 5 days per week for 2 weeks.	**Outcomes measured:** HAMD, BDI **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, 4 weeks. **Type of Analysis:** NR
Fitzgerald[4] 2007 Australia	**Patient Selection:** Patients were recruited between March 2003 and January 2005 and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Eleven patients with a mean age of 39.6 (10), 5 females and 6 males were randomized to low frequency right-sided rTMS. Fifteen patients with a mean age of 42.4 (11.2), 8 females and 7 males were randomized to high frequency left-sided rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Low:** 1 Hz rTMS to right DLPFC 110% MT for 4 trains, 5 days per week for 3 weeks. **High:** 10 Hz rTMS to left DLPFC 100% MT for 30 trains, 5 days per week for 3 weeks.	**Outcomes measured:** MADRS **Follow-up time:** 3 weeks **Outcome ascertainment:** Baseline, 3 weeks **Type of Analysis:** NR
Fitzgerald[5] 2009 Australia	**Patient Selection:** Patients were recruited from 1 outpatient clinic and by referral from private psychiatrists (recruitment dates not reported) and were randomized using computer generation. **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Eleven patients with a mean age of 46.5 (11.4), 3 females and 8 males were randomized to low frequency right DLPFC rTMS. Fifteen patients with a mean age of 42.1 (9.3), 8 females and 7 males were randomized to high frequency left DLPFC rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode	**Low:** rTMS to the right DLPFC 110% MT for 4 trains 180 seconds duration 5 days per week for 3 weeks (HZ not specified). **High:** rTMS to the left DLPFC 100% MT for 30 trains 5seconds duration 5 days per week for 3 weeks (HZ not specified).	**Outcomes measured:** MADRS, BDI, HAMD, BPRS, CORE rating of psychomotor disturbance, GAF, Hopkins verbal learning test, controlled oral word association test, Digit span, Brief visuospatial memory test-revised. **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 3 weeks, 4 weeks **Type of Analysis:** NR
Isenberg[6] 2005 United States	**Patient Selection:** Patients were recruited through community physicians (recruitment dates not reported) and allocated to treatment based on date of entry. **Inclusion Criteria:** NR **Exclusion Criteria:** Psychosis, significant medical illnesses, neurologic disorders, implanted metal devices, or other major Axis I psychiatric disorders. **Patient Characteristics:** Fourteen patients with a mean age of 55.6 (9.7), 8 females and 6 males received right-sided low frequency rTMS. Fourteen patients with a mean age of 43.4 (9.7), 8 females and 6 males received left-sided high frequency rTMS. **Definition of Treatment Resistance:** Failed to respond to at least 2 treatment trials of different antidepressant medication types, each used for an adequate period of time at an adequate dose.	**Low:** 1 Hz rTMS to the right DLPFC at 110% MT for 2 trains 5 days/week for 4 weeks. **High:** 20 Hz rTMS to the left DLPFC at 80% MT for 50 trains of 40 pulses 5 days/week for 4 weeks.	**Outcomes measured:** HAMD, BDI, CGI, SSTAI, MMSE, Cloninger's Temperament and Character Inventory **Follow-up time:** 10 sessions (up to 4 weeks) **Outcome ascertainment:** Baseline, 5 sessions, 10 sessions. **Type of Analysis:** NR

Miniussi[7] 2005 Italy	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and randomized (method not reported). **Inclusion Criteria:** HAMD score ≥ 12 or clinical improvement on the HRSD ≤ 50% obtained after treatment with at least two classes of anti-depressive drugs, no history of epilepsy or other neurological disorders. **Exclusion Criteria:** NR **Patient Characteristics:** Twenty inpatients (15 female and 5 male) were included in the first experimental treatment. Ten patients with a mean age of 52 years received low-frequency rTMS. Ten patients with a mean age of 58 years received left-sided high-frequency rTMS. Forty outpatients were included in the second experimental treatment. Twenty patients with mean age ranging from 48-59 years, received low-frequency rTMS group. Twenty patients with mean age ranging from 53-54 years, received high-frequency rTMS group. **Definition of Treatment Resistance:** NR	**Low:** 1 Hz rTMS to the left DLPFC at 110% of MT for two experimental treatments. Experimental Treatment 1: 1 Hz rTMS (real/sham) of 5 consecutive sessions that started on Monday, separated by 24 hrs. Experimental Treatment 2: Patients received either a) real 1 Hz-TMS, followed by a second block of sham 1 Hz-TMS; or b) sham 1 Hz-rTMS first, followed by real 1 Hz-TMS second. The two blocks of stimulation (real/sham or sham/real) were separated by an interval of 8 weeks. **High:** 17 Hz rTMS to left DLPFC at 110% of MT for two experimental treatments. Experimental Treatment 1: 17 Hz-TMS (real/sham) of 5 consecutive sessions that started on Monday, separated by 24 hrs. Experimental Treatment 2: Patients received either a) real 17 Hz-TMS, followed by a second block of sham 17 Hz-TMS; or b) sham 17 Hz-rTMS first, followed by real 17 Hz-TMS second. The two blocks of stimulation (real/sham or sham/real) were separated by an interval of 8 weeks.	**Outcomes measured:** HAMD, BPRS. **Follow-up time:** 1 week for the first experimental treatment. 10 weeks for the second experimental treatment. **Outcome ascertainment:** Baseline, 5 days after treatment for the first experimental treatment. Baseline, 5 days, 8 weeks and 9 weeks after the first treatment block for the second experimental treatment **Type of Analysis:** NR
Padberg[8] 1999 Germany	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** Patients with organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps were excluded. **Patient Characteristics:** Six patients with a mean age of 46.7 (14.7), 5 females and 1 male were randomized to the low-frequency rTMS group. Six patients with a mean age of 63.5 (15.8), 2 females and 4 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** Received at least two, 4-week trials of adequate antidepressant treatment, including one tricyclic antidepressant, without a therapeutic response.	**Low:** 0.3 Hz rTMS to left DLPFC at 90% of MT for 10 trains of 25 pulses, 250 stimuli per day for 5 successive days from Monday (day 1) to Friday (day 5). **High-frequency:** 10 Hz rTMS to left DLPFC at 90% of MT for 5 trains of 5s duration, 250 stimuli per day for 5 successive days from Monday (day 1) to Friday (day 5).	**Outcomes measured:** HAMD, MADRS, Adjective Mood and Depression (D-S/D-S') Scales, Verbal Learning Task. **Follow-up time:** 5 days **Outcome ascertainment:** Baseline and after the last rTMS treatment (day 5) **Type of Analysis:** NR
Richieri[9] 2012 France	**Patient Selection:** Patients were screened through retrospective chart reviews from 1 teaching hospital from January 2010, to August 2010 and September 2010 to December 2010. **Inclusion Criteria:** Met the DSM-IV criteria for major depressive disorder (unipolar or bipolar depression). **Exclusion Criteria:** Age under 18 years, neurological disorders or convulsive disorders, and previous rTMS or ECT treatments. **Patient Characteristics:** Twenty-eight patients with a mean age of 54.1 (12.8), 14 females and 14 males were randomized to the low-frequency rTMS group,,Thirty-three patients with a mean age of 55.6 (12.5), 18 females and 15 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** Not responsive to pharmacological treatment of depression using a minimum of two distinctly different classes of antidepressant medications for episodes occurring at the time of enrolment or earlier.	**Low:** 1 Hz rTMS to right DLPFC at a frequency at 120% of left MT, 60-second trains with a 30-second inter-train interval (360 pulses per day). Twenty treatment sessions were administered in a 4-week period (five sessions per week). **High:** 10 Hz rTMS to left DLPFC at 120% of right MT, 5-second trains with a 25-second inter-train interval (2000 pulses per day). Twenty treatment sessions were administered in a 4-week period (five sessions per week).	**Outcomes measured:** BDI,,CGI, STAI. **Follow-up time:** 4 weeks **Outcome ascertainment:** Twice at baseline and after 20 sessions (Week 4). **Type of Analysis:** NR
Rossini[10] 2010 Italy	**Patient Selection:** Patients consecutively admitted to 1 hospital were recruited from September 2006 to November 2007 and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** The presence of any concomitant axis I diagnosis, psychotic features, somatic or neurological illnesses impairing psychiatric evaluation, age younger than 18 years and older than 80 years, pregnancy, HAMD score less than 21, no history of seizures or bearing pacemakers, mobile metal implants, implanted medical pumps or metal clips placed inside the skull. **Patient Characteristics:** Forty-two patients with a mean age of 56.1 (13.1) for those with unipolar depression and 52.8 (10.7) for those with bipolar depression, 30 females and 12 males were randomized to the low-frequency rTMS group, Thirty-two patients with a mean age of 56.4 (8.9) for those with unipolar depression and 51.4 (14.1) for those with bipolar depression, 23 females and 9 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** NR	**Low:** 1 Hz rTMS to right DLPFC, 2 trains of 300 pulses for a total of 600 pulses/day. Stimulation was performed for 10 consecutive working days from Monday to Friday for 2 weeks (MT not reported). . **High:** 15 Hz rTMS to left DLPFC, 20 trains of 30 pulses (2sec each, with a 29sec intertrain interval), for a total or 600 pulses/day. Stimulation was performed for 10 consecutive working days from Monday to Friday for 2 weeks (MT not reported).	**Outcomes measured:** HAMD **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 2 weeks. **Type of Analysis:** NR

