

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR TREATMENT RESISTANT DEPRESSION

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) is asked to review the scientific evidence for the use of Repetitive Transcranial Magnetic Stimulation (rTMS) for treatment of major depression. The only currently FDA approved device is the NeuroStar TMS Therapy System; the approval states that it is “indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode.”

BACKGROUND

Depression is common, disabling, and often unrecognized in general medical practice. Even when recognized, physicians frequently do not provide systematic, longitudinal, evidence-based management. And from the perspective of the patient, stigma and other psychosocial barriers often diminish adherence to treatment recommendations. Therefore, despite robust documentation that depression is quite treatable, and the widespread availability of evidence-based guidelines, overall outcomes remain poor.¹

Major depressive disorder is associated with considerable disability, morbidity, and mortality. Epidemiologic studies demonstrate that depression causes as much, and often more, physical disability and social and role impairment than most other chronic illnesses. The World Health Organization has identified major depression as the fourth leading cause of disability worldwide and projects it will become the second leading cause of worldwide disability by 2020. Major depression is also a well documented and common comorbidity in most other chronic conditions: for example, heart disease, stroke, diabetes mellitus, cancer, Parkinson disease, arthritis, pulmonary disease, and others. Furthermore, when present as a comorbidity, depression accounts for significant increases in disability, morbidity, and mortality.

In addition to major depression, patients presenting with a depressed mood may be suffering from a number of other psychiatric and/or medical conditions. **Dysthymic disorder** is a less severe but more chronic form of depressive illness that is also associated with significant disability, and is even more likely to go undiagnosed than major depression. This disorder is diagnosed when depressed mood and at least two other symptoms of depression have been present “more than half the days” during the previous 2 years.

Adjustment disorder with depressed mood involves a reaction to an identifiable stressor, such as divorce or job loss. It presents with a sad or depressed mood, a level of impairment greater than expected for most individuals facing that specific stressor, and is diagnosed within the first six months after the stressor has occurred. **Bipolar disorder** is a common and severe mental illness, occurring in about three to four percent% of the general population, causing significant disability, and carrying 80–85% genetic heritability. Bipolar I disorder refers to patients with a history of at least one episode meeting full criteria for major depression and at least one other distinct episode meeting criteria for mania. Other bipolar spectrum disorders such as bipolar II disorder (a condition marked by episodes of major depression and at least one documented episode of hypomania, not mania) and cyclothymic disorder (no episodes meeting full criteria for either major depression or mania/hypomania) are probably much more common thought to occur in approximately four to six percent of the population. **Bipolar depression** refers to an episode of illness meeting criteria for major depression in a patient with a history of either mania or hypomania. Approximately 10–15% of all depression is caused by general medical illness, and is considered to be the direct physiologic result of a medical illness such as hypothyroidism or hyperthyroidism, pancreatic cancer, Parkinson disease, or stroke.

Epidemiologic studies demonstrate a lifetime prevalence of major depression in 7–12% of men and 20–25% of women. The point prevalence of major depression in a community sample is 2.3–3.2% for men and 4.5–9.3% for women. Numerous studies report a 10–15% prevalence of major depression in ambulatory medical settings with a substantially higher rate (20–40%) in patients with coexisting medical problems. Prevalence of depression varies among age groups. Recent data point to a cohort effect through which current “baby boomers” experience the highest rates of depression of any previous generation. Although the most current epidemiologic findings show a surprisingly low 1-year prevalence rate of major depression in the elderly (1–2%), the rate of major or minor depression in elderly patients who seek treatment in primary care practices is 5%, with rates ranging from 15 to 25% in nursing home residents.

The *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR)* criteria for major depression require that five of nine symptoms be present for a 2-week period (See Table 1). One of these nine symptoms must be either a persistent depressed mood (present most of the day, nearly every day) **or** pervasive anhedonia (loss of interest or pleasure in living).

Table 1. Diagnosis of major depression.

1. Depressed mood
2. Anhedonia (lack of interest or pleasure in almost all activities)
3. Sleep disorder (insomnia or hypersomnia)
4. Appetite loss, weight loss; appetite gain or weight gain
5. Fatigue or loss of energy
6. Psychomotor retardation or agitation
7. Trouble concentrating or trouble making decisions
8. Low self-esteem or guilt
9. Recurrent thoughts of death or suicidal ideation

Five symptoms from the above are required to make the diagnosis of depression and must include depressed mood and/or anhedonia. The symptoms must have been present most of the day, nearly every day for 2 weeks.

Evidence-based treatment for depression includes antidepressant medication, several forms of psychotherapy, a combination of medication and psychotherapy and, in refractory cases, electroconvulsive therapy (ECT). A number of biological and psychological therapies have been shown in randomized clinical trials to be effective for treatment of depression. The concept of “effectiveness,” however, hinges on the demonstration of a “response” to treatment defined as “50% improvement in symptoms.” A 50% improvement is certainly important clinically, but this criterion is broad enough to leave significant residual symptoms unresolved. The concept of “remission,” therefore, has been introduced to underscore the importance of helping the depressed patient reach full return of function and achieve relative absence of all depressive symptoms. Evidence demonstrates that antidepressant medications are effective for the treatment of major depression and dysthymia in many but not all patients. An adequate trial of an antidepressant requires a minimum of four to six weeks at appropriate doses. Of the non-pharmacological therapies, cognitive-behavioral therapy (CBT) and interpersonal psychotherapies (ITP) have the broadest evidence-base for effectiveness in treatment of depression. There is also evidence that several variants of CBT, such as mindfulness-based cognitive therapy (MBCT) and cognitive-behavioral analysis system of psychotherapy (CBASP), as well as problem-solving therapy, behavioral therapy, and psychodynamic therapy may be effective. At least 50% of patients with a major depressive episode will have a second episode, and patients who have had two or more episodes of major depression have a 75–90% likelihood of recurrence.

Approximately 60% of patients with major depression will not achieve remission with the first prescribed antidepressant. These patients have been classified as having **treatment resistant depression (TRD)**.² Guidelines and clinical practice are still evolving as to the classification and treatment of TRD, but evidence from the STAR-D trial suggests that about one-quarter to one-third of patients who fail a trial of one antidepressant will respond if either switched to another medication or if treatment is augmented with a

second agent.³⁻⁵ Similar results are obtained with switching or augmenting with evidence based psychotherapeutic strategies. In addition, a number of other treatments have been studied or have received FDA approval for treatment of TRD; these include vagus nerve stimulation, ECT, transcranial magnetic stimulation, the atypical antipsychotic medication aripiprazole⁶, and others.

