

# Repetitive Transcranial Magnetic Stimulation (rTMS) for Depression

## Plain language summary

Depression is a common mental health illness in Australia.

Medication and psychotherapy are the usual treatments, but for some people, these don't work. For these people, Electroconvulsive Therapy (ECT) may help.

During ECT, a patient is put to sleep using a general anaesthetic. While asleep their brain is given an electric shock. ECT can have side effects.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a new treatment. A magnetic pulse is used in rTMS. There is no need for an anaesthetic.

Four small studies have been identified which compare rTMS with ECT. No studies found that rTMS was better than ECT. Eighteen studies compared rTMS with no treatment. It is not clear if rTMS is better than no treatment.

There are different ideas on the best amount and strength of rTMS, but no one knows the best way to use rTMS yet. More good studies are needed.

Transport Accident Commission & WorkSafe Victoria

## **Evidence Service**

# **Repetitive Transcranial Magnetic Stimulation (rTMS) for Depression**

## **Evidence Review**

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## EXECUTIVE SUMMARY

### Overview

We updated the most comprehensive, up-to-date, high quality systematic review (Gaynes et al. 2011), which investigated the effectiveness of rTMS. Overall twenty one studies were reviewed by this report. The studies were inconsistent in their results, with half reporting rTMS was as effective as ECT and half reporting ECT as better. However, small sample sizes and vast variability regarding rTMS parameter and outcomes has led the review to conclude that there is insufficient evidence to determine whether the benefits and harms of rTMS are better, worse or the same as ECT.

### **What is the effectiveness and safety of transcranial magnetic stimulation (rTMS) in treating acute-phase depressive symptoms (e.g., response and remission)?**

The evidence to answer this question is inconclusive.

### **What is the effectiveness and safety of transcranial magnetic stimulation (rTMS) in maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?**

The evidence to answer this question is inconclusive.

### **In what setting, inpatient or outpatient, is rTMS most effective in treating acute-phase depressive symptoms OR maintaining response or remission?**

The evidence to answer this question is inconclusive.

### **What rTMS protocols i.e. what number of treatments over what time period, are effective in treating acute-phase depressive symptoms OR maintaining response or remission?**

The evidence to answer this question is inconclusive.

## BACKGROUND

### Patient group and treatment pathway

Major depressive disorder (MDD) is a common mental health disorder defined by the presence of a depressed mood every day for more than two weeks. Clinical diagnosis of MDD is made based on the presence of a number of symptoms including:

- *Depressed mood most of the day*
- *Loss of interest or pleasure in all or most activities*
- *Large increases or decreases in appetite*
- *Significant weight loss or gain*
- *Insomnia or excessive sleeping*
- *Agitation or restlessness*
- *Fatigue or loss of energy*
- *Feelings of worthlessness or excessive or inappropriate guilt*
- *Diminished ability to concentrate or indecisiveness*
- *Recurrent thoughts of death or suicide*<sup>1</sup>

In Australia, mental health disorders are the largest cause of nonfatal disease burden.<sup>2</sup> MDD is often a recurrent disorder, thus long-term treatment is necessary to prevent new episodes from occurring. For patients with MDD, first-line therapy involves pharmacological treatment (e.g., tricyclic antidepressants, serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors), psychotherapy, or a combination of both. Where there is treatment failure on a pharmacological agent, a switch to an antidepressant drug with a different mode of action is the preferred second-line treatment. If the depressive illness persists, several options are available, namely, adding an augmenting agent, such as lithium carbonate or triiodothyronine, switching to a monoamine oxidase inhibitor for patients with atypical major depression, or adding either cognitive therapy or another form of psychotherapy.<sup>3</sup>

For patients who have not responded or are refractory to pharmacologic agents and/or psychotherapy, treatment options can include electroconvulsive therapy (ECT), vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS).<sup>4</sup> ECT is generally considered the next line of therapy for MDD patients. ECT involves the delivery of an electrical current to induce a seizure for therapeutic purposes. Before the administration of ECT patients are anaesthetised and an

appropriate muscle relaxant is administered. ECT is usually given twice a week and the number of sessions undertaken for patients to respond usually ranges from six to twelve.<sup>5</sup>

Although ECT has been shown to be effective, it is associated with cognitive side effects and risks associated with repeated anaesthesia,<sup>5</sup> for this reason rTMS has emerged as a potential alternative treatment, as it does not require anaesthesia.

