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.

It is illegal to post this copyrighted PDF on any website. © 2015 Copyright Physicians Postgraduate Press, Inc.
Supplementary Table 1: Characteristics of Studies Assessing the Efficacy of rTMS Versus Sham

<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Patient Selection</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Avery** 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 patients (all females) received active rTMS. Two patients (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** 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 and/or serotonin reuptake inhibitors and one failed clinical trial with a tricyclic antidepressant  
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 patients with a mean age of 44.3(10.3), 21 females and 14 males were randomized to the active group. Thirty-six patients 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 ineffective medication for 4 months or medication-free for 2 weeks  
Type of Comparator active 10 Hz rTMS to left DLPFC at 110% motor threshold for 15 sessions over 4 weeks (24000 total pulses) | Outcomes measured: Hamilton Depression Rating Scale, Beck Depression Inventory, Clinical Global Impression, 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** 2013 Belgium            | Patient Selection: Patients were selected 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: History of epilepsy, neuropsychological interventions, pacemaker, metal or magnetic objects in the brain, Alcohol dependence, suicide attempts in prior 6 month  
Patient Characteristics: Twenty participants (15 females, 5 males), mean age 49.33(12.50) were included and received both sham and active rTMS in cross-over design.  
Definition of Treatment Resistance: Minimum of two unsuccessful treatment trials with serotonin reuptake inhibitors/ norepinephrine 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 medication; 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** 2012 Turkey              | Patient Selection: Patients volunteered at a 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. Two participants with a mean age of 44.4(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 |
| **Bates** 2009 Czech Republic      | Patient Selection: Patients were recruited from the Prague Psychiatric Centre between June 2003 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: Age 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 45.1(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 venlafaxine 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 |
**Berman** 2007

**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, meet 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 years and 14 males were included. Three sham discontinued due to lack of response

**Type of Control:** sham rTMS with unchanged 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 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 21 on 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, mMed 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 neuropsychological illness or a history of seizures, acute suicidal, pregnant, metal implants in the cranial, had a known diagnosis of dementia or a current MMSE score less than 26, had received benzodiazepines (dose equivalent > 7.5 mg/day), monoamine oxidase inhibitors, or bupropion during the previous four weeks, received prior treatment with TMS for any indication **Patient Characteristics:** Twenty-six patients with a mean age of 54.8 (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 ITT

---

**Bortolomasi 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:** 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 of at 90% motor threshold (800 stimuli per session) 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

---

**Bouwers 2005**

**United States**

**Patient Selection:** Outpatients meeting the inclusion criteria were randomized using a computer generated sequence **Inclusion Criteria:** Diagnosis of major depression, Treatment resistant, score of at least 20 on HAM-D, age 18-75, meet DSM-IV criteria for current major depressive disorder, treatment resistant **Exclusion Criteria:** Suicide 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 to provide 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, Beck Depression Inventory

**Follow-up time:** 12 weeks

**Outcome ascertainment:** Baseline and days 3, 5, 6, 8, 10

**Type of Analysis:** Not reported

---

**Brelan 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 deteriorating esclatoalopram treatment, pregnancy **Patient Characteristics:** Twenty-two participants, with a mean age of 57.8 ± 10, 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, Beck Depression Inventory, Young Mania Rating Scale

**Follow-up time:** 12 weeks

**Outcome ascertainment:** Baseline, and 23,5,8, and 12 weeks

**Type of Analysis:** Not reported

---

**Chen 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, 3 males and 7 females, were randomized to receive active rTMS. Ten participants, with an average age of 47.3 ± 5, 6 males and 4 females, were randomized to receive sham rTMS

**Definition of Treatment Resistance:** 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

**Outcome ascertainment:** 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 Control sham rTMS
Type of Comparator: 10 Hz rTMS to HFL 100% motor threshold for 20 trains (1000 stimul 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 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 disorder.
Patients: Twenty patients with a mean age of 49.5 (14.24), 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 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 stimul 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 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 medical illness, another Axis I psychiatric disorder, treatment resistance.
Patients: Twenty-five participants, mean age 46.8 (10.7), 10 males and 15 females were randomized to receive sham rTMS. Twenty patients with a mean age of 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
Type of Comparator: 10 Hz 120% motor threshold for 30 trains for 3 weeks