Repetitive Transcranial Magnetic Stimulation

The NeuroStar TMS device received FDA clearance in October 2008 for use in patients with depression who failed at least one six-week trial of antidepressant medication. Transcranial magnetic stimulation (TMS) is a non-invasive technique for stimulating the cerebral cortex and causing neuronal depolarization and other changes in brain activity.⁷ A pulsed magnetic field of the same type and strength as those produced by a magnetic resonance imaging (MRI) machine is generated by an insulated coil applied to the patient's scalp.⁸ Treatment sessions last about 40-minutes and do not require anesthesia or sedation. Over the past decade, treatment with TMS has moved to use of higher frequency and number of pulses as well as to more treatment sessions. Transcranial magnetic stimulation can be administered in high or low frequency and as single or repeated pulses. Higher frequency leads to the activation of stimulated brain regions while low frequency has an inhibitory effect. Currently, with the FDA approved device, treatment is administered daily for four to six weeks (20-30 treatments). Magnetic field pulses are generated and aimed at the left, dorsolateral prefrontal cortex (DLPFC) and the magnetic field pulses pass unimpeded through the hair, skin, and skull and into the brain. Once inside the brain, the magnetic field pulses induce an electrical current that is thought to lead to the release of neurotransmitters important in depression such as serotonin, norepinephrine and dopamine (<http://www.neurostartms.com/home.asp>; accessed April 2009). The DLPFC is thought to be important in the regulation of mood; specifically, the left DLPFC is thought to be responsible for producing and regulating positive affect while the right hemisphere influences negative affect. Low frequency (or inhibitory) stimulation of the right DLPFC or high frequency (activation) of the left DLPFC may be used to enhance mood.⁷ When used for treatment of depression, rTMS is generally administered in high frequency (or "fast") rTMS.

The most common side effects reported during clinical trials were headache and scalp pain or discomfort. Other reported adverse effects reported more commonly with rTMS than with sham treatment include eye pain, toothache and muscle twitching.⁸ Seizures have been reported with TMS devices but were not reported in the clinical trials. In addition, administration of the magnetic pulses is associated with a knocking sound similar to that generated by an MRI scanner. Contraindications to use of rTMS include patients with implanted metallic devices or non-removable metallic objects in or around the head. Patients with braces and metal fillings are acceptable for treatment; however, patients with other metal within their mouth should

discuss this with their physician. Other contraindications include patients with implants controlled by physiological signals including pacemakers, implantable cardioverter defibrillators (ICDs), and vagus nerve stimulators (VNS) (<http://www.neurostartms.com/home.asp>; accessed April 2009).

In addition to its use for depression, transcranial magnetic stimulation is being investigated for use in treatment of tinnitus, chronic pain and fibromyalgia among other potential indications.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The NeuroStar® TMS System (Neuronetics, Inc., Malvern, PA) received FDA 510(k) clearance in October 2008.

There are several magnetic stimulators that have received FDA 510(k) clearance, however, they have been approved for other uses and their use in TRD would be off-label.

TA criterion1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Key health outcomes

The main primary and secondary outcomes assessed in randomized trials of therapies for major depression include improvement in symptoms as measured by validated depression scales, most commonly the Hamilton Rating Scale for Depression (HAM-D: 17, 21, and 24 item variants) and the Montgomery-Asberg Depression Rating Scale (MADRS). Other scales used include the Beck Depression Inventory, the Brief Psychiatric Rating Scale (BPRS), the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR).

The most important health outcome for the treatment of depression is the remission of symptoms and the return to full psychosocial functioning. In clinical trials, this is usually defined as a reduction in symptoms below a threshold, although many scales have been used and a variety of cutoffs used for each scale.⁹ The most commonly used definition is a score of 7 or less on the HAM-D17. The other commonly accepted definition has been a score of 10 or lower on the MADRS.⁹ Both of these cut points have been criticized as

too high^{10, 11}, but they remain the standard. Usually remission requires that patients maintain low levels of symptoms for at least two to three weeks and recovery requires symptom control for at least four to six months.⁹ For rTMS, it is particularly important to demonstrate that remission is sustained after cessation of active treatment as active treatment requires that patients come in to a treatment facility five days a week – an unrealistic burden compared with taking pills at home.

Remission rates in depression trials are typically low, particularly after failure of one or more prior therapies. For instance, in the STAR*D trial the remission rate after first line therapy was about 37%, but this decreased to 31% when switching to a second line therapies, and was only 14% for third line therapies.^{3-5, 12-17}

Response to a therapy is usually defined by a 50% reduction in symptoms. Response rates are typically ten to 15% greater than remission rates. Predictors of both response and remission include being white, female, more highly educated, and fewer co-morbidities. It is important to understand that the STAR*D trial was designed to enroll a broad spectrum of patients, who were more representative of real-world patients than those enrolled in most clinical trials. Thus, their study subjects had more complex psychiatric and medical disease than patients typically enrolled in clinical trials.¹⁶ Patients in STAR*D who would have qualified for most phase 3 clinical trials of medications for depression had about ten percent higher response and remission rates than those who did not meet typical inclusion and exclusion criteria.¹⁸

Search results

The Medline database, EMBASE, Cochrane clinical trials and reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “depression”, or “major depression”, or “major depressive disorder”, and “repetitive transcranial magnetic stimulation” or “rTMS” or “transcranial magnetic stimulation” from 1966 to May 2009. The bibliographies of systematic reviews and key articles were manually searched for additional references. Abstracts of citations were reviewed and all relevant articles reviewed in full.

The Figure describes the search results. In brief, a total of 424 references were reviewed (236 from Embase, 184 from PubMed, and 4 from the combined Cochrane databases). Because of the evolution in rTMS treatment methodology through early experimentation, the large number of randomized trials and concerns about publication bias, we included only trials that randomized at least 40 patients with treatment resistant depression. Earlier systematic reviews and meta-analyses^{7, 19-29} have included many of the early, small trials.³⁰⁻⁶⁰ Results from these meta-analyses will be used to summarize the early literature.