### **Repetitive transcranial magnetic stimulation**

Transcranial magnetic stimulation involves placing an electromagnetic coil against the forehead near an area of the brain involved in mood regulation. TMS works by creating magnetic pulses in the loops of the coil. These magnetic field pulses produce small electric currents that stimulate nerve cells in the brain. When the pulses are delivered repeatedly, it is referred to as repetitive transcranial magnetic stimulation (rTMS). In contrast to ECT, rTMS does not involve passing electrical currents directly through the scalp and therefore does not require anaesthesia. rTMS is usually given in a discrete course, most commonly daily for between 15 and 30 consecutive weekdays with treatment sessions, lasting between 30 and 45 minutes.<sup>6</sup>

The rTMS technique can vary in many different ways, such as:<sup>7,8</sup>

- Coil placement (usually the left or right dorsolateral prefrontal cortex (DPFC))
- Stimulation intensity (determined by the individual's motor threshold)
- Stimulation frequency (usually 1 to 20Hz over the left DPFC, and lower frequencies (<1Hz) over the right DPFC)
- Number of pulses/stimulations per session (a typical treatment session might incorporate 10 to 30 stimulation trains several seconds apart (the inter-train interval). Thus, a typical session delivers 1,000 to 1,200 pulses)
- The amount of time between pulses/stimulations during a session (inter-train interval)
- Treatment duration (duration of each session and duration of treatment as a whole, treatments are generally conducted on weekdays for two to four weeks)

Currently there is no consensus on the most appropriate rTMS parameters to use when treating depression.<sup>8</sup>

### **Regulatory status**

Although rTMS is seen as an alternative for ECT it is unclear for which indication it would be most effective; in an update of their review of rTMS, the Medical Services Advisory Committee (MSAC) poses the question: *"should rTMS therapy be restricted to patients who have failed to respond to two different classes of antidepressant drug therapy (despite appropriate dose, duration and compliance), or should the indications be broadened to allow treatment after patients have failed to*

*respond to one class of antidepressant therapy, and failed to respond to one form of psychological therapy (such CBT or interpersonal therapy, IPT)?”<sup>9</sup>*

In the United States, the Food and Drug Administration has provided guidance that rTMS is intended to be used to treat the symptoms of MDD without inducing seizure in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy.<sup>10</sup>

In Australia the magnetic stimulator manufactured by MagVenture, has been approved for listing on the Australian Register of Therapeutic Goods (ARTG) for the intended purpose of *“treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from two prior antidepressant medications, at or above the minimal effective dose and duration in the current episode”*.

In 2008 rTMS was refused funding under the Australian Medicare Benefits Schedule (MBS).<sup>8</sup> The Medical Services Advisory Committee is currently reconsidering funding for this technology.<sup>11</sup>

### Intended purpose of the review

The Transport Accident Commission (TAC) and WorkSafe Victoria (WSV) requested a review of the evidence to determine whether repetitive transcranial magnetic stimulation is an effective treatment for major depressive disorder. This report sought to answer the following questions:

1. What is the effectiveness and safety of rTMS in treating acute-phase depressive symptoms (e.g., response and remission)?
2. What is the effectiveness and safety of rTMS in maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?
3. In what setting, inpatient or outpatient, is rTMS most effective in treating acute-phase depressive symptoms OR maintaining response or remission?
4. What rTMS protocols, i.e., what number of treatments over what time period, are effective in treating acute-phase depressive symptoms OR maintaining response or remission?

## METHODS

The review methods are outlined briefly below. More detailed information about the methodology used to produce this report is available in Appendices 1 and 2. All Appendices are located in the Technical Report accompanying this document.

### Stage 1: Identify relevant research

A comprehensive search of Medline, Embase, All EBM Reviews (Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED), CINAHL and Web of Knowledge was undertaken in July 2012 to identify relevant synthesised research (i.e., evidence-based guidelines (EBGs), systematic reviews (SRs), health technology assessments (HTAs)); and relevant randomised controlled trials (RCTs) and controlled clinical trials (CCTs). A comprehensive search of the Internet, relevant websites and electronic health databases was also undertaken.

Studies identified by the searches were screened for inclusion by two reviewers (ED & JW) using specific selection criteria. Any discrepancies in study selection decisions were discussed and resolved. Due to the number of primary studies identified, studies that were reported only in abstract form were excluded, as they provide limited information thus precluding quality appraisal from being conducted.

For further information, see Appendix 2, Table A2.1 for inclusion and exclusion criteria, Tables A2.2-2.4 for further search strategy details, and Appendix 3 for lists of included studies by study type.

### Stage 2: Develop an evidence map of synthesised studies

Due to the large number of synthesised studies identified on this topic we developed an evidence map to identify their currency, comprehensiveness and quality. A detailed description of the evidence map methodology can be found in Appendix 1.

#### *Currency*

The currency of the review was assessed using the year of publication and search date.

#### *Comprehensiveness*

Comprehensiveness was assessed by the breadth of studies that the reviews included. We cross-referenced the RCTs identified by our search and the RCTs included in the reviews to identify whether any studies were missing.

#### *Quality assessment*

Quality assessment was conducted using the AMSTAR tool (for the 'Assessment of Multiple SysTemAtic Reviews')<sup>12</sup> (see Appendix 4, Tables A4.2 and A4.3). The AMSTAR is an eleven-item tool designed to give an overall score for SRs based on their methodological quality. These scores give an indication of the risk of bias of each SR with 0/11 representing lowest quality (highest risk of bias), and 11/11 highest quality (lowest risk of bias). For reviews in which no meta-analysis has been



performed, the AMSTAR score is calculated with a denominator of nine instead of 11, as the two AMSTAR items that relate specifically to meta-analysis are not applicable.

### Stage 3: Identify and update the most recent, comprehensive, high quality synthesised study

Based on the results of the evidence map, we identified the most recent, comprehensive, high-quality synthesised study on which to base our review. This review then underwent a more detailed quality appraisal and new studies not included in the original report were incorporated.