Outcomes measured: MADRS, Hamilton Depression Rating Scale, Beck Depression Inventory, Brief Psychiatric Rating Scale, CORE Rating of psychomotor disturbance, Global Assessment of Functioning Scale, Clinical Global Impression
Follow-up time: 6 weeks
Outcome ascertainment: baseline, 2 weeks, 3.4, 5, and 6
Type of Analysis: Intention-to-treat

Fitzgerald 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.
Patients: Twenty-five patients with a mean age of 43.4 (12.7), 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, Hamilton Anxiety Rating Scale, Hamilton Anxiety 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 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 medical illness, pacemaker or hearing aid, pregnancy, women of childbearing potential lacking effective contraceptive, high suicidal risk.
Patients: 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 50.1 (15.9) 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
Type of Comparator: patients taking stable doses of antidepressants for the six weeks prior to trial

Outcomes measured: Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Clinical Global Impression
Follow-up time: Four weeks
Outcome ascertainment: baseline, week 1, 2, and 4
Type of Analysis: Not reported

Garcia-Toro 2006 Spain
Patient Selection: Not reported. Randomization occurred using sealed envelopes.
Inclusion Criteria: Age > 18, unipolar major depression
Exclusion Criteria: high suicidal risk.
Patients: Ten participants 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 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 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, previous 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.
Patients: Ninety-two participants (34 male, 58 female) with a mean age of 47.0 (10.6) received active rTMS. Ninety-eight participants (45 male, 53 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
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-Asberg Depression Rating Scale, Beck Depression Inventory, 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
Participants were recruited from the Mood Disorders Unit of the Bellvitge University Hospital. Inclusion Criteria: Age 21-65, right handed, meet DSM-IV criteria for major depressive episode due to major depressive disorder, no history of subcortical stroke, 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 Risk factors for seizures

Participants 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

Participants were 164 patients who were treatment resistant were randomized to receive active rTMS. Sixty-seven participants (42 males), 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 at least one adequate trial of antidepressant

Type of Control sham rTMS with medication free
Type of Comparator 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex 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 Test, Trail Making Test A and B, Controlled Oral Word Association Test, Visual Object and Space Perception Battery, Clock Drawing 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, week 1 and 2 after final session

Type of Analysis: Intention-to-treat

Type of Comparator 10 Hz rTMS stimulation to the left 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

Type of Comparator 10 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 treatment

Definition of Treatment Resistance: Failure to respond to at least one trial of adequate antidepressant

Outcomes measured: Hamilton Rating Scale

Follow-up time: three weeks

Outcome ascertainment: Baseline, week 1, 2 and 3

Type of Analysis: Not reported

Participants were recruited by physician referral, referral from centers doing ECT, and media advertisements between January 1998 and December 1999

Exclusion 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 Definition of Treatment Resistance: Failure to respond to at least three antidepressant trials

Type of Control sham rTMS
Type of Comparator 10 Hz rTMS stimulation to the left prefrontal cortex delivered using 110% motor threshold for 10 sessions over two weeks

Outcomes measured: Hamilton Depression Rating Scale, ATHF, IDS-SR, Clinical Global Impression

Outcome ascertainment: unblinded at 4 weeks

Type of Analysis: Not reported

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

Participants were 164 patients who were treatment resistant were randomized to receive active rTMS. Sixty-seven participants (42 males), 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 at least one 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, 40 pulse duration with 266 interval (40 pulses for each pulse train), 75 pulse trains, 3000 pulses

Outcomes measured: Montgomery-Asberg Depression Rating Scale, Hamilton Depression Scale, ATHF, IDS-RR, 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

Type of Comparator 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex delivered at 100% motor threshold for 15 sessions over 3 weeks

Outcomes measured: Hamilton Depression Rating Scale

Follow-up time: Three weeks

Outcome ascertainment: Baseline, week 1, 2 and 3

Type of Analysis: Not reported

Type of Comparator 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex delivered at 100% motor threshold for 15 sessions over 3 weeks

Definition of Treatment Resistance: Failure to respond to at least one trial of adequate antidepressant

Outcomes measured: Hamilton Rating Scale

Follow-up time: three weeks

Outcome ascertainment: Baseline, week 1, 2 and 3

Type of Analysis: Not reported

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

Exclusion 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 Definition of Treatment Resistance: Failure to respond to at least three antidepressant trials