Speer[11] 2009 United States	**Patient Selection:** NR **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Twenty-two patients with either bipolar illness (n=9) or unipolar major depression (n=13) were included in the multiple cross-over study and 19 of these patients received both high- and low-frequency active rTMS. **Definition of Treatment Resistance:** NR	**Low:** 1 Hz rTMS to left PFC at 100% of MT, given in a continuous train of 1600 pulses over 26 min 40s. **High:** 20 Hz rTMS to left PFC at 100% of MT, 2s on and 28 s off, 40 times, for a total of 1600 stimulations per 20-minute session. Patients were first randomized to receive 10 daily sessions (five times/week) of a) high- or low-frequency active rTMS, or b) sham rTMS. Those receiving active rTMS were then crossed over to the opposite frequency in the second two weeks to evaluate response within individuals. Those receiving sham rTMS first were then exposed to both of the other rTMS frequencies for two weeks. After patients were exposed to both active frequencies, they were allowed to enter a continuation phase (at the rTMS frequency to which they had responded the best) for treatment confirmation and optimization.	**Outcomes measured:** HAMD expanded version (HAMD-28). **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline and the end of weeks 1, 2, 3 and 4. **Type of Analysis:** NR
Speer[12] 2013 United States	**Patient Selection:** Patients were recruited between October 2000 and April 2003 and were randomized (method not reported)**.** **Inclusion Criteria:** NR **Exclusion Criteria:** A history of seizure disorders or other major comorbid medical problems or psychiatric diagnoses, and not previously undergone ECT. **Patient Characteristics:** Eight patients with a mean age of 39.6 (9.0), 5 females and 3 males were randomized to the low-frequency rTMS group. Eight patients with a mean age of 41.3 (14.5), 5 females and 3 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** Failed at least two previous antidepressant trials.	**Low:** 1 Hz rTMS to the left PFC at 110% of MT was given in a continuous train of 1,600 pulses over 26 min, 40 s. Patients received 15 daily sessions of rTMS (5-times/week). **High:** 20 Hz to the left PFC at 110% of MT was administered with 2s on and 28 s off, 40 times, for a total of 1600 stimulations/20 min session. Patients received 15 daily sessions of rTMS (5-times/week) over.	**Outcomes measured:** HAMD expanded version (HAMD-28). **Follow-up time:** 7 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 7 weeks. **Type of Analysis:** NR
Stern[13] 2007 United States	**Patient Selection:** Patients were recruited from outpatients of 1 teaching hospital (recruitment dates not reported) who had been referred for ECT having failed an adequate course of antidepressant medication and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** A history of any psychotic disorder, including schizophrenia or schizoaffective disorder; bipolar disorder; obsessive compulsive disorder; personality disorder; substance abuse (except nicotine) within past year; current acute or chronic medical condition requiring treatment with psychoactive medication; a history of epilepsy or unprovoked seizures or other neurological disorder; abnormal neurological examination; family history of medication-resistant epilepsy; prior brain surgery; metal in the head; an implanted medical device; pregnancy; or unable to tolerate the medication withdrawal (14-day washout period). **Patient Characteristics:** Ten patients with a mean age of 52.3 (9.4), 6 females and 4 males were randomized to the left-sided low-frequency rTMS group. Ten patients with a mean age of 52.8 (9.5), 7 females and 3 males were randomized to the right-sided low-frequency rTMS group. Ten patients with a mean age of 53.2 (12), 6 females and 4 males were randomized to the left-sided high-frequency rTMS group. **Definition of Treatment Resistance:** NR	**Low A:** 1 Hz rTMS to left DLPFC at 110% MT, 1 train per session, duration of 1600s. Patients received rTMS treatment for 10 days. **Low B:** 1 Hz rTMS to right DLPFC at 110% MT, 1 train per session, duration of 1600s. Patients received rTMS treatment for 10 days. **High:** 10 Hz rTMS to left DLPFC rTMS at 110% MT, 20 train per session (8s train and 52s intertrain interval), duration of 1200s per session. Patients received rTMS treatment for 10 days.	**Outcomes measured:** HAMD **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 4 weeks. **Type of Analysis:** NR
Su[14] 2005 Taiwan	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** A history of epilepsy, history of physical or neurological abnormalities, an implanted pacemaker, showed any signs of substantial risk of suicide during the trial, or previously had major head trauma or displayed any psychotic symptoms, not previously had rTMS treatment or ECT. **Patient Characteristics:** Ten patients with a mean age of 43.2 (10.6), 8 females and 2 males were randomized to the low-frequency rTMS group. Ten patients with a mean age of 43.6 (12.0), 7 females and 3 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** Failed to respond to at least two adequate trials of antidepressant medications (a minimum of 6 weeks of treatment with a dosage adequate for treatment of depression in the majority of patients) prior to rTMS treatment.	**Low:** 5 Hz rTMS to left DLPFC at 100% MT, in 40 8-second trains over 20 mins for 10 weekdays (total= 16,000 pulses)**.** **High:** 20 Hz rTMS to left DLPFC at 100% MT, in 40 2-second trains over 20 mins for 10 weekdays (total= 16,000 pulses).	**Outcomes measured:** HAMD, CGI-S, BDI. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 2 weeks. **Type of Analysis:** NR

BDI Beck Depression Inventory; **CGI** Clinical Global Impression; **DLPFC** Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **MT** Motor Threshold; **NR** Not reported; **rTMS** Repetitive Transcranial Magnetic Stimulation; **SD** Standard Deviation; **SSRI** Selective Serotonin Reuptake Inhibitor

Reference List

1. Eche J, Mondino M, Haesebaert F, Saoud M, Poulet E, Brunelin J. Low- vs High-Frequency Repetitive Transcranial Magnetic Stimulation as an Add-On Treatment for Refractory Depression. *Front Psychiatr* 2012;3:13.
2. Fitzgerald PB, Brown TL, Marston NAU, Daskalakis ZJ, de Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 2003;60(10):1002-1008.
3. Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *Int J Neuropsychopharmcol* 2006;9(6):655-666.
4. Fitzgerald PB, Sritharan A, Daskalakis ZJ, de Castella AR, Kulkarni J, Egan G. A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. *J Clin Psychopharmacol* 2007;27(5):488-492.
5. Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J. A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. *Depress Anxiety* 2009;26(3):229-234.
6. Isenberg K, Downs D, Pierce K et al. Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. *Ann Clin Psychiatry* 2005;17(3):153-159.
7. Miniussi C, Bonato C, Bignotti S et al. Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: an efficacious therapy for major drug-resistant depression? *Clin Neurophysiol* 2005;116(5):1062-1071.
8. Padberg F, Zwanzger P, Thoma H et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 1999;88(3):163-171.
9. Richieri R, Boyer L, Padovani R et al. Equivalent brain SPECT perfusion changes underlying therapeutic efficiency in pharmacoresistant depression using either high-frequency left or low-frequency right prefrontal rTMS. *Prog Neuropsychopharmacol Biol Psychiatry* 2012;39(2):364-370.
10. Rossini D, Lucca A, Magri L et al. A symptom-specific analysis of the effect of high-frequency left or low-frequency right transcranial magnetic stimulation over the dorsolateral prefrontal cortex in major depression. *Neuropsychobiology* 2010;62(2):91-97.
11. Speer AM, Benson BE, Kimbrell TK et al. Opposite effects of high and low frequency rTMS on mood in depressed patients: relationship to baseline cerebral activity on PET. *J Affect Disord* 2009;115(3):386-394.
12. Speer AM, Wassermann EM, Benson BE, Herscovitch P, Post RM. Antidepressant efficacy of high and low frequency rtms at 110% of motor threshold versus sham stimulation over left prefrontal cortex. *Brain Stimul* 2013;No.
13. Stern WM, Tormos JM, Press DZ, Pearlman C, Pascual-Leone A. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. *J Neuropsychiatry Clin Neurosci* 2007;19(2):179-186.
14. Su TP, Huang CC, Wei IH. Add-on rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *J Clin Psychiatry* 2005;66(7):930-937.