In this report we present an evidence map of existing studies on the effectiveness of rTMS for depression (Table 1) and an update of the most recent, high-quality review (Gaynes et al 2011<sup>4</sup>).

## RESULTS

Database searches yielded 2,757 articles. After de-duplication, 1,499 were screened against our selection criteria. Of these, 248 full text articles were retrieved and screened, and of these 104 papers were identified as relevant to the review. One further study was identified through the screening of Google search results.

In total, 105 papers were included, consisting of:

- 21<sup>4,8,13-31</sup> synthesised studies (SRs, MA, or EBGs)
- 84<sup>32-113</sup> primary study references (RCTs or CCTs)

**Table 1. Evidence map of identified studies**

Synthesised studies	Primary studies	TOTAL
21 (20 SRs/MA + 1 EBG)	84 (81 RCTs + 3 CCTs)	105

**Key:** SR = systematic review; MA = meta-analysis; EBG = evidence-based guideline; RCT = randomised controlled trial; CCT = controlled clinical trial

## SUMMARY OF SYNTHESISED STUDIES

The 21 synthesised studies were reviewed to identify their currency, comprehensiveness and quality.

Overall eight of the 21 reviews were published in the last five years, i.e., between 2013 and 2009. The most recent of these were Minichino 2012,<sup>25</sup> Gaynes 2011,<sup>4</sup> and Allan 2011.<sup>14</sup> The most up to date search was conducted by Gaynes 2011<sup>4</sup> with a search date of November 2010.

Inclusion criteria for depression varied across reviews. For example, some reviews focused on patients with MDD, others on patients with MDD or depression alone, while others had mixed populations, e.g., MDD or bipolar; or, MDD or Treatment Resistant Depression (TRD). Only Gaynes 2011<sup>4</sup> specifically focused on the indication of TRD.

With regards to the comparator, six reviews included evidence for both rTMS vs. ECT and rTMS vs. sham rTMS.<sup>4, 13, 26-28, 31</sup> Thirteen reviews exclusively compared the effect of rTMS with sham rTMS<sup>14-24, 29, 30</sup> and two exclusively compared rTMS to ECT.<sup>8, 25</sup>

Using the AMSTAR tool we assessed the quality of each of the reviews. Overall the quality of these reviews was poor with only four of the 21 reviews scoring greater than 8/11. Only one review, Gaynes 2011,<sup>4</sup> attained a perfect score on the AMSTAR tool (see Tables A4.2-A4.3).

Based on our assessment of the evidence map, the most high-quality, recent, synthesised study was the SR by Gaynes 2011.<sup>4</sup> An update of this review is presented in this report.

## UPDATE OF MOST RECENT, HIGH QUALITY, SYNTHESISED STUDY

The SR by Gaynes 2011<sup>4</sup> is a large and detailed report prepared for the US Agency for Health Care Research and Quality. This review examined nonpharmacologic interventions for TRD in adults. Interventions assessed in this report included: rTMS, ECT, VNS and evidence-based psychotherapy (i.e., cognitive behavioural therapy). This report was published in 2011, with evidence searches conducted up until November 2010. For the purpose of this report we only focused on updating the section relevant to rTMS compared to placebo or ECT. Using the AMSTAR tool and a detailed quality assessment tool, this SR was found to be of high quality, meeting all quality criteria (see Tables A4.2 and A7.1 of Technical Report).

In updating this review we identified five new RCTs;<sup>32, 51, 67, 70, 108</sup> four comparing rTMS with sham rTMS and one comparing rTMS to ECT. Overall, including the studies reviewed by Gaynes 2011,<sup>4</sup> a total of 22 RCTs reported across 25 publications were reviewed in this report. Of these, four studies compared rTMS to ECT and 18 studies compared rTMS with sham therapy. The characteristics of all included studies are outlined in Tables A5.1–A5.6 of the Technical Report.

We investigated the possibility of updating the meta-analysis of rTMS vs. sham provided in the Gaynes report<sup>4</sup> with the addition of four new studies (Fitzgerald 2012,<sup>51</sup> Aguirre 2011,<sup>32</sup> Triggs 2010<sup>108</sup> and Jakob 2008<sup>67</sup>). However, this was not possible due to a lack of data regarding remission or response rates in the new papers, and inconsistent reporting of the primary outcome measure between studies (i.e., different papers used different measurement scales, or reported results in percentage, or graph form only).

## Studies comparing rTMS with ECT

### Study characteristics

Four studies (reported across six publications) were identified comparing rTMS with ECT.

#### *Sample size*

All studies had small study populations ranging from 40 to 73 patients.

#### *Patient population*

All studies included patients with MDD. The diagnostic instruments used to define MDD varied between studies with one study using DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition), one study using HAM-D (Hamilton Rating Scale for Depression). Two studies did not report on how MDD was defined.

#### *Treatment failure*

Prior treatment failure to pharmacotherapy differed among studies: two studies Rosa 2006<sup>100</sup> and Keshtkar 2011<sup>70</sup> recruited patients with two or more prior treatment failures and one study<sup>58</sup> recruited patients with one or more prior treatment failures. Two studies<sup>46, 73</sup> did not report on prior treatment failure.