Type of Control sham rTMS
Type of Comparator 10 Hz rTMS stimulation to the left dorsolateral 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, Strong 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

Outcome ascertainment: unblinded at 4 weeks

Type of Analysis: Intention-to-treat

Type of Comparator 10 Hz rTMS stimulation to the left prefrontal cortex delivered using 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

Outcome ascertainment: Baseline, week 2, week 3

Type of Analysis: Intention-to-treat

Participants were recruited from 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

Participants were 164 patients who were treatment resistant were randomized to receive active rTMS. Sixty-seven participants (42 males), 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 at least one adequate antidepressant trial
Patient Selection: Known
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: 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: Twenty-one participants (8 females, 13 males), mean age 45.7 (15.0) received sham rTMS.
Definition of Treatment Resistance: Failure to respond to at least one adequate antidepressant trial
Outcomes measured: Montgomery-Asberg Depression Rating Scale, CARE, Beck Depression Inventory, Hamilton Depression Scale, AUDIT, Young 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 months post-rTMS, 6 month follow-up, Blind broken at 2 weeks
Type of Analysis: Intention-to-treat

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: clear 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.
Definition of Treatment Resistance: Failure to respond to at least 3 trials of antidepressant medications during the current episode
Outcomes measured: Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, CRPS, other self-rated Beck Depression Inventory, American Medical Association, MDS-14, Beck Depression Inventory, Self-administered Zung anxiety scale, Clinical Global Impression, Clinical Global Impression, Global Severity, Self-reported social adaptation scale.
Follow-up time: 2 months
Outcome ascertainment: Baseline, week 2, month 1, month 2, month 3
Type of Analysis: Intention-to-treat
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: Ten 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 Comparator 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. F test

Follow-up time: 4-6 weeks

Outcome ascertainment: Baseline, 1 week after treatment.

Type of Analysis: Not Reported

Moller19 2006

Iceland

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 Comparator Sham without medication

Type of Comparator 20Hz rTMS to the left dorsolateral prefrontal cortex, delivered at 80% 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, 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

Mosel20 2007

United States

Patient Selection: Ten patients 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: 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±13.3 received sham rTMS.

Definition of Treatment Resistance: Failure to respond to at least two adequate antidepressant trials during current depressive episode.

Type of Comparator 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: Montgomery-Asberg Depression Rating Scale, Adjective Mood (Bf-Sr/Bf-S9) and Depression (D-SrD-S9) Scales, Verbal Learning Task.

Follow-up time: 14 days

Outcome ascertainment: Baseline, week 2.

Type of Analysis: Not Reported

Mossman21 2004

United States

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: 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 Comparator Sham with no antidepressants

Type of Comparator rTMS to the left dorsolateral prefrontal cortex delivered at 120% motor threshold, 10 pulses 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

O Reardon22 2005

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, ≥2 Clinical Global Impression, ≥2 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, neurological 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±11.1 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 antidepressants

Type of Comparator Sham with no antidepressants

Type of Comparator rTMS to the left dorsolateral prefrontal cortex delivered at 120% motor threshold, 10 pulses 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

Padberg23 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) 6 patients were randomized to the high-frequency rTMS group; 2 women and 4 men, with a mean age of 63±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 Comparator Sham rTMS

Type of Comparator rTMS at 10 Hz administered as 5 trains of 5s duration (1500 stimuli/day, 15 trains, 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

Follow-up time: 5 days

Outcome ascertainment: Baseline and after the last rTMS treatment (day 5).

Type of Analysis: Not Reported

Padberg24 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 Comparator Sham rTMS

Type of Comparator 100% stimulation intensity related to MT (1500 stimuli/day, 10 Hz, 10×15 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.

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\textsuperscript{10} 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-four patients (43 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 medications 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 impulses 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

**Outcome 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\textsuperscript{9} 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 established 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 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 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.

**Outcome measured:** Hamilton Depression Rating Scale, Clinical Global Impression of Illness – Severity (CGI-S).

**Follow-up time:** Not reported

**Type of Analysis:** Not reported

---

Peng\textsuperscript{12} 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, naive to rTMS.