The seven trials⁶¹⁻⁶⁷ that met the inclusion and exclusion criteria randomized a total of 578 patients. The methodologic quality of the trials is summarized in Table 2. The two most recent trials^{65, 66} were of the highest quality and only the O'Reardon trial was sufficiently powered to detect differences in response and remission rates.⁶⁶

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Table 2: Quality of the randomized trials of high frequency transcranial magnetic stimulation compared with sham controls

Study	Randomization	Allocation concealment	Comparable groups at randomization	Co-interventions equivalent	Patients blinded	Outcome assessment blinded	Loss to follow-up reasonable and comparable?	Intention to treat analysis	Overall quality
Fitzgerald 2003	Yes	Yes	Yes, though large NS age differences	Yes	Yes, but unblinded at 2 weeks	Yes	Yes	Yes	Fair, but two weeks of treatment before unblinding and treatment changes is too short.
Rossini 2005	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	Fair, but underpowered and likely some unblinding
Avery 2006	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Fair, but used one-sided statistical tests for primary outcomes and Bonferroni correction for harms
Fitzgerald 2006	Yes	Yes	Yes	No, not after 2 weeks	Yes, but unblinded at 2 weeks.	Yes	No, 100% vs. 88% at 2 weeks; by week 5, 0% in sham arm	Yes	Fair through 2 weeks, unreliable comparisons after that time point.
McDonald 2006	Yes though details NR	NR	No: significant differences in number of prior medications, % male, % BAD, % R hand dominant	Yes	Yes	Yes	NR	Yes	Poor: many baseline differences calls randomization into question, poor reporting of methods.
O'Reardon 2007	Yes though details NR	NR	Yes, though MADRS score higher in sham group (p=0.036)	Yes	Yes	Yes	Yes	Yes	Fair to good. Baseline differences, loss to f/u, poor reporting, no blinded comparisons after treatment completed
Mogg 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good, but small and not all patients were treatment resistant.

NR: Not reported

Table 3: Description of Study Procedures and Participants the Randomized Trials of High Frequency Transcranial Magnetic Stimulation Compared with Sham Controls

Study	rTMS procedure	N	Design	Follow-up	Age	Drugs failed, N	Depression	Inclusion criteria	Exclusion criteria	Comment
Device					Sex, %F		Scale			
Fitzgerald 2003 Magstim Super Rapid Magnetic Stimulator	HFL-rTMS 10 Hz 100% MT 20 trains 5 s on, 25 s off 5/wk x 4 weeks LFR-rTMS 1 Hz 100% RMT 5 trains 60 s on, 60 s off 5/wk x 4 weeks	60	Two centers RCT	4 weeks	46 years 43%	5.7 lifetime	<u>MADRS</u> 36.5	18-70 years old MDD or BAD by DSM IV Medications OK MADRS > 20 Failed ≥ 2 meds x 6 weeks	Other Axis I disorders "Significant" medical or neurological disorder	The study included patients failing ECT (n=16), left handed patients (n=5), and patients with bipolar disorder with a depressive episode (n=6).
Rossini 2005 Magstim Super Rapid Magnetic Stimulator	HFL-rTMS 15 Hz 80% or 100% MT 20 trains 2 s on, 28 s off 5/wk x 2 weeks	54	Single site RCT	5 weeks	56 years 70%	NR	<u>HAMD21</u> 28.7	18-75 years old MDD by DSM IV Medications OK HAMD21 ≥ 26 Failed ≥ 2 meds this episode	Seizure disorder Neurologic disease ECT this episode Pregnancy Pacemaker Metal clips in head	
Avery 2006 Dantec Magpro Magnetic Stimulator, Medtronic	HFL-rTMS 10 Hz 110% MT 32 trains 5 s on, 25 s off 5/wk x 3 weeks	68	Single site RCT	5 weeks up to 6 months	44 years 54%	1.5 current 3.2 lifetime adequate 8.2 total med trials	<u>HAMD17</u> 23.5	21-65 years old MDD by DSM IV Medications OK HAMD17 ≥ 17 Failed ≥ 2 meds in past	Suicidality or prior suicide attempt BAD ≥ 9 failed ECT Episode > 5 years Antisocial or borderline PD Other major illness	
Fitzgerald 2006 Medtronic Magpro 30 Magnetic Stimulator	LFR-rTMS 1 Hz 110% MT 3 trains 140 s on, 30 s off followed by: HFL-rTMS 10 Hz 100% MT 15 trains 5 s on, 25 s off 5/wk x 2 to 6 weeks	50	Two centers RCT	2+ weeks	45 years 62%	5.9	<u>HAMD17</u> 21.1	18-70 years old MDD or BAD by DSM IV Medications OK MADRS > 20 Failed ≥ 2 meds x 6 weeks	Other Axis I disorders "Significant" medical or neurological disorder	0% lost to follow-up in active, 12% in sham at 2 weeks. At 5 weeks, 56% lost to follow-up in active, 100% in sham.

Study	rTMS procedure	N	Design	Follow-up	Age	Drugs failed, N	Depression	Inclusion criteria	Exclusion criteria	Comment
Device					Sex, %F		Scale			
McDonald 2006 Neuronetics High Speed Magnetic Stimulator	HFL-rTMS 10 Hz 110% MT 20 trains 5 s on, 55 s off and LFR-rTMS 1 Hz 110% RMT 1 train 600 s on 5/week x 2 weeks	62	Single site RCT	3 months	~50 years 52%	8	<u>HAMD21</u> ~27	18-70 years old MDD by DSM IV Medication free HAMD17 ≥ 20 Failed ≥ 3 meds this episode	Psychosis Seizure disorder Neurologic disease Pregnancy Pacemaker Metal clips in head Prior TMS Serious medical disease	
O'Reardon 2007 Neuronetics Model 2100 Therapy System	HFL-rTMS 10 Hz 120% MT 75 trains 4 s on, 26 s off 5/wk x 6 weeks. 3 week taper	325	Multicenter RCT	6 weeks. Unblinded at 4 weeks if < 25% reduction in HAMD17	48 years 53%	1.6	<u>HAMD17</u> 30.3	18-70 years old MDD by DSM IV Medication free CGI-S ≥ 4 HAMD17 ≥ 20 Failed 1 to 4 meds	Episode > 3 years Psychosis BAD OCD Failed ECT Prior rTMS or VNS Seizure disorder	22/165 (13%) TMS lost by 4 weeks 26/160 (16%) sham lost by 4 weeks
Mogg 2008 Magstim Super Rapid Magnetic Stimulator	HFL-rTMS 10 Hz 110% MT 20 trains 5 s on, 55 s off 5/week x 2 weeks	59	Single site RCT	4 months	54 years 63%	3.1	<u>HAMD17</u> 21.0	≥ 18 years MDD by DSM IV Right handed Stable medications for 4 weeks	Seizure disorder Head injury with LOC Neurologic disease Other Axis I diagnosis Prior rTMS Metal clips in head Brain surgery	78% had failed 2 and 53% failed ≥ 3 treatments for this depressive episode.