Supplementary Table 3: Characteristics of Studies Assessing the Efficacy of Unilateral rTMS Versus Bilateral rTMS

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Blumberger[1] 2012 Canada	**Patient Selection:** Patient recruited from 3 outpatient clinics between January 2006 and January 2009 and were randomized using a computer-generated list. **Inclusion Criteria:** Age 18-85, DSM-IV diagnosis of MDD without psychotic features based on the Structured Clinical Interview for DSM-IV, score of greater than 21on HAMD-17, receiving stable doses of psychotropic medications for at least four weeks prior to randomization, capable to consent as assessed based on their ability to provide a spontaneous narrative description of the key elements of the study using the MacArthur Competence Assessment Tool for Clinical Research, currently an outpatient. **Exclusion Criteria:** DSM-IV substance dependence in the last 6 months (excluding nicotine) or DSM-IV substance abuse in the last month, met DSM-IV criteria for borderline personality disorder or antisocial personality disorder based on the Structured Clinical Interview for DSM-IV Axis II Disorders, Bipolar I, II or NOS, had a significant unstable medical or neurologic illness or a history of seizures, acutely suicidal, pregnant, metal implants in the cranium, had a known diagnosis of dementia or a current MMSE score less than 26, had received benzodiazepines (dose equivalent > lorazepam 2 mg/day), monoamine oxidase inhibitors, or buproprion during the previous four weeks, received prior treatment with rTMS for any indication. **Patient Characteristics:** Twenty-six patients with a mean age of 58.0 (12.5), 14 females and12 males were randomized to unilateral rTMS. Twenty-two patients with a mean age of 48.9 (13.4), 12 females and 10 males were randomized to Bilateral rTMS. **Definition of Treatment Resistance:** Failed to achieve a clinical response, or did not tolerate, at least two separate trials of antidepressants from different classes at sufficient dose for at least 6 weeks according to Stage II criteria outline by Thase and Rush (1995).	**Unilateral:** 10 Hz rTMS to left DLPFC at 100% MT for 29 trains of 50 pulses (1450 total treatment) 5 days per week for 3 weeks. **Bilateral:** 1 Hz rTMS to right DLPFC at 100% MT for 4+1 trains of 65 pulses (465 pulses total treatment), then 10 Hz rTMS to left DLPFC at 100% MT for 15 trains of 50 pulses (750 total treatment) 5 days per week for 3 weeks.	**Outcomes measured:** HAM-D, RBANS, HVLTR, BVMT-R, Grooved Peg Board test. **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline and every 5 treatments. **Type of Analysis:** Modified Intention to Treat
Fitzgerald[2] 2011 Australia	**Patient Selection:** Patients were recruited from inpatients of 4 hospitals between January 2006 and May 2009 and were randomized using computer generation. **Inclusion Criteria:** HAMD-17 score > 13 **Exclusion Criteria:** Significant currently active medical illness, current neurological disease, contraindication to rTMS, a current DSM-IV diagnosis of alcohol or substance dependence, other concurrent axis 1 psychiatric disorders. **Patient Characteristics:** Seventy-one patients with a mean age of 47.9 (14.1), 47 females and 24 males were randomized to unilateral right low frequency rTMS. Seventy-one patients with a mean age of 45.7 (13.7), 52 females and 19 males were randomized to bilateral right low frequency, left high frequency rTMS. Seventy-six patients with a mean age of 47.9 (13.7), 48 females and 28 males were randomized to bilateral right low frequency, left low frequency rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Unilateral:** 1 Hz rTMS to the right PFC at 110% MT for 1 train (900 pulses), 5 days per week for 2 weeks. **Bilateral low/high:** 1 Hz rTMS to the right hemisphere at 110% MT for 1 train (900 pulses); 10 Hz rTMS to the left hemisphere at 110% MT for 18 trains (900 pulses), 5 days per week for 2 weeks. **Bilateral low/low:** 1 Hz rTMS to the right hemisphere at 110% MT for 1 train (900 pulses); 1 Hz to the left hemisphere at 110% MT for 1 train (900 pulses), 5 days per week for 2 weeks.	**Outcomes measured:** HAMD, BDI, BAI **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, and 4 weeks. **Type of Analysis:** NR
Fitzgerald[3] 2012 Australia	**Patient Selection:** Patients were recruited from a single site between January 2008 and November 2010 and were randomized (method not specified). **Inclusion Criteria:** HAMD-17 score > 15 **Exclusion Criteria:** Bipolar disorder**,** significant currently active medical illness, current neurological disease, contraindication to rTMS. **Patient Characteristics:** Twenty-four patients with a mean age of 43.4 (12.7.1), 15 females and 9 males were randomized to unilateral left high frequency rTMS. Twenty-two patients with a mean age of 40.5 (15.5), 14 females and 8 males were randomized to bilateral right low frequency, left high frequency rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Unilateral left:** 10 Hz rTMS to the left hemisphere at 120% MT for 30 trains for 3 weeks. **Bilateral:** 1 Hz rTMS to the right hemisphere at 120% MT for 1 train; 10 Hz to the left hemisphere at 120% MT for 30 trains for 3 weeks.	**Outcomes measured:** HAMD, MADRS BDI, CORE, STAI, DPDI, Wechsler Test of Adult Reading, Rey Auditory Verbal Learning Test, Brief Visual Spatial Memory Test, Digit Span, Trail Making Test A & B, Stroop and COWAT phonemic Fluency. **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, 3 weeks, and 6 weeks. **Type of Analysis:** NR
Fitzgerald[4] 2013 Australia	**Patient Selection:** Patients were recruited from inpatients at 4 hospitals between February 2009 and October 2010 and were randomized using computer generation. **Inclusion Criteria:** HAMD-17 score > 13 **Exclusion Criteria:** Current and significant active medical illness, current neurological disease or a contraindication to rTMS (e.g. history of a seizure disorder; the presence of a pacemaker or metal somewhere in the head other than the teeth). **Patient Characteristics:** Ninety-one patients with a mean age of 46.7 (14.2), 59 females and 32 males were randomized to unilateral right low frequency rTMS. Eighty-eight patients with a mean age of 48.5 (15.9), 66 females and 22 males were randomized to bilateral right low frequency, left high frequency rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Unilateral:** 1 Hz rTMS to right side at 110% MT for 1 train (900 pulses) 5 days per week for 4 weeks. **Bilateral:** 1 Hz rTMS to right side at 110% MT for 1 train (900 pulses) followed by left-sided 10 Hz at 110% MT for 15 trains of 50 pulses 5 days per week for 4 weeks.	**Outcomes measured:** HAMD, BDI, BAI **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, 4 weeks. **Type of Analysis:** NR

Pallanti[5] 2010 United States	**Patient Selection:** Participants were recruited from 1 hospital between March 2009 and October 2009 and were randomized (method not reported). **Inclusion Criteria:** HAMD score ≥18 **Exclusion Criteria:** Any additional psychiatric comorbidity, as assessed by the Structured Clinical Interview for Diagnosis; rTMS contraindications such as metallic implants, foreign bodies or history of seizures; substance abuse in the previous 6 months; any major medical disease; and inability or refusal to provide written informed consent. **Patient Characteristics:** Twenty patients with a mean age of 51.2 (2.53), 12 females and 8 males were randomized to the unilateral low frequency rTMS. Twenty patients with a mean age of 47.6 (12.33), 11 females and 9 males were randomized to the bilateral right low frequency rTMS, left high frequency rTMS.. **Definition of Treatment Resistance:** At least two previous failed antidepressant trials, each lasting at least 6 weeks.	**Unilateral:** 1 Hz rTMS to the right DLPFC at 110% of MT for 3 140-second trains, followed by a 30s intertrain interval (a total of 420 stimuli per session). Ffteen daily sessions were administered only on weekdays, beginning on Monday. **Bilateral:** 1 Hz rTMS to the right DLPFC at 110% MT for 3 140-s trains, followed by a 30s intertrain interval (a total of 420 stimuli per session), followed by 10 Hz rTMS to the left DLPFC at 100% MT,for 20 5-second trains and a 25-s intertrain interval (a total of 1000 stimuli per session were applied over the left DLPFC). Fifteen daily sessions were administered only on weekdays, beginning on Monday.	**Outcomes measured:** HAMD **Follow-up time:** 3 weeks **Outcome ascertainment:** Baseline, 1 week, 2 weeks, and 3 weeks. **Type of Analysis:** NR

BDI Beck Depression Inventory; **CGI** Clinical Global Impression; **DLPFC** Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **MADRES** Montgomery-Asberg Depression Rating Scale**; MT** Motor Threshold; **NR** Not reported; **rTMS** Repetitive Transcranial Magnetic Stimulation; **SD** Standard Deviation; **SSRI** Selective Serotonin Reuptake Inhibitor

Reference List

1. Blumberger DM, Mulsant BH, Fitzgerald PB et al. A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *World J Biol Psychiatry* 2012;13(6):423-435.
2. Fitzgerald PB, Hoy K, Gunewardene R et al. A randomized trial of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in treatment-resistant major depression. *Psychol Med* 2011;41(6):1187-1196.
3. Fitzgerald PB, Hoy KE, Herring SE et al. A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. *J Affect Disord* 2012;139(2):193-198.
4. Fitzgerald PB, Hoy KE, Singh A et al. Equivalent beneficial effects of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in a large randomized trial in treatment-resistant major depression. *Int J Neuropsychopharmcol* 2013;16(9):1975-1984.
5. Pallanti S, Bernardi S, Di Rollo A, Antonini S, Quercioli L. Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? *Neuroscience* 2010;167(2):323-328.