**Exclusion Criteria:** Psychiatric axis 1 and 2 disorders, epileptic seizures, any neurological disorder, metal implants, other clinically relevant abnormalities

**Patient Selection:** Seventeen patients (7 females, 10 males), mean age 27.46(14.5) were randomized to receive active rTMS. Thirty patients (4 females, 9 males), mean age 26.38(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:** 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.

**Outcome measured:** Hamilton Depression Rating Scale, 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

---

Rossini\textsuperscript{9} 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 of out 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 at to least two different treatments with antidepressants, at adequate dosage and duration, administered during the current episode.

**Type of Control:** Sham with 10mg/day escitalopram.

**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).

**Outcome measured:** Hamilton Depression Rating Scale, Clinical Global Impression of Illness – 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\textsuperscript{9} 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 either with 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 and 28 s off, 40 times, for a total of 1800 stimulations per 20-minute session. Stimulation was applied over the left PPC 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 by 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

**Outcome measured:** Hamilton Depression Rating Scale (2009 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
Sprint

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 20 s 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).

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).

Su

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 psychiatric symptoms, not previously had rTMS treatment or ECT. Patient Characteristics: Thirty patients (30 received rTMS) with unipolar depression 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
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.

Type of Control: Sham with 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.

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. Outcomes measured: Hamilton Depression Rating Scale (21-item).
It is illegal to post this copyrighted PDF on any website.

**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).

**Patient Selection:**

**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

**Outcome ascertainment:** Baseline, week 4

**Type of Analysis:** Not reported

**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

---

**Reference List**


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.


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

<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Patient Selection</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echelard, 2012 France</strong></td>
<td><strong>Patient Selection:</strong> Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported).</td>
<td><strong>Inclusion Criteria:</strong> MADRS score &gt; 20 despite prescription of an anti-depressant for at least 12 weeks.</td>
<td><strong>Exclusion Criteria:</strong> History of personal or family seizures, neurological or neuropsychological antecedent, inferior ear prosthesis, pacemaker, and anticonvulsive medication.</td>
</tr>
<tr>
<td><strong>Fitzgerald, 2003 Australia</strong></td>
<td><strong>Patient Selection:</strong> Patients were recruited from 2 outpatient clinics and by psychiatrist referral between October 2000 and September 2002 and were randomized via sealed envelopes. <strong>Inclusion Criteria:</strong> NR. <strong>Exclusion Criteria:</strong> Significant medical illness, neurologic disorders, or other Axis I psychiatric disorders. <strong>Patient Characteristics:</strong> 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. <strong>Definition of Treatment Resistance:</strong> Failed to meet 2 courses of antidepressants treatments for at least 6 weeks. <strong>Low:</strong> 5 Hz rTMS to right DLPFC 100% MT for 5 trains (300 stimuli per treatment) 5 days per week for 2 weeks. <strong>High:</strong> 10 Hz rTMS to left DLPFC 100% MT for 20 trains (1000 stimuli per treatment) 5 days per week for 2 weeks. <strong>Outcomes measured:</strong> 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 <strong>Follow-up time:</strong> 4 weeks <strong>Outcome ascertainment:</strong> Baseline, 2 weeks, 4 weeks <strong>Type of Analysis:</strong> NR.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fitzgerald, 2006 Australia</strong></td>
<td><strong>Patient Selection:</strong> Patients were recruited from 3 hospitals between May 2004 and January 2006 and were randomized using computer generated sequences. <strong>Inclusion Criteria:</strong> HAMD score &gt; 16. <strong>Exclusion Criteria:</strong> Significant medical illness, neurologic disorders, contraindications to rTMS, DSM-IV diagnosis of alcohol or substance dependence. <strong>Patient Characteristics:</strong> 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. <strong>Definition of Treatment Resistance:</strong> Failed to meet 2 courses of antidepressants medications for at least 6 weeks. <strong>Low:</strong> 2 Hz rTMS to right DLPFC 100% MT for 1 train (900 stimuli per treatment) 5 days per week for 2 weeks. <strong>High:</strong> 2 Hz rTMS to right DLPFC 110% MT for 1 train (1800 stimuli per treatment) 5 days per week for 2 weeks. <strong>Outcomes measured:</strong> HAMD, BDI, <strong>Follow-up time:</strong> 4 weeks <strong>Outcome ascertainment:</strong> Baseline, 2 weeks, 4 weeks <strong>Type of Analysis:</strong> NR.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fitzgerald, 2007 Australia</strong></td>
<td><strong>Patient Selection:</strong> Patients were recruited between March 2003 and January 2005 and were randomized (method not reported).</td>
<td><strong>Inclusion Criteria:</strong> NR.</td>
<td><strong>Exclusion Criteria:</strong> NR. <strong>Patient Characteristics:</strong> Eleven patients with a mean age of 42.4 (11.2), 8 females and 7 males were randomized to high frequency left-sided rTMS. Fifteen patients with a mean age of 48.1 (14.0), 38 females and 25 males were randomized to high frequency rTMS. <strong>Definition of Treatment Resistance:</strong> Failed to meet 2 courses of antidepressants medications for at least 6 weeks.</td>
</tr>
<tr>
<td><strong>Fitzgerald, 2009 Australia</strong></td>
<td><strong>Patient Selection:</strong> Patients were recruited from 1 outpatient clinic and by referral from private psychiatrists (recruitment dates not reported) and were randomized using computer generation.</td>
<td><strong>Inclusion Criteria:</strong> NR.</td>
<td><strong>Exclusion Criteria:</strong> NR. <strong>Patient Characteristics:</strong> 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. <strong>Definition of Treatment Resistance:</strong> Failed to meet 2 courses of antidepressants medications for at least 6 weeks.</td>
</tr>
<tr>
<td><strong>Isenberg, 2005 United States</strong></td>
<td><strong>Patient Selection:</strong> Patients were recruited through community physicians (recruitment dates not reported) and allocated to treatment based on date of entry.</td>
<td><strong>Inclusion Criteria:</strong> NR.</td>
<td><strong>Exclusion Criteria:</strong> Psychosis, significant medical illnesses, neurologic disorders, implanted metal devices, or other major Axis I psychiatric disorders. <strong>Patient Characteristics:</strong> Fourteen patients with a mean age of 55.6 (9.7), 8 females and 6 males received right-sided rTMS. Fourteen patients with a mean age of 43.4 (9.7), 8 females and 6 males received left-sided high frequency rTMS. <strong>Definition of Treatment Resistance:</strong> 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.</td>
</tr>
</tbody>
</table>
Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported).