Table 3 summarizes the details of the patient populations studied and the rTMS parameters used in each study. There were important differences in the definition of treatment resistant depression across the studies. Some required that subjects fail only one medication for their current episode of depression, while other studies required subjects to fail at least three adequate drug trials before enrolling them in the study. In some studies, subjects were allowed to continue antidepressant medication during treatment with rTMS, while other studies required study subjects to be antidepressant free. Similarly, some studies excluded patients with bipolar disease, psychosis, or failed ECT, while other studies allowed patients with these characteristics to be enrolled. Finally, some studies only included right-handed patients to be randomized while others included left-handed patients.

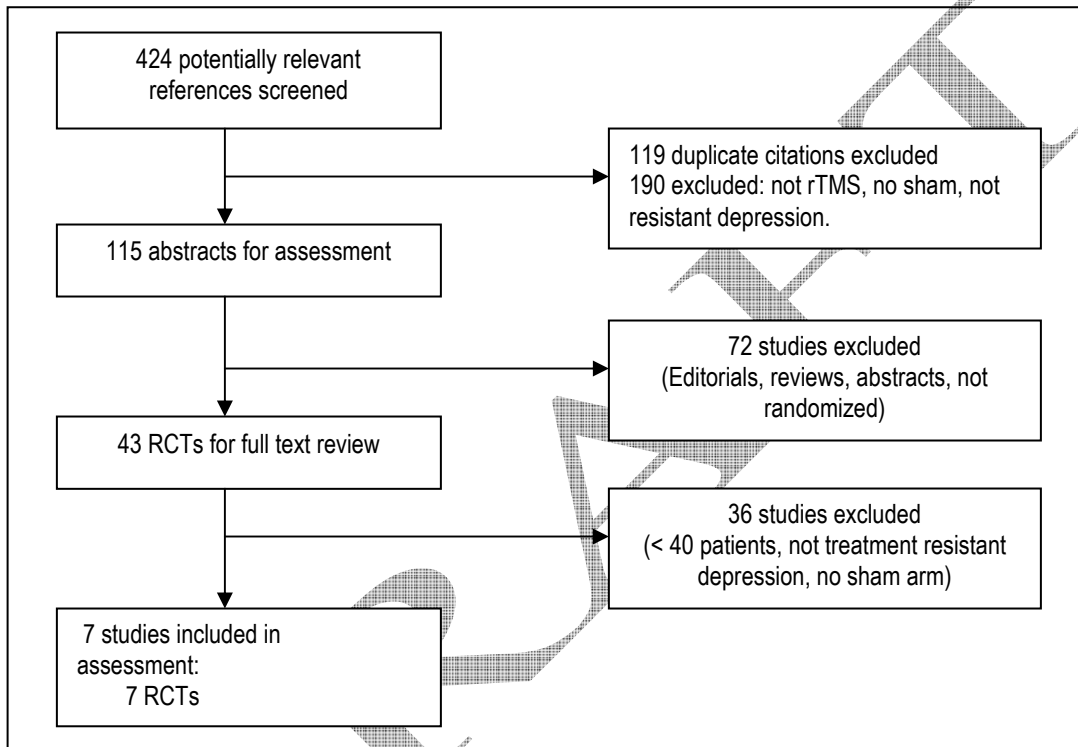
The differences in rTMS parameters were even greater than the differences in the patient populations studied. Several of the systematic reviews^{22, 29} have noted that there has been a trend towards more intensive rTMS therapy with use of a higher field strength (from 80% of the motor threshold in early studies^{31, 32, 40, 46, 50} to greater than 100% in recent studies^{61, 62, 64-66}), with more pulses per session (less than 1000 in early studies^{32, 35, 40, 46, 55} to more than 2000 in recent studies^{51, 61, 66}) and more total sessions (from five^{50, 55} to 20 or more^{49, 66, 68}). Such variability in the application of rTMS continues in the recent, larger clinical trials of rTMS for treatment resistant depression. The studies used a mix of high frequency rTMS (10 to 15 Hz) applied to the left prefrontal cortex and low frequency rTMS (1 Hz) to the right prefrontal cortex. Some used both left and right sided therapy in sequence^{62, 64}, while others studied only rTMS therapy directed at one cerebral hemisphere.^{61, 63, 65-67} The length of therapy varied from two weeks^{64, 65, 67} to six weeks⁶² with one study tapering rTMS over weeks five through seven.⁶⁶

Two other aspects of these studies limit our ability to determine the role rTMS should play as a therapy for treatment resistant depression. First, and most important, none of the studies maintained blinding in both arms of the trial after the end of the active treatment phase. Thus, there were no blinded comparisons of the stability of any treatment effect once rTMS therapy has ended. No one is proposing long term daily treatment with rTMS, so blinded assessment of the durability of treatment response is essential. Prior systematic reviews have suggested that rTMS appears to be more effective than sham during active therapy, but have found no continued benefits after treatment stops.^{19, 26} Second, none of these trials compare rTMS to active therapy with new medications, augmentation, or cognitive therapy. There are trials comparing rTMS to ECT, but most find ECT to be more effective and more cost-effective.^{58, 69-74}

In summary, the literature on rTMS continues to evolve. As noted in prior systematic reviews, rTMS appears to have an effect during active treatment, but it may be short-lived. Investigators continue to vary both the

patient populations studied and the parameters of rTMS itself in order to identify an effective use of the technology. In the pharmaceutical environment, the therapy would still be in early phase dose-finding studies. Approaches to blinding have improved over time, but most studies break the blind early, which limits the quality of the assessment of treatment response after active therapy has stopped.

Figure: Selection of studies for inclusion in review



Overall, the scientific evidence does not permit conclusions concerning the effectiveness of rTMS in the treatment of patients who have failed treatment with one or more antidepressant medications.