Supplementary Table 4: Characteristics of Studies Assessing the Efficacy of High Intensity rTMS versus Low Intensity rTMS

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Bakim[1] 2012 Turkey	**Patient Selection:** Patient were recruited from 1 psychiatric outpatient clinic (recruitment dates not reported) and were randomized by computer program. **Inclusion Criteria:** Age 18-65, a diagnosis of unipolar major depression, recurrent or single episode and without psychotic features, right-handed, HAMD-17 score ≥ 18 or MADRS score ≥ 20. **Exclusion Criteria:** Comorbidity of any other Axis I disorder, including alcohol and substance use disorders, current or past history of epilepsy, head trauma, encephalitis, meningitis, or any other cerebrovascular disease, pregnancy, any pace-maker or medical pumps replaced in the body or a metal implant in the skull, any use of ECT, antipsychotics or anticonvulsants which may interfere with the excitability of cortical neurons and change the MT, inability to read and understand the Turkish language. **Patient Characteristics:** Twelve participants with a mean age of 38.8 (9.9), 10 females and 2 males were randomized to low intensity rTMS. Eleven participants with a mean age of 43.1 (8.2), 10 females and 1 male were randomized to high intensity rTMS. **Definition of Treatment Resistance:** No response to adequate courses (at least 6 weeks) of at least two different classes of antidepressants used at optimal doses.	**Low:** 20 Hz rTMS to left DLPFC at 80% MT for 20 trains of 40 pulses (24000 total treatment) once per day for 6 weeks. **High:** 20 Hz rTMS to left DLPFC at 110% MT for 20 trains of 40 pulses (24000 total treatment) once per day for 6 weeks.	**Outcomes measured:** HAMD, MADRS **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline and every week for 6 weeks. **Type of Analysis:** NR
Padberg[2] 2002 Germany	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** Organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps. **Patient Characteristics:** Ten patients with a mean age of 60.3 (4.1), 7 women and 3 men were randomized to low-intensity rTMS. Ten patients with a mean age of 62.1 (4.6), 6 women and 4 men were randomized to high intensity rTMS,. **Definition of Treatment Resistance:** At least two antidepressant trials of adequate duration and dosage without significant clinical improvement.	**Low:** 10 Hz rTMS to left DLPFC at 90% intensity MT, for 1500 stimuli/day, 10 s, 15 trains, 30 s intertrain-interval). Patients underwent 10 afternoon sessions of within two weeks. **High-intensity:** 10 Hz rTMS to left DLPFC at 100% MT, for 1500 stimuli/day, 10 s, 15 trains, 30 s intertrain-interval). Patients underwent 10 afternoon sessions of within two weeks.	**Outcomes measured:** HAMD, MADRS, CGI, VAS and brief questionnaires to document side effects, tolerability, and rTMS-induced sensations. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, 1 week and 2 weeks. **Type of Analysis:** NR
Rossini[3] 2005 Italy	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized according to a computer-generated list. **Inclusion Criteria:** NR **Exclusion Criteria:** Age younger than 18 years and older than 75 years, history of seizures or neurological illnesses, severe medical conditions that could interfere with the clinical evaluation, pregnancy, mental retardation, and Edinburgh Handedness Inventory score below +70, and patients bearing pacemakers, mobile metal implants, implanted medical pumps or metal clips placed inside the skull. **Patient Characteristics:** Eighteen patients with a mean age of 54.0 (11.2), 15 females and 4 males were randomized to low intensity rTMS,. Eighteen patients with a mean age of 57.4 (8.7), 12 females and 6 males were randomized to the high-intensity rTMS group.. **Definition of Treatment Resistance:** A lack of improvement to at least two different treatments with antidepressants, at adequate dosage and duration, administered during the current episode.	**Low:** 15 Hz rTMS at 80% of MT, 2s train of stimulation. The inter-train interval was 28 s, and every subject received 20 trains of pulses per session. Patients underwent 10 sessions of stimulation over a 2-week period (Monday to Friday). **High-intensity:** 15 Hz rTMS at 100% of MT, 2 s train of stimulations. The inter-train interval was 28 s, and every subject received 20 trains of pulses per session. Patients underwent 10 sessions of stimulation over a 2-week period (Monday to Friday).	**Outcomes measured:** HAMD, CGI-S, and CGI-I. **Follow-up time:** 5 weeks **Outcome ascertainment:** Baseline (with the exception of CGI-I) and weekly for 5 weeks. **Type of Analysis:** NR

BDI Beck Depression Inventory; **CGI** Clinical Global Impression; **DLPFC** Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **MADRES** Montgomery-Asberg Depression Rating Scale**; MT** Motor Threshold; **NR** Not reported; **rTMS** Repetitive Transcranial Magnetic Stimulation

Reference List

1. Bakim B, Uzun UE, Karamustafalioglu O et al. The combination of antidepressant drug therapy and high-frequency repetitive transcranial magnetic stimulation in medication-resistant depression. *Klin Psikofarmakol Bul* 2012;22(3):244-253.
2. Padberg F, Zwanzger P, Keck ME et al. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology* 2002;27(4):638-645.
3. Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res* 2005;137(1-2):1-10.

Supplementary Table 5: Characteristics of Studies Assessing the Efficacy of rTMS Versus Various Other rTMS Protocols