1 Hz rTMS to the left DLPFC at 110% of MT

HAMD, BPRS.

Follow-up time: 10 weeks for the second experimental treatment.

Type of Analysis: NR

Patient Selection: Patients were recruited from 1 hospital (recruitment dates not reported) and were 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 high-frequency rTMS.

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-TMS 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-TMS 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

Patient Selection: Patients were recruited from 1 hospital (recruitment dates not reported) and randomized (method not reported).

Inclusion Criteria: Patients with organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps were excluded.

Exclusion Criteria: NR

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 1000 pulses (2 sec each, with a 29 sec intertrain interval), for a total of 6000 pulses/day. Stimulation was performed for 10 consecutive working 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

Patient Selection: Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported).

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: Eighty-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: Twice at baseline and after 20 sessions (Week 4). Type of Analysis: NR

Patient Selection: Patients consecutively admitted to 1 hospital were recruited from September 2006 to November 2007 and were randomized (method not reported).

Inclusion 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 hearing 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 (11.1) 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 800 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
Patients were recruited from outpatients of 1 teaching hospital (recruitment dates not reported) who had been referred.

Patients were recruited between October 2000 and April 2003 and were randomized (method not reported).

1 Hz rTMS to left PFC at 100% of MT, given in

Inclusion Criteria:

 NR

Exclusion Criteria:

 NR

Definition of Treatment Resistance: NR

Patient Selection: 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

Patient Selection: Patients were recruited between October 2000 and April 2003 and were randomized (method not reported).

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 rTMS 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

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).

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), 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

Patient Selection: Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported).

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 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 2-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


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.