Level of evidence: 1,2

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

Randomized clinical trials

The protocol for sham treatment has been a major issue for randomized trials of rTMS. The machines make noise and the patients often feel pain or twitching during active treatment. Most commonly, the coil has been tilted at 45° or 90° from the active angle (see Table 4). Both have been criticized: the 45° angle for potentially having some effect on brain activity and thus not being a true placebo⁷⁵; the 90° angle for being less painful and thus potentially unblinding participants. Given the power of the placebo effect in trials of depression, this is an important issue. More recently investigators have developed sham coils that produce similar sensations without generating magnetic flux.^{51, 65, 76, 77} The better quality randomized trials have attempted to assess the degree of unblinding of study subjects by asking them whether or not they thought they received the active treatment (see Table 3). Most studies did not allow the staff members operating the rTMS device, who were by necessity unblinded, to have any other role in the assessment of the subjects' response to therapy.

Table 4 summarizes the outcomes of treatment for the seven randomized trials⁶¹⁻⁶⁷ meeting our inclusion and exclusion criteria. Almost all of the studies report greater improvements in the depression scales (HAMD17 or 21, MADRS, or BDI) at the end of active therapy. Two of the seven trials reported significant differences in remission rate.^{61, 62} In both of these trials there were higher rates of adverse events reported in the active arm and more subjects in the active arms of each trial guessed that they received rTMS, though the differences were not statistically significant. Unless unblinding is greater than reported, these data suggest that rTMS has some real effect in decreasing symptoms of major depression during the active treatment phase. Most trials unblinded participants at the end of active treatment in the trial, particularly if they did not have a significant response to therapy, making it difficult to objectively assess the continued effect compared to sham treatment. The two most recent and highest quality studies will be described in detail below.^{65, 66}

Table 4: Outcomes and Adverse Events for the Randomized Trials of High Frequency Transcranial Magnetic Stimulation Compared with Sham Controls

Study	Procedure	N	Follow-up*	HAMD17	MADRS	BDI	CGI-S	Response	Remission	Guesses received rTMS	Adverse events
Fitzgerald 2003	HFL-rTMS	20	2 weeks	NR	36.1 to 30.8	33.1 to 26.7	NR	0%	0%	42% (combined active)	No difference (p = 0.08). Details not reported, but participants in the HFL group tended to report more pain.
	LFR-rTMS	20			37.7 to 32.2	35.0 to 27.2		5%	0%		
	Sham 45°	20			35.7 to 35.4	32.3 to 29.0		0%	0%		
					p = 0.004	p = 0.03		p NS	p NS	p NR	
Rossini 2005	HFL-rTMS 100%	18	5 weeks	28.8 to ~8.6	NR	NR	Results NR, but favoring rTMS p<0.0001	61.1%	50% ^a	NR	NR
		19		28.6 to ~15.7				27.8%	27.8%		
	HFL-rTMS 80%	17		28.7 to ~24.4				6.2%	0%		
	Sham 45°			HAMD21 p<0.001				p = 0.0008	p NR		
Avery 2006	HFL-rTMS	35	4 weeks	23.5 to 15.7 (-7.8)	NR	28.1 to 16.8 (-11.3)	NR	30.6%	20%	58%	Pain: 41% vs. 0%, p < 0.05 Limited reporting
Sham 90°	33	23.5 to 19.8 (-3.7)			28.4 to 23.6 (-4.8)		6.1%	3%	43%		
				p < 0.05		p = 0.003		p=0.008	p=0.033	p NR	
Fitzgerald 2006	HFL+LFR-rTMS	25	2 weeks	22.5 to ~12.3	34.0 to 26.2 (-7.7)	29.2 to 18.3	NR	44%	36%	60%	Headache (20% vs. 8%) Nausea (12% vs. 0%)
	Sham 45°	25		19.8 to ~18.7	34.1 to 30.9 (-3.2)	29.3 to 21.6		8%	0%	50%	
				p < 0.001	p < 0.001	p = 0.01		p < 0.05	p = 0.005	p > 0.05	
McDonald 2006	L then R	25	2 weeks	NR to 16.2	NR	NR to 15.3	48%	28%	12%	NR	NR
	R then L	25		NR to 22.3		NR to 22.8	12%	12%	0%		
	Sham 90°	12		NR to 19.8		NR to 22.8	17%	8%	0%		
				p NR		p NS	p NR	p NS	p NR		
O'Reardon 2007	HFL-rTMS	165	4 weeks	22.6 to 17.4	32.8 to 27.0	NR	"Greater" response with rTMS p = 0.009	18.1	7.1	NR	Toothache (7.3% vs. 0.6%) Pain at site (35.8% vs. 3.8%) Muscle twitching (20.6% vs. 3.2%)
	Sham coil	160		22.9 to 19.4	33.9 to 29.8			11.0	6.2		
				p = 0.006	p = 0.057		p < 0.05	p > 0.10			
Mogg 2008	HFL-rTMS	29	2 weeks	20.5 to ~16.0	38.2 to ~24	NR	NR	32%	25%	70%	No significant differences (p = 0.43), but the details are not reported.
	Sham coil	30		21.6 to ~18.9	36.3 to ~32			10%	10%	38%	
				p = 0.09 Difference at 2 weeks: 2.9, 95% CI -0.7 to 6.5 At 4 weeks, the difference favors the sham.	p = 0.60			p = 0.06	p = 0.20	p = 0.03	

* Follow-up for primary endpoint

~ = value estimated from graph or other data in the published report.

By far the largest clinical trial of rTMS was reported by O'Reardon et al in 2007.⁶⁶ The investigators randomized 325 participants to rTMS (n=165) or sham rTMS (n=160) at 23 sites, primarily in the United States. The next largest study of rTMS randomized 105 patients. Patients were eligible for this trial if they were between the ages of 18 and 70 with a DSM-IV diagnosis of major depression with the current episode lasting less than three years. The depression severity was required to score at least 20 on the HAMD17 and at least 4 on the Clinical Global Impressions Severity of Illness score. Subjects had to fail between one and four antidepressant treatments in the current or most recent episode of depression (definition of treatment resistant depression) and they had to be off of all antidepressant medications for at least one week. Patients with any history of psychosis, bipolar disease, obsessive compulsive disorder, or post-traumatic stress disorder were excluded. In addition, the study excluded patients who failed prior ECT, received rTMS, or vagus nerve stimulation, had a personal or family history of seizures, pregnancy, conditions lowering the seizure threshold, or any unstable medical condition.