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Image Guidance			
Fitzgerald[1] 2009 Australia	**Patient Selection:** Patients were recruited from 1 outpatient clinic and private psychiatrists between December 2005 and April 2007 and were randomized using computer generation. **Inclusion Criteria:** Age 18-70 years, major depressive disorder without psychosis, MADRS score > 20. **Exclusion Criteria:** Significant active medical illness, any history of epilepsy or other neurological illness, any contra-indication to MRI scanning. **Patient Characteristics:** Twenty-seven patients with a mean age of 43.9 (12.4), 18 females and 9 males were randomized to standard localization (5 cm method). Twenty-four patients with a mean age of 38.0 (12.2), 11 females and 13 males were randomized to targeted stimulation using neuro-navigation aided rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode	**5 cm localization:** Patients underwent MRI then localization of the motor cortical site for optimal stimulation of a hand muscle and measurement 5 cm anteriorly along the scalp surface. 10 Hz rTMS AT 100% MT for 30 trains (1500 pulses per day, 30000 treatment total). **Neuro-navigation-aided localization:** Patients underwent MRI and stimulation sites in the DLPFC were identified based on task completion and gyral landmarks. 10 Hz rTMS AT 100% MT for 30 trains (1500 pulses per day, 30000 treatment total) .	**Outcomes measured:** MADRS, BDI, BPRS, CORE GAF, CGI, Hopkins verbal learning test, controlled oral word association test, Digit span, Brief visuospatial memory test-revised. **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 3 weeks, 4 weeks. **Type of Analysis:** NR
Garcia-Toro[2] 2006 Spain	**Patient Selection:** Patient recruitment method and dates not reported. Randomization was performed using sealed envelopes. **Inclusion Criteria:** Age > 18, unipolar major depression. **Exclusion Criteria:** High suicidal risk **Patient Characteristics:** Ten patients with a mean age of 48.5 (13.3), 4 females and 6 males received rTMS. Ten patients with a mean age of 51.1 (13.8), 4 females and 6 males received SPECT-guided rTMS. **Definition of Treatment Resistance:** Failed at least 2 trials of antidepressants medications	**rTMS:** Alternating 1 Hz at 110% MT for 30 trains with 20 Hz at 110% MT for 30 trains. **SPECT guided rTMS:** Alternating 1 Hz at 110% MT for 30 trains with 20 Hz at 110% MT for 30 trains with four regional responses guiding placement of the coil.	**Outcomes measured:** HAMD, GCI **Follow-up time:** 10 sessions (4 weeks) **Outcome ascertainment:** Baseline, 1 week, 2 weeks, 4 weeks **Type of Analysis:** NR
Paillère Martinot[3] 2010 France	**Patient Selection:** Patients were recruited 5 five teaching hospitals (recruitment dates not reported) and stratified randomization was performed in blocks using biostatistician-generated lists. **Inclusion Criteria:** NR **Exclusion Criteria:** Age > 65 years, alcohol or substance dependence in the past 6 months, ECT treatment in the past 6 months, any present medical condition, history of epileptic seizures, history of neurological disorders or substantial brain damage, and contraindication to magnetic fields. **Patient Characteristics:** Twenty patients with a mean age: 48.19 (7.77), 11 females and 9 males were randomized to standard rTMS. Sixteen patients with a mean age of 46.9 (7.26), 10 females and 6 males were randomized to the PET-guided group. **Definition of Treatment Resistance:** At least two trials of antidepressants of different classes given at adequate doses (>150 mg/d in an equivalent dose of imipramine) and duration (at least 4 wk for each drug).	**Standard:** rTMS target location was based on motor cortex location. 10 Hz rTMS at 90% of MT for 20 trains of 8 s with 60-s inter-train intervals resulting in a total of 1600 pulses over 20 min. rTMS was administered on 10 consecutive working days, providing a total of 16000 impulses. **PET-guided:** PET 3D-images were used to guide rTMS target location, either on the left or right hemisphere. 10 Hz rTMS at 90% of MT, 20 trains of 8 s with 60-s inter-train intervals resulting in a total of 1600 pulses over 20 min. rTMS was administered on 10 consecutive working days, providing a total of 16000 impulses.	**Outcomes measured:** MADRS, HAMD, and CGI-S. **Follow-up time:** 10 days **Outcome ascertainment:** Baseline and the last day of treatment (Day 10) **Type of Analysis:** Intention to treat
Right vs. Left Dorsolateral Prefrontal Cortex			
Pascual-Leone[4] 1996 Spain	**Patient Selection:** Patients were recruited from 1 hospital and 1 outpatient clinic (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR. **Exclusion Criteria:** NR **Patient Characteristics:** Seventeen patients with a mean age of 48.6 (SD not reported) entered into the multiple cross-over study (mean age, number of females and males were not reported by treatment group). **Definition of Treatment Resistance:** At least three episodes of depression that had been resistant to multiple medications, despite combinations and high dosage.	**Right-sided:** 10 Hz rTMS to right DLPFC at 90% of MT applied at different scalp positions. Five courses of rTMS were administered, each consisting of five sessions over 5 (consecutive) days. Each session consisted of 20 trains of 10 s duration separated by 1 min pauses. **Left-sided:** 10 Hz rTMS to left DLPFC at 90% of MT applied at different scalp positions. Five courses of rTMS were administered, each consisting of five sessions over 5 (consecutive) days. Each session consisted of 20 trains of 10 s duration separated by 1 min pauses.	**Outcomes measured:** HAMD and Beck's Questionnaire for patient self-rated mood. **Follow-up time:** 5 months **Outcome ascertainment:** Baseline and weekly throughout the study **Type of Analysis:** NR
Triggs[5] 2010 United States	**Patient Selection:** Participants were recruited from private psychiatrist practices, tertiary care center clinics, and the community by newspaper advertisements (recruitment dates not reported) and were randomized 1:1. **Inclusion Criteria:** NR **Exclusion Criteria:** A lifetime history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar illness, alcohol or drug abuse within the past year; a positive urine drug test; axis II diagnosis of Cluster A (paranoid, schizoid, or schizotypal) or Cluster B (antisocial, borderline, histrionic, or narcissistic) personality disorder or mental retardation; use of medications that may lower seizure threshold (e.g. metronidazole) if the particular medication could not be stopped or altered without affecting the patient's medical care; history of neurological illness, epilepsy or seizure disorder, intracranial tumor, or major head trauma leading to	**Right-sided:** 5 Hz rTMS to right DLPFC at 100% of MT. Each daily treatment consisted of 2000 stimuli divided into 50 trains of 40 stimuli. Train duration was 8 s and inter-train interval was 22 s. Participants received 10 daily weekday sessions of either rTMS or sham rTMS over a 2-week period. **Left-sided:** 5 Hz rTMS to left DLPFC at 100% of MT. Each daily treatment consisted of 2000 stimuli divided into 50 trains of 40 stimuli. Participants received 10 daily weekday	**Outcomes measured:** HAMD, BDI, STAI. **Follow-up time:** 3 months **Outcome ascertainment:** Baseline (on 3 separate occasions during the 2-week period prior to rTMS), weekly during the 2-week rTMS treatment period, and 1 week, 1-month and 3-months following rTMS. **Type of Analysis:** NR

	loss of consciousness of any duration; evidence of central nervous system disease based on baseline complete neurological examination, EEG and contrast-enhanced computerized tomography or magnetic resonance imaging of the brain; history of implanted pacemaker or medication pump, metal plate in skull, or metal objects in the eye or skull; need for rapid clinical response due to conditions such as inanition, psychosis, or suicidality (defined as suicide attempt during the current major depressive episode or having a specific plan for committing suicide); a medical condition that was not well controlled, such as diabetes or hypertension, or concomitant medical or nutritional problems necessitating hospitalization; use of anticonvulsant mood stabilizers (e.g. carbamazepine, valproic acid); or inability to personally grant informed consent. **Patient Characteristics:** Sixteen patients with a mean age of 48.5 (10.8), 9 females and 7 males were randomized to right-sided rTMS group,. Eighteen patients with a mean age of 46.7 (15.3), 14 females and 4 males were randomized to left-sided rTMS. **Definition of Treatment Resistance:** Failed historically to respond to at least two separate trials (minimum duration 4 weeks) of therapeutic dosages of antidepressant medication (including at least one SSRI) or were intolerant of at least three different antidepressant medications (including at least one SSRI).	sessions of either rTMS or sham rTMS over a 2-week period.	
Scheduling			
Galletly[6] 2012 Australia	**Patient Selection:** Patients were recruited from private psychiatrists between August 2008 and Feb 2011 and were randomized using computer generation. **Inclusion Criteria:** Fluency in English, diagnosis of major depression. **Exclusion Criteria:** Neurological disorders, metal plates or other implants in the skull, a history of epilepsy, withdrawing from drugs or alcohol. **Patient Characteristics:** Thirty-five patients with a mean age of 45.6 (12.5), 24 females and 11 males were randomized to five days/week rTMS. Forty-two patients with a mean age of 51.0 (13.8), 27 females and 14 males were randomized to 3 days/week rTMS (spaced). **Definition of Treatment Resistance:** Failed at least 1 course of antidepressants medications in the current episode.	**Daily:** 10 Hz rTMS to left DLPFC at 110% of MT (1500 pulses) then 1 Hz to right DLPFC at 110% MT (900 pulses), 5 days per week for 4 weeks. **Spaced:** 10 Hz rTMS to left DLPFC at 110% of MT (1500 pulses) then 1 Hz to right DLPFC at 110% of MT (900 pulses), 3 days per week for 6 weeks.	**Outcomes measured:** HAMD, MADRS, Zung SDS, HARS. **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, 4 weeks, 6 weeks. **Type of Analysis:** NR
Turnier-Shea[7] 2006 Australia	**Patient Selection:** Patients were recruited from 1 hospital and from private outpatient clinics (recruitment dates not reported) and were randomized by coin flip. **Inclusion Criteria:** Major depressive episode (DSM-IV), between 20 and 65 years, HAMD-17 score ≥ 18, and no medication change for a minimum of 2 weeks before commencement of the study. **Exclusion Criteria:** Concurrent neurological disorder (including epilepsy), other concurrent serious medical illness, history of significant head injury, recent alcohol or other drug misuse, and intracranial metal object. **Patient Characteristics:** Eight patients with a mean age of 40.5 (10.1), 4 females and 4 males years were randomized to daily rTMS, Eight patients with a mean age of 46.4 (10.7), 6 females and 2 males were randomized to spaced rTMS,. **Definition of Treatment Resistance:** Failure to respond to trials of at least two different antidepressants, at maximum manufacturer recommended doses, for at least 4 weeks.	**Daily:** 20 Hz rTMS to left DLPFC at 100% of MT, 30 2-second trains, with an inter-train interval of 28 seconds. rTMS was delivered on days 1–5 and 8–12 for a total of 10 treatments over 2 weeks. **Spaced:** 20 Hz rTMS to left DLPFC at 100% of MT, 30 2-second trains, with an inter-train interval of 28 seconds. rTMS was delivered on days 1, 3, 5, 8 and 12 for a total of five treatments over 2 weeks.	**Outcomes measured:** HAMD, VAS. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, 1 week, and 2 weeks **Type of Analysis:** NR
Electroencephalography-timed			
Price[8] 2010 Australia	**Patient Selection:** Participants were recruited from outpatient clinics (recruitment dates not reported) and were randomized using predetermined lists. **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Twenty-three patients with a mean age of 46.3 (13.0), 9 females and 14 males were randomized to standard rTMS group. Twenty-one patients with a mean age of 40.2 (12.9), 11 females and 10 males were randomized to interactive rTMS. **Definition of Treatment Resistance:** Failed at least one previous antidepressant treatment.	**Standard:** 10 Hz rTMS comprised of forty 5-second trains at 90-100% of MT with a 25-second inter-train interval. **Interactive:** 10 Hz rTMS where stimuli were applied in response to real-time analysis of the background EEG. The total of stimuli in each train was one more (17x3) than the standard technique with a 15-second inter-train interval.	**Outcomes measured:** HAMD, BDI. **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, and 4 weeks. **Type of Analysis:** Intention to treat
Combination Protocols			
Conca[9] 2002 Austria	**Patient Selection:** Patients were recruited from inpatients from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Twelve patients with mean age of 48.2 (16.1), 9 females and 3 males were randomized to high/low frequency rTMS on both right and left side. Twelve patients with a mean age of 44.8 (14.8), 8 females and 4 males were randomized to high/low frequency rTMS on left side only. Twelve patients with a mean age of 46.8 (10.3), 8 females and 4 males were randomized to high frequency on the left side only. **Definition of Treatment Resistance:** Failure to respond to two different adequate monotherapy trials of medications with different pharmacological profiles and the failure to response to a second augmentation strategy.	**High/Low 1:** 10 Hz rTMS to left DLPFC at 110% MT for 10 trains of 60 pulses and 1 HZ rTMS to right DLPC 110% MT for 1 train of 300 pulses (6500 total treatment) for 5 days. **High/Low 2:** 10 Hz rTMS to left DLPFC at 110% MT for 10 trains alternating with 1 Hz 30 train (6500 total treatment) for 5 days. **High**: 10 Hz rTMS to left DLPFC at 110% MT for 13 trains (6500 total treatment) for 5 days.	**Outcomes measured:** CGI **Follow-up time:** 5 days **Outcome ascertainment:** baseline and 5 days **Type of Analysis:** NR