#### *rTMS parameters*

The rTMS parameters used to administer treatment differed between studies. The frequency at which the pulses were administered was 10Hz in three studies.<sup>58, 100, 114</sup> One did not report the frequency used. The motor threshold was 90% in two studies,<sup>58, 70</sup> 100% in one study<sup>100</sup> and 110% in one study.<sup>114</sup> The number of trains varied from two to twenty with variation in the length of train from five to 60 seconds. The inter-train interval varied between 20 and 160 seconds. The number of pulses varied from 408 to 2500 pulses per session. The number of treatments varied between 9-15 sessions. Number of sessions per week varied between three and five sessions per week.

#### *ECT parameters*

Studies varied between bilateral or unilateral electrode placement. Studies varied in intensity of ECT treatment, between 1.5 and 4.5 times seizure threshold.

#### *Setting*

Two publications reported that studies were conducted in both inpatient and outpatients settings, three were exclusively set within an inpatient setting and one did not report on setting.

#### *Outcomes*

All studies assessed the effectiveness of rTMS in treating acute-phase depressive symptoms, no studies assessed maintenance of response or remission. All of the studies except one used a version

of the Hamilton Rating Scale for Depression (HAM-D17<sup>58, 114</sup> and HAM-D24<sup>70</sup>) to assess improvements in depression. Other scales used to assess response included Clinical Global Impression Scale<sup>100</sup> and the Beck Depression Inventory (BDI).<sup>70</sup> Definition of response and remission differed between studies. For example Rosa 2006<sup>100</sup> defined response as HAM-D17  $\leq 7$  while Grunhaus 2003<sup>58</sup> defined response as a decrease of 50% or more, or HAM-D17  $\leq 10$  and a final Global Assessment of Function Scale rating  $\geq 60$ . In terms of remission Rosa 2006<sup>100</sup> defined it as HAM-D17  $\leq 7$ , while McLoughlin 2007<sup>114</sup> and Grunhaus 2003<sup>58</sup> defined remission as HAM-D17  $\leq 8$ . The majority of studies exclusively assessed outcomes at end of treatment, only McLoughlin 2007<sup>114</sup> assessed outcomes at six months.

## Results

With regards to the effectiveness of rTMS compared to ECT, two studies found no significant difference<sup>100,58</sup> and two studies<sup>114,70</sup> found rTMS to be less effective than ECT.

### *Response to treatment*

Rosa 2006 and Graunhaus 2003 reported no significant difference in endpoint scores between rTMS and ECT measured on HAM-D17<sup>58</sup> and Clinical Global Impression Scale.<sup>100</sup> In addition, for those studies reporting response rates<sup>58, 100</sup> no significant difference between rTMS and ECT was observed. Keshtkar 2011<sup>70</sup> and McLoughlin 2007<sup>114</sup> observed significantly lower endpoint scores on the HAM-D24 and BDI; and the HAM-D17 respectively.

### *Remission*

Of the three studies reporting on end of treatment remission, two<sup>100,58</sup> found no significant difference between rTMS and ECT. One other<sup>114</sup> found the rate of remission was lower for rTMS compared to ECT at the end of treatment, although this effect was not sustained at six months with both treatment arms being equivalent.

### *Severity of symptoms*

Keshtkar 2011<sup>70</sup> found ECT to be more effective in reducing post-treatment BDI and HAM-D suicide scores compared to rTMS.

### *Neurological functioning*

Two studies<sup>100, 114</sup> conducted neurological assessments before and after treatment. Neither study found a significant difference in neurological functioning between rTMS and ECT post-treatment.

### *Adverse effects*

No significant difference in adverse effects was observed between rTMS and ECT treatment for two studies.<sup>70, 100</sup> Overall the main side effects reported for rTMS included localised pain or mild headache. The study by Keshtkar 2011<sup>70</sup> withdrew two patients in the ECT group due to a loss of consciousness. Adverse events were not compared between groups for two studies, as Grunhaus

2003<sup>58</sup> did not report adverse events for the ECT group, and McLoughlin 2007<sup>114</sup> did not report adverse events for either group.

## Studies comparing rTMS with sham rTMS

### Study characteristics

Eighteen RCTs (reported across 19 publications) were identified comparing rTMS with sham rTMS. Characteristics of these studies are shown in Table 2.

#### *Sample size*

The sample sizes of the 18 included studies ranged between 12 and 325 patients. The majority of studies had small sample size, five had a sample size of 20 or less,<sup>65, 69, 82, 94, 96</sup> and 11 studies had between 21 and 68 patients. Among these studies there were two large trials, with sample sizes of 199,<sup>55</sup> and 325<sup>92</sup> patients.