Active treatment was six weeks of daily treatment followed by three weeks of reduced frequency to taper off rTMS and start antidepressant therapy. Active treatment was five days per week (30 sessions) of ten magnetic pulses per second at 120% of the patient's motor threshold in 75 trains of four seconds and 26 seconds off for a total of 3000 pulses per session. This study used the highest motor threshold, the greatest number of pulses per session, for the largest number of sessions of any published trial of rTMS. The rTMS parameters in this study were the most intense of any published study to date. Sham therapy utilized coils with similar weight, appearance, and acoustic properties as the active coil. After four weeks of initial treatment, patients with less than a 25% improvement in symptoms using the HAMD17 were allowed to crossover to an open, extension trial. Thus, the blinded treatment period in this study was effectively four weeks of active or sham therapy. The primary outcome of the trial was the difference between the MADRS scores for the active and sham rTMS groups after four weeks of therapy. Missing data was estimated using a last observation carried forward protocol.

There was modest loss to follow-up in both groups. Among the 165 patients randomized to active treatment 150 (91%) completed the week two follow-up visit and 143 (87%) completed the week four follow-up visit. Similarly, among the 160 patients randomized to sham treatment 143 (89%) completed the week two follow-up visit and 134 (84%) completed the week four follow-up visit. Only a small number of patients discontinued due to adverse events (seven in active, four in sham). Patients in the active and sham groups with some follow-up data (n=301) had similar baseline demographics and clinical measurements with the exception of their score on the MADRS (32.8 versus 33.9, p=0.036). This small absolute difference is unlikely to have had

a large impact on the results of the study, although this rating scale was the primary outcome measure for the study.

The authors report outcomes at weeks two, four, and six though follow-up is only reported through week four and many patients were unblinded at week four. The week four results are summarized here. The Montgomery-Asberg Depression Rating Scale decreased from 32.8 to 27.0 (-5.8) in the treatment group and from 33.9 to 29.9 (-4.0) in the sham group. The difference in the change scores was not statistically ($p=0.057$) or clinically significant, though the trend favored the active treatment group. There was a greater reduction in 17-item Hamilton Depression Rating Scale in favor of active treatment (22.6 to 17.4 versus 22.9 to 19.4, $p < 0.01$), though the absolute difference in the change scores was modest (less than two points). Another continuous outcome measure, the clinician-rated global illness severity, improved more in the active group by week 4 ($p = 0.009$). The response rate at week four using the MADRS was greater in the active group (18.1% versus 11.0%, $p < 0.05$), but there was no difference in the remission rate (**primary outcome measure** of the study: 7.1% versus 6.2%, $p > 0.10$).

Although unblinded and with non-protocol medications added at week six, the authors do report response and remission rates at the end of the tapering off of rTMS (week nine). In the active rTMS group, the final response rate was 27.7% and the remission rate was 20.6%. In the sham group, the final response rate was 13.7% and the remission rate was 8.9%.

There may have been unintentional unblinding during treatment as more patients in the active arm reported pain at the treatment site (59 versus six) and muscle twitching (34 versus five). The authors did not report asking the participants about which group they thought they were in. They did report that they found no association between these symptoms and the outcome measures, though the details of those analyses were not shown.

There were no seizures or deaths in the study. Serious adverse events were similar in the two groups (nine versus seven) including suicidality (0.6% versus 1.9%) and worsening of depression (0.6% versus 1.9%). Mild side effects, like those reported in the prior paragraph, were more common in the active treatment group.

In summary, the O'Reardon study⁶⁶ randomized three times as many patients as the next largest study of rTMS and used the highest magnetic field setting for more pulses per session and more sessions than any other study. Despite this, they found no difference between the two groups in the primary outcome measure

of the study (remission rate at four weeks: 7.1% vs. 6.2%). There were significant differences between the two groups in favor of rTMS on several outcome measures, but these were usually modest in size and may be explained to some extent by partial unblinding of study subjects.

Mogg et al published most recent randomized trial in 2008.⁶⁵ They randomized 59 right-handed patients over the age of 18 with a diagnosis of major depression. Treatment resistance was not required, though the study population was predominantly treatment-resistant with 78% of patients having failed at least two treatment steps and an average of 3.1 medications. Patients were allowed to continue their medications as long as the dose had been stable for at least four weeks. Patients were excluded if they had a history of seizures, brain surgery, significant head trauma, metallic implants, dementia, or prior rTMS treatment.

Active treatment was five days per week for two weeks (ten sessions) of ten magnetic pulses per second at 110% of the patient's motor threshold in 20 trains of five seconds on and 55 seconds off for a total of 1000 pulses per session. Sham rTMS was administered in the same way using a specially built sham coil designed to address concerns about angling an active coil at an angle of 45 or 90 degrees. Patients were evaluated after one and two weeks of treatment and again six weeks and four months after the end of the treatment period. Follow-up at the end of treatment was available for 57 patients (97%), at six weeks for 53 patients (90%), and at four months for 49 patients (83%).

Baseline characteristics were similar in the two groups. The primary outcome measure, change in the HAMD17, was not significant ($p=0.09$). There was a trend toward benefit with rTMS during active treatment, but by six weeks and four months after treatment, scores were slightly better in the sham group. The difference at the end of treatment (2.9 points) was less than the prespecified clinically significant difference of 3.5 points on the HAMD17. There were also no significant differences between groups on the Beck Depression Inventory, the Visual Analog Mood Scales, or the Brief Psychiatric Rating Scale.

There were few side effects and no subjects withdrew from the active arm because of them. Two patients withdrew from the sham arm due to dizziness and tinnitus. One patient in the sham group reported having a seizure after the final treatment, though no cause was found and he had no further seizures. The investigators carefully assessed cognitive function for adverse effects. There were no differences between groups in the cognitive section of the Cambridge Examination for Mental Disorders of the Elderly, the Mini-Mental State Examination, Forward Digit Span, Backward Digit Span, Grooved Pegboard, or Digit Symbol test.

Methodologically, the Mogg study⁶⁵ appeared quite strong, with careful attention given to randomization, allocation concealment, patient blinding, and blinding of staff assessing patient outcomes. However, unblinding was a problem in this trial as it likely was in most trials of rTMS. 70% of patients in the active group guessed they were on rTMS compared with 38% of patients receiving sham treatment ($p = 0.03$). Outcome assessors were also partially unblinded: they guessed that 74% of patients in the active group were on rTMS compared with 36% of patients receiving sham treatment ($p = 0.01$). As in the prior study, there were no significant side effects, but no clinically important benefit either.