<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Patient Selection</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumberger† 2012 Canada</td>
<td>Patient Selection: Patient recruited from 3 outpatient clinics between January 2006 and January 2009 and were randomized using a computer-generated list.</td>
<td>Unilateral: 10 Hz rTMS to left DLPCS 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 DLPCS at 100% MT for 4+1 trains of 65 pulses (465 pulses total treatment), then 10 Hz rTMS to left DLPCS at 100% MT for 15 trains of 50 pulses (750 total treatment) 5 days per week for 3 weeks.</td>
<td>Outcomes measured: HAM-D, REANS, HVLT-R, 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</td>
</tr>
<tr>
<td>Fitzgerald§ 2011 Australia</td>
<td>Patient Selection: Patients were recruited from inpatients of 4 hospitals between January 2006 and May 2009 and were randomized using computer generation.</td>
<td>Unilateral: 1 Hz rTMS to the right PPC 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.</td>
<td>Outcome ascertainment: Baseline, 2 weeks, and 4 weeks. Type of Analysis: NR</td>
</tr>
<tr>
<td>Fitzgerald§ 2012 Australia</td>
<td>Patient Selection: Patients were recruited from a single site between January 2008 and November 2010 and were randomized (method not specified).</td>
<td>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.</td>
<td>Outcome ascertainment: Baseline, 3 weeks, and 6 weeks. Type of Analysis: NR</td>
</tr>
<tr>
<td>Fitzgerald§ 2013 Australia</td>
<td>Patient Selection: Patients were recruited from inpatients of 4 hospitals between February 2009 and October 2010 and were randomized using computer generation.</td>
<td>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.</td>
<td>Outcome ascertainment: Baseline, 2 weeks, and 4 weeks. Type of Analysis: NR</td>
</tr>
</tbody>
</table>
**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.

**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). Fifteen 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

---

**Reference List**

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

<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Patient Selection</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakim 2012 Turkey</td>
<td>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.</td>
<td>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.</td>
<td>Outcomes measured: HAMD, MADRS Follow-up time: 6 weeks Outcome ascertainment: Baseline and every week for 6 weeks. Type of Analysis: NR</td>
</tr>
<tr>
<td>Padberg 2002 Germany</td>
<td>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: 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.</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td>Rossini 2005 Italy</td>
<td>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.</td>
<td>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).</td>
<td>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</td>
</tr>
</tbody>
</table>

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

### Reference List

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

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Patient Selection</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fitzgerald</strong>&lt;sup&gt;a&lt;/sup&gt;, 2009 Australia</td>
<td>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 &gt; 18 years, major depressive disorder without psychosis. MADRS score &gt; 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.</td>
<td>5 cm localization: Patients underwent MRI then localization of the motor cortical area 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).</td>
<td>Outcomes measured: MADRS, BDI, BPRS, CORE GAF, CGI, Hopkins verbal learning test, controlled oral word association test, Digi test, Brief visuospatial memory test-revised. Follow-up time: 4 weeks Outcome ascertainment: Baseline, 3 weeks, 4 weeks. Type of Analysis: NR</td>
</tr>
<tr>
<td><strong>Garcia-Toro</strong>&lt;sup&gt;b&lt;/sup&gt;, 2006 Spain</td>
<td>Patient Selection: Patient recruitment method and dates not reported. Randomization was performed using sealed envelopes. Inclusion Criteria: Age &gt; 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.</td>
<td>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.</td>
<td>Outcomes measured: HAMD, GCI. Follow-up time: 10 sessions (4 weeks) Outcome ascertainment: Baseline, 1 week, 2 weeks, 4 weeks Type of Analysis: NR</td>
</tr>
<tr>
<td><strong>Paillière-Martinet</strong>&lt;sup&gt;c&lt;/sup&gt;, 2010 France</td>
<td>Patients were selected 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 &gt; 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 (&gt;150 mg/d in an equivalent dose of imipramine) and duration (at least 4 wk for each drug).</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td><strong>Pascual-Leone</strong>&lt;sup&gt;d&lt;/sup&gt;, 1996 Spain</td>
<td>Patients 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.</td>
<td>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.</td>
<td>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</td>
</tr>
<tr>
<td><strong>Triggs</strong>&lt;sup&gt;e&lt;/sup&gt;, 2010 United States</td>
<td>Patients 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 narcisistic) personality disorder or mental retardation; use of medications that may lower seizure threshold (e.g. metomridazole) 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</td>
<td>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</td>
<td>Outcomes measured: HAMD and Beck’s Questionnaire for patient self-rated mood. 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</td>
</tr>
</tbody>
</table>
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:**

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).