Fitzgerald[10] 2008 Australia	**Patient Selection:** Participants were recruited from 1 outpatient clinic and by psychiatrist referral between September 2005 and January 2007 and were randomized using a single, computer-generated, random-number sequence. **Inclusion Criteria:** Age 18-70, diagnosis of major depressive episode or bipolar affective disorder, score of more than 20 on MADRS, ability to attend hospital daily for four weeks of treatment, treatment resistant. **Exclusion Criteria:** NR **Patient Characteristics:** Twenty-eight patients with a mean age of 44.8 (11.4), 13 female and 15 male were randomized to receive non-primed rTMS., Thirty participants with a mean age of 45.7 ± 10.8 years, 20 female and 10 male were randomized to receive primed rTMS,. **Definition of Treatment Resistance:** Failure to respond to at least 2 antidepressant medications for at least 6 weeks during the current episode.	**Non-primed:** A sham priming stimulation was first provided with the coil angled away from the scalp at 45 degrees from the side of the coil, with a 6 Hz stimulation for twenty trains of 5 seconds duration at 90% of the MT, applied with a 25-second intertrain interval. Then 1 Hz rTMS at 110% of MT for one continuous, 15-minute train. Patients received 10 sessions of treatment on a daily basis, 5 days per week. **Primed:** An active priming stimulation was first provided at 6 Hz for twenty trains of 5 seconds duration, at 90% of the MT, applied with a 25-second intertrain interval. Then 1 Hz rTMS at 110% of MT for one continuous, 15-minute train. Patients received 10 sessions of treatment on a daily basis, 5 days per week.	**Outcomes measured:** MADRS, BDI, BPRS, CORE Rating of Psychomotor Disturbance, GAF, CGI, and Edinburgh Handedness Inventory. **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks and 4 weeks. **Type of Analysis:** Intention to treat
Levkovitz[11] 2009 Israel	**Patient Selection:** Patients were recruited from 1 hospital between April 2006 and May 2008 and were randomized by computer generation **Inclusion Criteria:** Age 18-65, right-handedness, un ipolar depression, CGI-S score ≥4, HAMD-24 score ≥ 22. **Exclusion Criteria:** History of DSM-IV Axis I disorders apart from depression, severe personality disorder, hospitalization due to exacerbation related to borderline personality disorder, neurological disorder or medication therapy known to alter seizure threshold, epilepsy in first degree relatives, existence of metallic particles in the head or its vicinity, implanted cardiac pacemaker, implanted neurostimulators, surgical clips, cochlear implants or any medical pumps, prior treatment with TMS, electroconvulsive therapy <9 months prior to study entry, vagus nerve stimulator implant, history of a convulsive disorder of candidate or first degree relative of candidate, substantial suicidal risk or attempted suicide in the past year, participation in a clinical study within 30 days prior or concurrent to this study, drug abuse or alcoholism in the past year, pregnancy or lack of a reliable method of birth control. **Patient Characteristics:** Twenty-three patients with a mean age of 45.6 (13.3), 11 females and 12 males were randomized to deep brain stimulation preferentially left-sided low intensity rTMS. Twenty-two patients with a mean age of 45.8 (12.0), 11 females and 11 males were randomized to deep brain stimulation bilateral low intensity rTMS. Eleven patients with a mean age of 44.3 (11.4), 7 females and 4 males were randomized to deep brain stimulation left-sided high intensity rTMS. Eight patients with a mean age of 49.9 (9.5), 5 females and 3 males were randomized to deep brain stimulation left-sided high intensity rTMS. **Definition of Treatment Resistance:** Failed at least 2 trials of antidepressants medications.	**Deep brain left:** 20 Hz at 110% MT for 42 trains (1680 pulses per session) 5 days/week for 4 weeks. **Deep brain bilateral:** 20 Hz at 110% MT for 42 trains (1680 pulses per session) 5 days/week for 4 weeks. **Deep brain left 110%:** 20 Hz at 120% MT for 42 trains (1680 pulses per session) 5 days/week for 4 weeks. **Deep brain left 120%:** 20 Hz at 120% MT for 42 trains (1680 pulses per session) 5 days/week for 4 weeks.	**Outcomes measured:** HAMD, CGI, PSQI, CANTAB. **Follow-up time:** 3 months **Outcome ascertainment:** baseline, 1 week, 2 weeks, 3 weeks, 4 weeks, 3 months. **Type of Analysis:** Intention to treat
McDonald[12] 2006 United States	**Patient Selection:** Patients were recruited from the community (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** SCID criteria for Unipolar Depression (UP) or Bipolar Disorder (BP), depressed phase, and HAMD-17 > 20. **Exclusion Criteria:** Evidence of dementia on neuropsychological testing or meeting SCID criteria for Organic Brain Syndrome, Organic Mood Disorder, Substance Dependence within the last 6 months, a diagnosis of a significant central neurological disorders, pregnancy, the presence of cardiac pacemakers, cochlear implants, or other intracranial implants with the exception of dental fillings, presence of psychiatric symptoms of significant severity, requirement of continued treatment with antidepressant medications, acute, unstable medical conditions, previous TMS. **Patient Characteristics:** Twenty-five patients with a mean age of 49.0 (SD not reported), 18 females and 7 males received left-sided high frequency then right-sided low frequency rTMS. Twenty-five patients with a mean age of 49.0 (SD not reported), 9 females and 16 males received right-sided low frequency then left-sided high frequency rTMS. **Definition of Treatment Resistance:** Failed at least 3 trials of antidepressants medications during the current episode.	**Left-sided high frequency/right-sided low frequency:** 10 Hz rTMS to left DLPFC at 110% MT for 20 trains (1000 pulses) followed by 1 Hz to right DLPFC at 110% MT for 20 trains (600 pulses) for 5 days/week for 2 weeks. **Right-sided low frequency/left-sided high frequency:** 1 Hz rTMS to right DLPFC at 110% MT for 20 trains (600 pulses) followed by 10Hz to left DLPFC at 110% MT for 20 trains (1000 pulses) for 5 days/week for 2 weeks.	**Outcomes measured:** HAMD, CGI, BDI, BPRS. **Follow-up time:** 3 months **Outcome ascertainment:** Baseline, 2 weeks, 1 month , 2 months, 3 months **Type of Analysis:** Intention to treat
Rybak[13] 2005 Australia	**Patient Selection:** Participants were recruited from 1 hospital and private outpatient clinics (recruitment dates not reported) and were randomized by order of presentation **Inclusion Criteria:** Right handedness, 20-75 years of age, suffering DSM-IV major depressive episode (unipolar or bipolar) with a HAMD-17 score ≥ 18, clinical circumstances indicating that a physical treatment would be an appropriate next step. **Exclusion Criteria:** A history of epilepsy, concurrent serious medical illness, alcohol or drug abuse, and presence of intracranial metal objects. **Patient Characteristics:** Nine patients with a mean age of 53.4 (13.3), 6 females and 3 males were randomized to standard rTMS. Nine patients with a mean age of 47.0 (12.3), 6 females and 3 males were randomized to experimental rTMS. **Definition of Treatment Resistance:** Failure to respond to at least a four week trial at maximum recommended doses of medication from at least one family of antidepressants.	**Standard:** 20 Hz rTMS to left DLPFC at 100% of MT, for 30 2s trains, followed by 200 1 Hz placebo to right DLPFC. Each patient received 1200 stimuli at each treatment session. Stimulation was provided for ten days over two weeks. **Experimental:** 20 Hz rTMS to left DLPFC at 100% of MT for 25 2s trains, followed by 200 1 Hz stimulations to right DLPFC. Each patient received 1200 stimuli at each treatment session. Stimulation was provided for ten days over two weeks.	**Outcomes measured:** HAMD, VAS. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, 1 week, and 2 weeks. **Type of Analysis:** NR