Systematic Reviews

In general, the systematic reviews and meta-analyses of rTMS conclude that there is a statistically significant benefit during treatment, although the clinical effect is modest. For example, the Cochrane review concluded that: “. . . there is no strong evidence for benefit from using transcranial magnetic stimulation to treat depression.”²⁸ In their narrative review of rTMS in treatment of depression Rachid and Bertschy⁷⁸ conclude: “rTMS is a promising antidepressant treatment with overall minor adverse effects. Because the clinical efficacy of rTMS as an antidepressant remains questionable, further systematic, large scale multicenter studies comparing rTMS to sham and/or to an antidepressant medication along with more stringent stimulation parameters are warranted in order to identify patient populations most likely to benefit and treatment parameters most likely to optimize its antidepressant efficacy.” Lam²⁵ in a systematic review and meta-analysis of rTMS in patients with TRD concludes: “However, the relatively low response and remission rates, the short durations of treatment, and the relative lack of systematic follow-up studies suggest that further studies are needed before rTMS can be considered as a first line monotherapy treatment for TRD.”

Finally, in a recent systematic review including 30 sham-controlled randomized trials, Schutter²⁹ concludes that rTMS is superior to sham. He goes on to say that: “ However, at this point caution should be exercised because the integrity of blinding and the lack of a proper control condition are considered limitations of rTMS trials. . . . All in all, the present findings suggest that rTMS may be an alternative for patients suffering from major (non-psychotic) depression, and especially for those patients who do not tolerate the side-effects associated with regular pharmacological treatment.”

Patient Safety

Clinical trials have found a higher incidence of pain, especially headache and neck pain, and scalp discomfort in the active treatment arm compared with sham.^{63, 66} Facial twitching, nausea and skin pain have also been reported.^{50, 63, 66} Pain associated with rTMS treatment may increase over the course of treatment; one RCT

reported that one-third of patients in the rTMS arm experienced pain compared with three percent in the sham arm.⁶¹ No increased deaths or increase in suicidality has been observed with rTMS. A small increased risk of seizure induction has been observed with use of rTMS with some having occurred in healthy subjects or in those with depression or other conditions not known to increase seizure risk.⁷⁹⁻⁸² This risk has been significantly reduced with adherence to safety guidelines and no seizures have been reported in recent clinical trials of rTMS for depression. Unlike electroshock therapy, rTMS is not associated with memory loss or other negative neuro-cognitive effects. There is some evidence that similar to antidepressant medication, rTMS may contribute to an exacerbation or unmasking of mania.⁴⁹

Ongoing Clinical Trials of rTMS

There are a large number of ongoing clinical trials of rTMS for depression. A search of ClinicalTrials.gov for rTMS and depression revealed 53 trials, 29 actively recruiting and another two about to start recruitment. This undoubtedly reflects the potential of rTMS to improve the lives of patients with depression, but also highlights its uncertain role in the armamentarium of therapeutics for major depression.

Summary

The largest and most recent clinical trials of rTMS for depression failed to demonstrate significant improvements on their primary outcome measures. However, the trend in most studies, as noted in the systematic review, was for a small reduction in depression symptoms. Given the lack of consensus on how to perform rTMS, the lack of evidence supporting continued efficacy after cessation of therapy, some mild side effects, and the active ongoing research clinical trials research in the field, it is premature to conclude that rTMS improves net health outcomes for patients with TRD.

TA criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Major depressive disorder (MDD) represents a heterogeneous group of disorders. It is likely that future research will eventually provide greater diagnostic specificity to these disorders leading to more targeted and effective treatments. Furthermore, TRD is diagnostically even less specific than MDD making it more difficult to compare patient groups and treatment interventions across studies.

A wide variety of biological and psychological therapies have been shown in to be effective for treatment of depression in randomized clinical trials. The concept of “effectiveness,” however, hinges on the demonstration of a “response” to treatment defined as “50% improvement in symptoms.” A 50%

improvement is certainly important clinically, but this criterion is broad enough to leave significant residual symptoms unresolved. The concept of “remission,” therefore, has been introduced to underscore the importance of helping the depressed patient reach full return of function and achieve relative absence of all depressive symptoms.¹

Evidence-based treatment for depression includes antidepressant medication, several forms of psychotherapy, a combination of medication and psychotherapy and, in refractory cases, ECT, CBT and ITP have the broadest evidence-base for effectiveness in treatment of depression. There is also evidence that several variants of CBT, such as MBCT and CBASP, as well as problem-solving therapy, behavioral therapy, and psychodynamic therapy may be effective. The evidence from many randomized clinical trials is that these psychotherapies are as effective as antidepressant medication (in mild-to-moderate MDD) in achieving a significant reduction of symptoms (over 50% response rate) after ten to 16 weeks of treatment. Although the response to antidepressants is generally greater in the first four weeks, response to psychotherapy catches up and by 12 weeks the efficacy of medication and psychotherapy are roughly similar. There is some reason to believe that antidepressant medication and psychotherapy of depression achieve their benefits through different neurobiological mechanisms, so it is not surprising that combination treatments (medication and psychotherapy) have generally been found to be more effective than either one alone and is recommended in patients with more severe or resistant depression.

Evidence based pharmacotherapy for depression consists of the cyclic antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), a noradrenaline and specific serotonin antagonist (NaSSa) and the tricyclic antidepressants (TCAs). Antidepressants begin to provide some symptom improvement after one to two weeks of treatment and an adequate trial of an antidepressant requires a minimum of four to six weeks at appropriate doses. Overall, antidepressant response rates approximate 60–70%, however the STAR-D trial demonstrated that only about 30% to 40% of patients will reach remission with an adequate trial of an initial SSRI antidepressant.^{3, 5} Patients with no response or minimal response to the initial antidepressant used can be switched to another agent in the same or different class or can be managed with augmentation strategies such as a second antidepressant or psychotherapy. Of note, 25–30% of patients who fail to remit at step one of treatment will respond to a different SSRI on a second trial or to an augmentation of the initial treatment. Depending on the context and the regulatory authority, patients who fail to respond to at least one, or at most two, adequate treatment trials are considered to have TRD.² However, TRD is diagnostically much less specific than MDD making it difficult to compare patient groups and treatment interventions across studies.