### Scheduling

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Selection</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Treatment Protocol</th>
<th>Outcome Ascertainment</th>
<th>Type of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galletly, 2012, Australia</td>
<td>Patients were recruited from private psychiatrists between August 2008 and Feb 2011 and were randomized using computer generation.</td>
<td>Fluency in English, diagnosis of major depression.</td>
<td>Neurological disorders, metal plates or other implants in the skull, a history of epilepsy, withdrawing from drugs or alcohol.</td>
<td>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 6 weeks.</td>
<td>Outcome measured: HAMD, MADRS, Zung SDS, HARS.</td>
<td>Follow-up time: 6 weeks</td>
</tr>
<tr>
<td>Turner-Shia, 2006, Australia</td>
<td>Patients were recruited from 1 hospital and from private outpatient clinics (recruitment dates not reported) and were randomized by coin flip.</td>
<td>Major depressive episode (DSM-IV), between 20 and 65 years, HAMD-17 score $\geq 18$, and no medication change for a minimum of 2 weeks before commencement of the study.</td>
<td>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.</td>
<td>10 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.</td>
<td>Outcome measured: HAMD, VAS.</td>
<td>Follow-up time: 2 weeks</td>
</tr>
<tr>
<td>Price, 2010, Australia</td>
<td>Participants were recruited from outpatient clinics (recruitment dates not reported) and were randomized using predetermined lists.</td>
<td>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.</td>
<td>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.</td>
<td>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.</td>
<td>Outcome measured: HAMD, BDI.</td>
<td>Follow-up time: 4 weeks</td>
</tr>
<tr>
<td>Conca, 2002, Austria</td>
<td>Patients were recruited from inpatients from 1 hospital (recruitment dates not reported) and were randomized afterfood not reported).</td>
<td>Failure to respond to 2 different adequate monotherapy trials of medications with different pharmacological profiles and the failure to response to a second augmentation strategy.</td>
<td>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.</td>
<td>10 Hz rTMS to left DLPFC at 110% MT for 13 trains alternating with 1 Hz 30 train (6500 total treatment) for 5 days.</td>
<td>Outcome measured: CGI.</td>
<td>Follow-up time: 5 days</td>
</tr>
</tbody>
</table>

Sessions of either rTMS or sham rTMS over a 2-week period.
### Fitzgerald 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:** Eighty-two patients with a mean age of 44.8 (11.4), 13 females and 15 male were randomized to receive non-primed rTMS. Thirty participants with a mean age of 45.7 ± 10.8 years, 20 females 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 the sec 45 degrees from the side of the coil, with a 6 Hz stimulation for twenty trains of 5 seconds duration at 90% of 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.

### Levkovitz 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, unipolar depression, CGI-S score ≥ 24, 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 6 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 bilateral high intensity rTMS.

**Definition of Treatment Resistance:** Failed at least 2 trials of antidepressants medications.

### McDonald 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 Amnesia 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.