BDI Beck Depression Inventory; **CGI** Clinical Global Impression; **DLPFC** Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **MADRES** Montgomery-Asberg Depression Rating Scale**; MT** Motor Threshold; **NR** Not reported; **rTMS** Repetitive Transcranial Magnetic Stimulation

Reference List

1. Fitzgerald PB, Hoy K, McQueen S et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology* 2009;34(5):1255-1262.
2. Garcia-Toro M, Salva J, Daumal J et al. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. *Psychiatry Res* 2006;146(1):53-57.
3. Paillere Martinot ML, Galinowski A, Ringuenet D et al. Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: a [(18)F]-fluorodeoxyglucose PET and MRI study. *Int J Neuropsychopharmcol* 2010;13(1):45-59.
4. Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 1996;348(9022):233-237.
5. Triggs WJ, Ricciuti N, Ward HE et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. *Psychiatry Res* 2010;178(3):467-474.
6. Galletly C, Gill S, Clarke P, Burton C, Fitzgerald PB. A randomized trial comparing repetitive transcranial magnetic stimulation given 3 days/week and 5 days/week for the treatment of major depression: is efficacy related to the duration of treatment or the number of treatments? *Psychol Med* 2012;42(5):981-988.
7. Turnier-Shea Y, Bruno R, Pridmore S. Daily and spaced treatment with transcranial magnetic stimulation in major depression: a pilot study. *Aust N Z J Psychiatry* 2006;40(9):759-763.
8. Price GW, Lee JWY, Garvey CA, Gibson N. The use of background EEG activity to determine stimulus timing as a means of improving rTMS efficacy in the treatment of depression: a controlled comparison with standard techniques. *Brain Stimul* 2010;3(3):140-152.
9. Conca A, Di Pauli J, Beraus W et al. Combining high and low frequencies in rTMS antidepressive treatment: Preliminary results. [References]. *Human Psychopharmacology: Clinical and Experimental* 2002;17(7):353-356.
10. Fitzgerald PB, Hoy K, McQueen S et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol* 2008;28(1):52-58.
11. Levkovitz Y, Harel EV, Roth Y et al. Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. *Brain Stimul* 2009;2(4):188-200.
12. McDonald WM, Easley K, Byrd EH et al. Combination rapid transcranial magnetic stimulation in treatment refractory depression. *Neuropsychiatr dis treat* 2006;2(1):85-94.
13. Rybak M, Bruno R, Turnier-Shea Y, Pridmore S. An attempt to increase the rate and magnitude of the antidepressant effect of transcranial magnetic stimulation (TMS). A pilot study. *Germ J Psychiatry* 2005;8(4):59-65.

Supplementary Table 6: Characteristics of Studies Assessing the Efficacy of rTMS Versus ECT

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Grunhaus[1] 2003, Israel	**Patient Selection:** Participants were recruited from the Psychiatry Division at the Sheba Medical Center, and had been referred for ECT. **Inclusion Criteria:** Diagnosis of unipolar major depression by DSM-IV, score of at least 18 on Hamilton Rating Scale for Depression, 18 years or older, treatment resistant **Exclusion Criteria:** Additional Axis I diagnoses, major depression with psychosis, major depression due to medical condition or substance abuse **Patient Characteristics:** Twenty other participants were randomized to receive rTMS (14 female, 6 male) with a mean age of 57.6(13.7). Twenty participants were randomized received ECT (15 female, 5 male), with a mean age of 61.4(16.6). **Definition of Treatment Resistance:** Failure to respond to at least 1 adequate trial of antidepressant treatment.	**Type of rTMS** 10 Hz rTMS, delivered at 90% motor threshold to the left dorsolateral prefrontal cortex 5 days per weeks over 4 weeks (1,200 pulses per day, 24,000 total over rTMS treatment). **Type of Comparator** ECT conducted using the guidelines of the American Psychiatric Association. Participants were given 1mg/kg methohexital and .75mg/kg succinylcholine. Treatments were performed at 2.5 times threshold charge, and increased by 10-20% to maintain seizure length of at least 25 seconds.	**Outcomes measured:** Hamilton Rating Scale for Depression, Brief Psychiatric Rating Scale, Global Assessment of Function Scale, Global Depression Scale, Pittsburgh Sleep Quality Index, Mini-Mental State Examination **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, end of treatment (4 weeks **Type of Analysis:** Not reported
Janicak[2] 2002, United States	**Patient Selection:** Not reported **Inclusion Criteria:** Age 18-75, met DSM-IV criteria for unipolar or bipolar major depression, clinically appropriate for course of ECT, score of at least 20 on the Hamilton Rating Depression Scale, treatment resistant **Exclusion Criteria:** None reported **Patient Characteristics:** Thirteen participants were randomized to receive rTMS. Nine participants were randomized to receive ECT with a mean age of 42.73(14).There were no statistically significant differences in age. **Definition of Treatment Resistance:** Not Reported	**Type of rTMS** 10 Hz rTMS, delivered at 110% motor threshold to the left dorsolateral prefrontal cortex five times per week for 10-20 sessions (1,000 stimulations per session) **Type of Comparator** ECT three times per week for 3-12 bitemporal treatments. Participants were given 1mg/kg of methohexital and 1mg/kg succinylcholine	**Outcomes measured:** Hamilton Depression Rating Scale, Brief Psychiatric Rating Scale, Young Mania Rating Scale, Clinical Global Impression Scale. **Follow-up time:** End of treatment (between 2-4 weeks) **Outcome ascertainment:** Baseline, weekly, end of treatment **Type of Analysis:** Not reported
Keshtkar[3] 2011, Iran	**Patient Selection:** Patients who were referred for ECT were recruited from southwestern Iran and randomized to receive rTMS or ECT by coin toss. **Inclusion Criteria:** Diagnosis of major depressive disorder by DSM-IV **Exclusion Criteria:** previous rTMS, implanted device, history of seizure, bipolar disorder, substance abuse, history of significant head trauma, severe medication condition, previous nonresponse to ECT, pregnancy **Patient Characteristics:** Thirty three participants (20 females, 13 males), mean age 34 (9.9) were randomized to receive rTMS. Forty participants (32 female, 8 male), mean age 35.6(8.1) were randomized to receive ECT. **Definition of Treatment Resistance:** Failure to respond to at least 2 adequate trials of antidepressant treatment.	**Type of rTMS** rTMS to the left dorsolateral prefrontal cortex delivered at 90% motor threshold for 10 sessions (408 simulations per session for a total of 4080 stimulations per patient) **Type of Comparator** bilateral ECT with constant current for 10 sessions (3 times per week). Seizures were at least 20 seconds in length. Participants were given Thiopental and Succinylcholine.	**Outcomes measured:** Beck Depression Inventory, Hamilton Depression Rating Scale **Follow-up time:** Post-intervention (with the intervention period ranging from 10d for rTMS and 3weeks and 1 day for ECT) **Outcome ascertainment:** Baseline, and post-intervention **Type of Analysis:** Per protocol
Pridmore[4] 2000, Australia	**Patient Selection:** Patients were drawn from out-patient, in-patient, public and private service. **Inclusion Criteria:** Treatment resistant, DSM-IV diagnosis of major depressive disorder, right-handed, age 25-70, no history of epilepsy **Exclusion Criteria:** Intracranial metal objects **Patient Characteristics:** Eleven participants were randomized to receive rTMS (6 females, 5 males) with a median age of 48. Eleven other participants were randomized to receive ECT (5 females, 6 males) with a median age of 46. The two groups did not differ in age or gender. **Definition of Treatment Resistance:** Failure to respond to at least one month trial of two families of antidepressant medications, at the manufacturers recommended maximum dosage.	**Type of rTMS** Two cycles of 1 day ECT followed by 4 days rTMS. 20 Hz rTMS, at 100% motor threshold.. **Type of Comparator** Unilateral ECT 3 times per week for 2 weeks. Participants were given 1-1.5mg/kg methohexitonium and 0.5mg/kg suxamethonium	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Visual Analogue Scale, Global Assessment of Functioning Scale, Side-effects scale **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, week 1, week 2 **Type of Analysis:** Not reported
Pridmore[5] 2000, Australia	**Patient Selection:** Consecutive patients at the Royal Hobart Hospital, who met the inclusion criteria, were invited to participate **Inclusion Criteria:** DSM-IV major depressive episode, score of at least 18 on the Hamilton Depression Rating Scale, treatment resistant, right-handed, no history of epilepsy **Exclusion Criteria:** Serious medical illness, intracranial metal objects, mood disorder due to medical condition or substance abuse, co-morbidity for mental disorder **Patient Characteristics:** Sixteen participants (12 females, 4 males), mean age 44(11.9) were randomized to receive rTMS. Sixteen participants (13 females, 3 males), mean age 41.5(12.9) were randomized to receive ECT. **Definition of Treatment Resistance:** Failure to respond to at least one 4 week trial of antidepressants at the maximum recommended dose.	**Type of rTMS** 20 Hz rTMS using 100% motor threshold delivered to the left prefrontal cortex for five days per week. **Type of Comparator** ECT 3 days per week on non-dominant hemisphere. Participants were given 1-1.5 mg/kg methohexitone and 0.5 mg/kg suxamethonium	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory, Visual Analogue Scale, Side-effects scale **Follow-up time:** Last treatment **Outcome ascertainment:** Baseline, 3 times per week during treatment and end of study **Type of Analysis:** Not reported