#### *Patient populations*

All studies recruited patients with major depression/MDD. Major depressive disorder was defined differently across studies, with nine studies using DSM-IV; one using DSM-IV or SCID (Structured Clinical Interview for DSM disorders); one using HAM-D25; one using DSM-IV or HAM-D17 or MADRS (Montgomery-Åsberg Depression Rating Scale) or BDI; one using DMS-IV or SCID or HAM-D21. Two studies did not report how major depression was defined. Other definitions included major/minor depression (DSM-IV),<sup>82</sup> medication-resistant depression of psychotic subtype (DSM-III),<sup>96</sup> moderate to severe TRD (HAM-D17), and unipolar depression (DSM-IV).<sup>52</sup>

#### *Treatment failure*

Fourteen studies reported that patients specifically had two or more prior treatment failures with medications. Two studies had one or more treatment failures and two did not specify the number of treatment failures, but were judged to have a high probability of having two or more treatment failures.

#### *rTMS parameters*

Detailed rTMS parameters for the included studies are shown in Table 3. Location, frequency, motor thresholds, and duration of treatment varied across studies.

- Comparisons: Eleven studies compared rTMS to sham stimulation. The remaining seven studies compared either different frequency parameters,<sup>54, 67, 95</sup> different locations<sup>51, 94, 108</sup> or different frequencies in different locations<sup>106</sup> with sham.
- Location: rTMS was most frequently conducted over the the left DPFC, this occurred in 12 out of 18 studies. In six studies, rTMS was conducted over the right DPFC. In the

remaining studies, rTMS was applied anterior to the right motor cortex,<sup>69</sup> in varying locations,<sup>54, 96</sup> or to an unspecified location.<sup>67</sup>

- Frequency and motor threshold: In the 13 studies that used L DPFC rTMS, frequencies ranged between 1Hz and 20Hz, with 10Hz most common (six studies) followed by 20Hz (four studies). Motor thresholds in L DPFC studies ranged between 80% and 120%, with 110% most common (five studies) followed by 120% (three studies). In the six studies that used R DPFC rTMS, frequencies ranged between 0.3Hz and 5Hz, with 1Hz the most common (four studies). Motor thresholds in R DPFC studies ranged between 90% and 120%, with 110% most common (three studies).
- Duration: treatment consisted of five sessions per week for all studies, with the number of weeks ranging between one and four-to-six weeks. The most common treatment duration was two weeks (eight studies), followed by one week and four weeks (four studies each). The studies that had a one week duration tended to be the oldest studies in the group (published between 1996 and 2001), with the exception of Pallanti (2010).<sup>95</sup>

### *Setting*

Seven studies were conducted in an outpatient setting, one was conducted in both inpatient and outpatients settings, and the remaining ten did not specify the type of setting in which they were conducted.

### *Outcomes*

All studies exclusively assessed the effectiveness of rTMS for treating acute-phase depressive symptoms; no studies assessed maintenance of response or remission. All of the studies except two used a version of the Hamilton Rating Scale for Depression, HAM-D17, HAM-D21 and HAM-D25 (abbreviated as HRSD, HDRS, or HAM-D) to assess improvements in depression. One study<sup>55</sup> did not report the rating scale used, reporting only remission rates. One study measured improvements in depressive symptoms using the MADRS.<sup>92</sup>

**Table 2. Characteristics of rTMS vs. sham randomised controlled trials**

Year	Study	n	Diagnosis	Rx failure	Setting	Outcomes	Response definition	Remission Definition	Follow-up
2012	Fitzgerald(51)	67	TRD diagnosis of moderate to severe depression (>15 HAM-D17)	2+	NS	CDS (HAM-D17), response, MADRS, BDI, AE	50% reduction in HAMD score	N/A	EOT (3 wk) + FU (3 wk PT)
2011	Aguirre(32)	34	Major depression	2+*	OP	CDS (HAMD), response	HAMD < 8	N/A	EOT ( 4 wk) + FU (4 wk PT)
2010	Zheng(113)	34	Major depression (DSM-IV)	2+	NS	CDS (HAM-D17), BDI, response	not defined	N/A	4 wk, NS if EOT or FU
2010	Triggs(108)	48	MDD (DSM-IV, SCID)	2+	NS	CDS (HAM-D24), BDI, STAI-S, AE	N/A	N/A	EOT (2 wk) + FU (1 wk, 1 mo & 3 mo PT)
2010	Pallanti(95)	60	Major depression (DSM-IV)	2+	NS	CDS (<=10%, <=25%, <=50% & >50% reduction in HAM-D), number needed to treat, adverse events	N/A	N/A	EOT (3 wk)
2010	George(55)	199	MDD (DSM-IV)	2+	OP	CDS (HAM-D24), response, remission, MADRS, BDI, adherence, AE	>=50% decrease in HAMD	HAMD <=3, or 2 consecutive HAMD <10	EOT (3 wk)
2008	Jakob(67)	36	Major depression (moderate to severe unipolar DSM-IV) >18 on HAM-D17, MADRS or BDI	2+*	NS	CDS (HAMD, MADRS, BDI), tolerability	N/A	N/A	EOT (2 wk)
2007	Stern(106)	45	MDD unipolar recurrent (SCID & DSM-IV, HAM-D21 score >=20)	1+	OP	CDS (HAM-D21)	N/A	N/A	EOT (2 wk) + FU (2 wk PT)
2007	O'Reardon(92)	325	MDD (DSM-IV)	1+	NS	CDS (HAM-D17), response, remission, MADRS, AE	not defined	HAM-D17 < 8	EOT (4-6 wk)
2006	Garcia-Toro(54)	30	MDD unipolar	2+	OP	CDS (HAM-D21) GCI	N/A	N/A	EOT (2 wk) + FU (2 wk PT)
2006	Avery(35)	68	MDD (DSM-IV)	2+	OP	CDS ( HAM-D17), response, remission (HAM-D21), relapse at 6 months, BDI, AE, CF	not defined	HAM-D21 < 10	EOT (4 wk) + FU (1 wk PT, monthly FU for responders for 6 mo PT)
2004	Kauffman(69)	12	Major depression (DSM-IV)	2+	NS	CDS, response, relapse	HAM-D21<10	N/A	EOT (2 weeks) + FU (3 mo PT?)
2004	Holtzheimer(65)	15	MDD (DSM-IV)	2+	NS	CDS, AE	N/A	N/A	EOT (2 wk) + FU 1 wk PT
2002	Boutros(40)	21	Major depression (HAM-D25>=20)	2+	OP	CDS (HAM-D25), response, relapse, AE	30% or 50% improvement in HAM-D25	N/A	EOT (2 weeks) + FU for responders only (6 mo PT)
2001	Manes(82) & Moser(88)	20	Major/minor depression (DSM-IV)	2+	OP	CDS (HAM-D), response, remission, AE, CF	not defined	not defined	EOT (1 wk) + FU (1 wk PT)
2001	Garcia-Toro(52)	40	Unipolar depression (DSM-IV)	2+	NS	CDS (HAM-D17, BDI, GCI)	N/A	N/A	EOT (2 wk) + FU (2 wk PT)
1999	Padberg(94)	18	Major depression (DSM-IV)	2+	NS	CDS (HAM-D21)	N/A	N/A	EOT (1 wk)
1996	Pascual-Leone(96)	17	Medication-resistant depression of psychotic subtype (DSM-III-R) resistance	2+	IP & OP	CDS (HAM-D21, BDI)	N/A	N/A	EOT (5 mo, rTMS received for 1st 5 days, every mo for 5 mo)