### Rybak 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Frequency</th>
<th>Intensity</th>
<th>Outcome</th>
<th>Type of Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzgerald 2008</td>
<td>PDLPFC</td>
<td>20 Hz</td>
<td>100% MT</td>
<td>NR</td>
<td>Non-primed</td>
</tr>
<tr>
<td>Levkovitz 2009</td>
<td>PDLPFC, bilateral</td>
<td>1 Hz, 20 Hz</td>
<td>110% MT</td>
<td>1 Hz</td>
<td>Primed</td>
</tr>
<tr>
<td>McDonald 2006</td>
<td>PDLPFC</td>
<td>10 Hz</td>
<td>110% MT</td>
<td>NR</td>
<td>Non-primed</td>
</tr>
<tr>
<td>Rybak 2005</td>
<td>PDLPFC</td>
<td>20 Hz, 1 Hz</td>
<td>110% MT</td>
<td>NR</td>
<td>Non-primed</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Author, Year, Publication, Country</th>
<th>Patient Selection</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grunhaus 2003, Israel</td>
<td>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 TMS (14 female, 6 male) with a mean age of 57.6 (13.7). Twenty participants were randomized received CECT (15 female, 5 male), with a mean age of 61.4 (16.6).</td>
<td>Type of TMS 10 Hz rTMS, delivered at 90% motor threshold to the left dorsolateral prefrontal cortex five times per week for 10-20 weeks. Seizures were at least 20 seconds in length. Participants were given 1mg/kg methohexitone and 1mg/kg succinylcholine.</td>
<td>Outcomes measured: Hamilton Depression Rating Scale for Depression, Brief Psychiatric Rating Scale, Global Assessment of Functioning Scale, Clinical Global Impression Scale. Follow-up time: 4 weeks Outcome ascertainment: Baseline, 2 weeks, end of treatment</td>
</tr>
<tr>
<td>Janicak 2002, United States</td>
<td>Patient Selection: 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 TMS. Nine participants were randomized to receive ECT with a mean age of 42.7 (14). There were no statistically significant differences in age.</td>
<td>Type of TMS 10 Hz rTMS, delivered at 100% motor threshold to the left dorsolateral prefrontal cortex five times per week for 10-20 sessions (1,000 stimulations per session) Type of Comparator CECT three times per week for 3-12 bitemporal treatments. Participants were given 1mg/kg of methohexitone and 1mg/kg succinylcholine</td>
<td>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</td>
</tr>
<tr>
<td>Keshtkar 2011, Iran</td>
<td>Patient Selection: Patients who were referred for ECT were recruited from southwestern Iran and randomized to receive TMS or ECT by coin toss. Inclusion Criteria: Diagnosis of major depressive disorder by DSM-IV Exclusion Criteria: previous TMS, 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 TMS. Forty participants (32 female, 8 male), mean age 35.6 (8.1) were randomized to receive CECT.</td>
<td>Type of TMS rTMS to the left dorsolateral prefrontal cortex delivered at 90% motor threshold for 10 sessions (408 simulations per session for a total of 4800 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.</td>
<td>Outcomes measured: Beck Depression Inventory, Montgomery-Asberg Depression Rating Scale, Global Assessment of Functioning Scale, Side-effects 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</td>
</tr>
<tr>
<td>Prudmore 2000, Australia</td>
<td>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 TMS (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.</td>
<td>Type of TMS Two cycles of 1 day ECT followed by 4 days rTMS. 20 Hz TMS, at 100% motor threshold. Type of Comparator Unilateral ECT 3 times per week for 2 weeks. Participants were given 1-1.5 mg/kg methohexiton and 0.5mg/kg suxamethonium</td>
<td>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</td>
</tr>
<tr>
<td>Prudmore 2000, Australia</td>
<td>Patient Selection: Consecutive patients at the Royal Hobart Hospital, who met the inclusion criteria, were invited to participate 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 TMS. Sixteen participants (13 females, 3 males), mean age 41.5 (12.9) were randomized to receive ECT.</td>
<td>Type of rTMS 20 Hz rTMS using 100% motor threshold delivered in 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 methohexiton and 0.5 mg/kg suxamethonium</td>
<td>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</td>
</tr>
</tbody>
</table>
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 different 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.

Reference List


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

<table>
<thead>
<tr>
<th>Author, Year of Publication, Country</th>
<th>Patient Selection</th>
<th>Exposure</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloch, 2008, Israel</td>
<td>Participants were recruited from 1 inpatient adolescent ward and 1 outpatient clinic. Patient Selection: 1. 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.</td>
<td>10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex at 80% motor threshold for 14 sessions over 14 days.</td>
<td>Outcomes measured: Child Depression Rating Scale, 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.</td>
</tr>
<tr>
<td>Croarkin, 2012, United States</td>
<td>Participants were recruited from 2 inpatient treatment centers. Patient Selection: 1. 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.</td>
<td>10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex at 120% motor threshold for 30 sessions within 6-8 weeks.</td>
<td>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.</td>
</tr>
<tr>
<td>Mayer, 2012, Australia</td>
<td>Participants were recruited from a previously conducted open-label trial on rTMS conducted in 2006. Patient Selection: 1. 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.</td>
<td>Provided in 2008 study by Bloch et al.</td>
<td>Outcomes measured: Beck Depression Inventory Version II, Children’s Depression Rating Scale-Revised, Cambridge Neuropsychological Test Automated Battery. Outcome ascertainment: Three years post-treatment.</td>
</tr>
</tbody>
</table>

### Reference List