There are several treatments approved for treatment resistant (or refractory) depression in the United States including electroconvulsive therapy (ECT), vagal nerve stimulation (VNS) and rTMS. Other treatments under investigation include deep brain stimulation, magnetic seizure therapy, focal electrically administered stimulated seizure therapy, transcranial direct current stimulation and chronic epidural cortical stimulation. Of the available modalities, electroconvulsive therapy is considered to be the most appropriate treatment for many persons with refractory depression. It is the treatment of choice for patients with psychotic depression and for some treatment refractory patients who are acutely suicidal. Despite prejudices and fears about ECT, new methods of administration have proven it to be safe and effective.⁸³ In fact, ECT can be safer than antidepressant medication in the elderly.⁸⁴ Some short-term memory loss is common, but research indicates that this reverts to normal in most patients. In some cases, ECT does not lead to permanent remission of depression in patients susceptible to recurrence; thus, patients with recurrent depression who are treated with ECT should receive either prophylactic medication after a course of therapy (as an outpatient) or maintenance ECT.

A few trials have compared ECT with rTMS in the treatment of patients with non-psychotic depression. One randomized trial⁶⁹ found that patients treated with ECT were more likely to be in remission at the end of the 15 day treatment, but HAM-D scores were similar at six months. Another RCT⁷⁰ found that overall ECT was a more potent treatment for patients with MDD, this being particularly evident in patients with MDD and psychosis; however, in patients with MDD without psychosis the effects of rTMS were similar to those of

ECT. Janicak⁷² compared rTMS to ECT in severely ill, depressed patients in a two to four week randomized, prospective trial and concluded that rTMS and ECT produced comparable therapeutic effects. And finally, McLoughlin⁸⁵ and Knapp⁷³ concluded that ECT is a more effective and potentially more cost-effective antidepressant treatment than three weeks of rTMS as administered in this study. Overall, research to date indicates that ECT appears to be a more effective treatment than rTMS for patients with TRD but conclusions are limited by the significant variation in patient populations, treatment protocols and outcome measures among these trials.

TA criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

Since improvements in net health outcomes were not demonstrated in TA Criterion 3 and TA Criterion 4, TA Criterion 5 cannot be met.

TA criterion 5 is not met.

CONCLUSION

Major depression is a significant public health issue that is not adequately addressed by current medical, pharmacological or technological treatments. This is particularly true for patients with treatment resistant depression who continue to have significant symptoms in spite of an adequate trial of antidepressants. Over the past several years there has been extensive investigation of new methods for treating resistant depression including enhanced use of pharmacotherapy and new technologies such as vagal nerve stimulation, deep brain stimulation and rTMS. To date, there is one FDA approved rTMS device for use in treatment resistant depression, the NeuroStar TMS Therapy System. The FDA indications for the device state that it is “indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode.”

We evaluated the peer-reviewed literature on the use of rTMS in treatment resistant depression. There is an extensive literature on rTMS in treatment of depression and there have been several comprehensive meta-analyses and systematic reviews. Many of the individual studies randomized less than 20 patients and were underpowered to detect changes in net health outcomes, particularly remission of depression. The largest and most recent clinical trials of rTMS for depression failed to demonstrate significant improvements on their primary outcome measures. In addition there is no consensus on how to perform rTMS and a dearth of evidence on the efficacy of rTMS after cessation of therapy. Undoubtedly because of the evidence that treatment does have some clinical effect, there is active ongoing research into rTMS. However, it is too early to conclude that rTMS improves net health outcomes for patients with treatment resistant depression, much less that it is as effective as current alternatives such as augmentation, new drugs, or ECT.

DRAFT RECOMMENDATION

It is recommended that repetitive transcranial magnetic stimulation *does not* meet CTAF TA criteria 3-5 for efficacy and improvement in health outcomes in patients with treatment resistant depression.

June 17, 2009

This is the first assessment of this technology by the California Technology Assessment Forum

RECOMMENDATIONS OF OTHERS

BLUE CROSS BLUE SHIELD ASSOCIATION (BCBSA)

The BCBSA Technology Evaluation Center (TEC) is in the process of conducting an assessment of this technology.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

No National Coverage Decision or Local Coverage Decision was identified through a search of the CMS web site.

CALIFORNIA PSYCHIATRIC ASSOCIATION (CPA)

The CPA has been invited to provide an opinion and to have a representative attend the meeting and provide testimony.

DRAFT

ABBREVIATIONS USED

CTAF	California Technology Assessment Forum
rTMS	Repetitive Transcranial Magnetic Stimulation
ECT	Electroconvulsive therapy
CBT	Cognitive behavioral therapy
ITP	Interpersonal psychotherapies
MBCT	Mindfulness-based cognitive therapy
CBASP	Cognitive-behavioral analysis system of psychotherapy
TRD	Treatment resistant depression
TMS	Transcranial magnetic stimulation
MRI	Magnetic resonance imaging
DLPFC	Dorsolateral prefrontal cortex
ICDs	Implantable cardioverter defibrillators
VNS	Vagus nerve stimulators
HAMD	Hamilton Rating Scale for Depression
MADRS	Montgomery-Asberg Depression Rating Scale
BPRS	Beck Depression Inventory, the Brief Psychiatric Rating Scale
QIDS-SR	Quick Inventory of Depressive Symptomatology-Self Report
DARE	Database of Abstracts of Reviews of Effects
NR	Not reported
HFL-rTMS	<u>High</u> frequency repetitive transcranial magnetic stimulation to the <u>left</u> dorsolateral prefrontal cortex
LFR-rTMS	<u>Low</u> frequency repetitive transcranial magnetic stimulation to the <u>right</u> dorsolateral prefrontal cortex
MT	Motor threshold
RCT	Randomized controlled trial
BDI	Beck Depression Index
CGI-S	Clinical Global Impressions Severity Scale
BAD	Bipolar affective disorder
OCD	Obsessive-compulsive disorder
PD	Personality disorder
LOC	Loss of consciousness
MDD	Major depressive disorder

SSRIs	Selective serotonin reuptake inhibitors
SNRIs	Serotonin norepinephrine reuptake inhibitors
NaSSa	Noradrenaline and specific serotonin antagonist
TCA	Tricyclic antidepressants

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