\* = not specified, but a high probability of two or more treatment failures; 1+ = 1 or more treatment failures; 2+ two or more treatment failures; AE = adverse events; BDI = Beck Depression Inventory; CDS = change in depressive severity; CF = cognitive functioning; defn = definition; DSM-III-R = Diagnostic & Statistical Manual of Mental Disorders—3rd Edition Revised; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EOT = end of treatment; FU = follow-up; GCI = Global Clinical Impressions; HAMD = Hamilton depression rating scale; IP = inpatient; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = major depressive disorder; mo = month/s; n = number of patients; N/A = not applicable; NS = not specified; OP = outpatient; PT = post-treatment; Rx = treatment; SCID = Structured Clinical Interview for DSM disorders; TRD = treatment resistant depression; wk = week/s.

**Table 3. rTMS parameters for rTMS vs. sham randomised controlled trials**

Year	Study	Freq (Hz)	MT	Location	Trains	Train length	Interval (seconds)	Pulses per session	Sessions	Days/Weeks	Comments
2012	Fitzgerald(51) (L parameters)	10	120%	L DLPFC	30	5 s	NS	NS	15	3 weeks	L parameters only
2012	Fitzgerald(51) (SB arm - R parameters)	1	120%	R DLPFC	1	15 min	NS	NS	15	3 weeks	L followed by R parameters
2011	Aguirre(32)	1	110%	R DLPFC	20	60 s	45 s	1200	20	4 weeks	
2010	Pallanti(95) (low freq arm)	0.3	90%	R DLPFC	10	25 s	NS	75	5	1 week	
2010	Pallanti(95)(high freq arm)	10	90%	R DLPFC then L DLPFC	5	5 s	30 s	250	5	1 week	
2010	Zheng(113)	15	110%	L DLPFC	50	4 s	NS	3000	20	4 weeks	28 mins per session
2010	George(55)	10	120%	L DLPFC	75	4 s	26 s	3000	15	3 weeks	
2010	Triggs(108) (L sided arm)	5	100%	L DLPFC	50	8 s	22s	2000	10	2 weeks	
2010	Triggs(108) (R sided arm)	5	100%	R DLPFC	50	8 s	22 s	2000	10	2 weeks	
2008	Jakob(67) (standard arm)	20	100%	NS	NS	2 s	18 s	NS	10	2 weeks	
2008	Jakob(67)(ultrahigh freq arm)	50	100%	NS	NS	1 s	59 s	NS	10	2 weeks	
2007	Stern(106) (low freq L arm)	1	110%	L DLPFC	1	1600 s	N/A	NS	10	2 weeks	
2007	Stern(106) (high freq L arm)	10	110%	L DLPFC	20	8 s	52 s	1600	10	2 weeks	
2007	Stern(106) (low freq R arm)	1	110%	R DLPFC	1	1600 s	N/A	NS	10	2 weeks	
2007	O'Reardon(92)	10	120%	L DLPFC	75	4 s	26 s	3000	5/week	4-6 weeks	
2006	Garcia-Toro(54) (normal freq arm)	1	110%	various	30	60 s	15-25 s	1800	10	2 weeks	
2006	Garcia-Toro(54) (high freq arm)	20	110%	various	30	2 s	15-25 s	1200	10	2 weeks	
2006	Avery(35)	10	110%	L DLPFC	32	5 s	25-30 s	1600	15	4 weeks	
2004	Kauffman(69)	1	110%	anterior to R motor cortex	2	60 s	180 s	120	10	10 days	
2004	Holtzheimer(65)	10	110%	L DLPFC	32	5 s	30-60 s	1600	10	2 weeks	
2002	Boutros(40)	20	80%	L DLPFC	20	2 s	58 s	800	10	10 days	
2001	Garcia-Toro(52)	20	90%	L DLPFC	30	2 s	20-40 s	1200	10	10 days	
2001	Manes(82)&Moser(88)	20	80%	L DLPFC	20	2 s	60 s	800	5	1 week	
1999	Padberg(94) (SB arm - L parameters)	20	100%	L DLPFC	20	5 s	25 s	1000	5	1 week	R followed by L parameters
1999	Padberg(94) (R parameters)	1	110%	R DLPFC	3	140 s	30 s	420	5	1 week	R parameters only
1996	Pascual-Leone(96)	10	90%	Vertex, L or R DLPFC	20	10 s	60 s	2000	25	1 <sup>st</sup> 5 days each mo for 5 mo	