Rosa[6] 2006, Brazil	**Patient Selection:** Patients were recruited by physician referral at the Psychiatric Institute of the University of Sao Paulo **Inclusion Criteria:** Age 18-65, DSM-IV diagnosis of unipolar depressive disorder, score of at least 22 on the Hamilton Depression Rating Scale, treatment resistance **Exclusion Criteria:** Psychotic symptoms, history of epilepsy, history of neurosurgery with metal clips, co-morbid neurological or psychiatric diseases, cardiac pacemaker, pregnancy **Patient Characteristics:** Fifteen participants (7 female, 8 male), mean age 46(10.6) were randomized to receive ECT. Twenty participants (12 female, 8 male), mean age 41.8(10.2) were randomized to receive rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 antidepressants in difference classes (used for at least 4 weeks with adequate dosages), with augmentation (with lithium or thyroid hormone for at least one trial).	**Type of rTMS** 10 Hz rTMS at 100% motor threshold to the left prefrontal area 5 times per week for 4 weeks (2500 stimulations per session, 50,000 stimulations total) **Type of Comparator** right unilateral ECT conducted using the guidelines of the American Psychiatric Association. Participants were given 1-1.5mg/kg etomidate, 0.5-1.25mg/kg succinylcholine and 0.4-1.0 mg atropine.	**Outcomes measured:** Hamilton Depression Rating Scale, Visual Analogue Scale, Clinical Global Impression **Follow-up time:** End of treatment (4 weeks) **Outcome ascertainment:** Baseline, 2 weeks, end of treatment **Type of Analysis:** Intention-to-treat

DSM Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **Hz** Hertz; **rTMS** Repetitive Transcranial Magnetic Stimulation

Reference List

1. Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry* 2003;53(4):324-331.
2. Janicak PG, Dowd SM, Martis B et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. *Biol Psychiatry* 2002;51(8):659-667.
3. Keshtkar M, Ghanizadeh A, Firoozabadi A. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for the treatment of major depressive disorder, a randomized controlled clinical trial. *J ECT* 2011;27(4):310-314.
4. Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depress Anxiety* 2000;12(3):118-123.
5. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *Int J Neuropsychopharmacol* 2000;3(2):129-134.
6. Rosa MA, Gattaz WF, Pascual-Leone A et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. *Int J Neuropsychopharmcol* 2006;9(6):667-676.

Supplementary Table 7: Characteristics of Studies Included in Systematic Review of rTMS for Treatment Resistant Youth and Adolescents with Depression

Author, Year of Publication, Country	*Patient Selection*	*Exposure*	*Outcomes*
Bloch[1], 2008, Israel	**Patient Selection:** Participants were recruited from 1 inpatient adolescent ward and 1 outpatient clinic **Inclusion Criteria:** Age 16-18, diagnosis of major depression as defined by DSM-IV **Exclusion Criteria:** Schizophrenia, bipolar disorder, substance abuse, psychosis, history of epilepsy, any other neurological disorder **Patient Characteristics:** Nine participants were included (7 females, 2 males) with a mean age of 17.3 years **Definition of Treatment Resistance:** Failure of one trial of psychotherapy, and two courses of medications for 8 weeks each, at least one with fluoxetine	**rTMS:** 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex at 80% motor threshold for 14 sessions over 14 days	**Outcomes measured:** Child Depression Rating Scale, Child Anxiety Related Disorder screen, Suicide Ideation Questionnaire, Clinical Global Impression scale, Cambridge Neuropsychological Test Automated Battery **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, day 7 and 10 of therapy, end of therapy and 1 month post-therapy
Croarkin[2], 2012, United States	**Patient Selection:** Participants were recruited from 2 inpatient treatment centers **Inclusion Criteria:** stable therapy within prior 4 weeks **Exclusion Criteria:** Schizophrenia, Schizoaffective disorder, bipolar spectrum disorder, substance abuse/dependence, somatoform disorder, dissociative disorder, post-traumatic stress disorder, obsessive-compulsive disorder, eating disorder, mental retardation, pervasive developmental disorder, pregnancy, ongoing treatment with stimulants, antipsychotics, mood-stabilizers or non-serotonin-selective reuptake inhibitors **Patient Characteristics:** Seven participants (6 females, 1 male), with a mean age of 16.5, were included. **Definition of Treatment Resistance:** Failure to respond to at least two adequate antidepressants	**rTMS:** 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex at 120% motor threshold for 30 sessions within 6-8 weeks	**Outcomes measured:** Children's Depressive Rating Scale-Revised, Quick Inventory of Depressive Symptomatology **Follow-up time:** Five weeks **Outcome ascertainment:** Baseline, and weeks 2,4,5
Mayer[3], 2012, Australia	**Patient Selection:** Participants were recruited from a previously conducted open-label trial on rTMS conducted in 2006. **Inclusion Criteria:** Received treatment in 2006 study, consented to follow-up **Exclusion Criteria:** None reported **Patient Characteristics:** Eight participants (6 females, 2 males) with a mean age of 20.4 were included. All participants received rTMS in original 2006 study **Definition of Treatment Resistance:** Not reported	**rTMS:** Provided in 2008 study by Bloch et al.[1]	**Outcomes measured:** Beck Depression Inventory Version II, Children's Depression Rating Scale-Revised, Cambridge Neuropsychological Test Automated Battery **Outcome ascertainment:** Three years post-treatment

Reference List

1. Bloch Y, Grisaru N, Harel EV et al. Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: an open-label study. *J ECT* 2008;24(2):156-159.
2. Croarkin PE, Wall CA, Nakonezny PA et al. Increased cortical excitability with prefrontal high-frequency repetitive transcranial magnetic stimulation in adolescents with treatment-resistant major depressive disorder. *J Child Adolesc Psychopharmacol* 2012;22(1):56-64.
3. Mayer G, Aviram S, Walter G, Levkovitz Y, Bloch Y. Long-term follow-up of adolescents with resistant depression treated with repetitive transcranial magnetic stimulation. *J ECT* 2012;28(2):84-86.