DLPFC = dorsolateral prefrontal cortex; freq = frequency; L = left; mo = month; MT = motor threshold; N/A = not applicable; NS = not specified; R = right; SB = sequential bilateral.



## Results summary

### *Response to treatment*

Six studies reported a significant difference in effectiveness between rTMS and sham (in favour of rTMS) for the treatment of depression.<sup>35, 52, 54, 55, 92, 96</sup> Of these studies, George 2010<sup>55</sup> and O'Reardon 2007<sup>92</sup> had large sample sizes (n = 199 and n = 325 respectively). Four out of the six studies used a frequency of 10Hz for rTMS. Although Garcia-Toro<sup>52</sup> reported a significant difference between changes in HAM-D, the effect size was small and there was no significant difference in the percentage of responders between groups (this study used a 20Hz frequency). Three of the six studies measured the primary outcome at the end of treatment.<sup>52, 54, 55</sup> Two studies<sup>35, 96</sup> measured the primary outcome one week after active treatment. One study measured the primary outcome at the end of four weeks of treatment to allow cross-over of non-responders and an additional two weeks of treatment.<sup>92</sup>

Nine studies found no significant difference between rTMS and sham rTMS for the treatment of depression.<sup>32, 40, 65, 67, 69, 82, 94, 108, 113</sup> All of these studies had relatively small sample sizes (between 12 and 48 patients). Effectiveness of treatment was measured at the end of active treatment; for most studies active treatment lasted two weeks. Four studies made additional post-treatment follow-up assessments at one week,<sup>65, 82</sup> four weeks,<sup>32</sup> and six months.<sup>40</sup>

Three studies reported mixed results. One study found that unilateral but not bilateral rTMS was more effective than sham treatment.<sup>95</sup> One study found that high frequency (10Hz) rTMS to the left DPFC, and low frequency (1Hz) rTMS to the right DPFC, but not low frequency to the left was more effective than sham treatment.<sup>106</sup> One study reported unilateral left sided rTMS was more effective than sham or bilateral rTMS.<sup>51</sup> All three of the studies measured the primary outcome at the end of active treatment. One study had an additional two week follow-up<sup>106</sup> and one study had a cross-over of patients.<sup>51</sup>

### *Adverse events*

No serious adverse events were reported. Side effects generally included headache or localised pain/discomfort at the site of application. Some studies reported these side effects in both the sham and the active treatment groups. Seven studies reported that headaches occurred more frequently in the active group than the sham treatment group.<sup>52, 54, 55, 82, 92, 94-96</sup> None of the studies reported any significant differences between groups. Two studies reported on testing for neurophysiological adverse events and found that there was no significant difference between the groups.<sup>35, 82</sup>

## FINDINGS

**Table 4. Key information from most recent, comprehensive, high quality systematic review**

Gaynes BN, Lux LJ, Lloyd SW, Hansen RA, Gartlehner G, Keener P, et al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33. AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality. Available from: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

<b>Study design</b>	Systematic review
<b>Scope</b>	<p><b>Patient/population:</b> Patients with TRD.</p> <p><b>Intervention and comparators:</b> nonpharmacologic treatments including rTMS, sham rTMS, ECT, VNS, and evidence-based psychological treatments.</p> <p><b>Outcomes assessed:</b></p> <p><u>ECT vs. rTMS:</u> change in depressive severity, response and remission rate, adverse events, withdrawals due to adverse events, cognitive functioning.</p> <p><u>rTMS vs. sham:</u> change in depressive severity, response and remission rates, adverse events, withdrawals due to adverse events, cognitive functioning, health-related outcomes.</p>
<b>1. What is the effectiveness of rTMS in treating acute-phase depressive symptoms (e.g., response and remission)?</b>	<p><b>Effectiveness in treating acute-phase depressive symptoms</b></p> <p><b>rTMS vs. ECT (n = 4 studies)</b></p> <p>There is insufficient evidence to determine whether rTMS is more effective or even equivalent to ECT, with half of the studies reporting equivalence and half reporting rTMS as being inferior to ECT with regards to treating acute-phase depressive symptoms.</p> <p><b>rTMS vs. sham rTMS (n = 18 studies)</b></p> <p>Only one good quality study<sup>92</sup> was sufficiently powered to detect a significant difference between treatment arms. This study reported that rTMS was more effective than sham.</p> <p>There is insufficient evidence to determine the effect of rTMS, as the results of the studies were variable with six studies reporting rTMS to be more effective than sham, nine studies reporting no significant difference between rTMS and sham rTMS, and three reporting mixed results.</p> <p>Despite a large number of RCTs, the relatively small sample sizes of the studies and large variation in treatment parameters makes it difficult to assess the overall results.</p>

<p><b>2. What is the effectiveness of rTMS in maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?</b></p>	<p><b>rTMS vs. ECT:</b> There is no evidence to answer this question.</p> <p><b>rTMS vs. sham rTMS:</b> There is no evidence to draw conclusions on the effectiveness of rTMS on maintaining remission or preventing relapse when compared to sham rTMS.</p>
<p><b>3. In what setting, inpatient or outpatient, is rTMS most effective in treating acute-phase depressive symptoms OR maintaining response or remission?</b></p>	<p>There is insufficient evidence to assess the most appropriate treatment setting. The studies included in this review were either set in an inpatient environment or a mixed inpatient and outpatient setting. None of the studies indicated a trend in results according to setting and no studies compared the effect of rTMS in inpatient and outpatient settings.</p>
<p><b>4. What rTMS protocols i.e., what number of treatments over what time period, are effective in treating acute-phase depressive symptoms OR maintaining response or remission?</b></p>	<p>There is insufficient evidence to determine the most effective rTMS protocols. rTMS location, frequency, motor thresholds, and duration of treatment varied across studies.</p>
<p><b>5. What is the safety of rTMS for depression?</b></p>	<p>None of the studies reported any significant differences between groups.</p> <p><b>rTMS vs. ECT</b></p> <p><i>Cognitive functioning:</i> In some cases ECT can have an adverse impact on cognitive functioning.</p> <p><i>Withdrawals due to adverse events:</i> there was no difference in withdrawals due to adverse effects between rTMS and ECT.</p> <p><b>rTMS vs. sham rTMS</b></p> <p><i>Cognitive functioning:</i> the evidence on the effects of rTMS versus sham on cognitive functioning is insufficient to draw a conclusion.</p> <p><i>Specific adverse events:</i> rTMS groups reported significantly more scalp pain at the stimulation site (low strength of evidence).</p> <p><i>Withdrawals due to adverse events:</i> Findings were mixed as to whether rTMS groups had greater rates of withdrawals due to adverse events than groups receiving sham procedures.</p>
<p><b>Quality assessment results</b></p>	<p>This SR scored 11/11 using the AMSTAR tool, this means it was well conducted and considered to have a low risk of bias. However, the quality of the included studies varied, and many of them were small, and not sufficiently powered to detect a real effect.</p>

## DISCUSSION

### **1. What is the effectiveness and safety of rTMS in treating acute-phase depressive symptoms (e.g., response and remission)?**

There is insufficient evidence to determine whether rTMS is more effective or even equivalent to ECT, with half of the studies reporting equivalence and half reporting rTMS as being inferior to ECT. This uncertainty is further compounded by the fact that the two studies reporting equivalence were underpowered (i.e., the number of patients recruited was insufficient to identify a significant difference between treatment arms). Other issues also impacting on the overall effectiveness of rTMS was the variation in rTMS and ECT parameters across studies. The long-term effects of rTMS are also unclear as the majority of studies only assessed outcomes at the end of treatment.

With regards to rTMS vs. sham rTMS, the only study that was sufficiently powered to detect a significant difference between treatment arms was O'Reardon 2007<sup>92</sup>, which recruited 325 patients. This study indicated that rTMS was more effective than sham. The remaining studies all had relatively small sample sizes and were either underpowered or did not report power calculations.

Notwithstanding the issue of sample size, studies of rTMS vs. sham varied in the frequency of stimulation, the area of the brain to which it was applied, the amount of treatment given each session (the number of trains, length of trains, length of intervals between trains, and number of pulses per session), and the duration of treatment (see Table 3).

The variation between parameters makes it difficult to assess the results of these studies overall without making the assumption that all rTMS parameters are equally effective. Seven of the eighteen rTMS vs. sham trials<sup>51, 54, 67, 94, 95, 106, 108</sup> included several arms that compared different rTMS parameters with each other as well as with sham rTMS, these trials include some of the most recent publications on this topic, suggesting that the optimal rTMS parameters are still to be determined.

In terms of safety it would appear that there was no difference in adverse events between study arms, with no study reporting a significant difference between rTMS and ECT or sham.

Issues around whether treatment failure was an effect modifier could not be answered in this review, as the results were inconsistent across the studies regardless of how many treatment failures patients experienced.

### **2. What is the effectiveness and safety of rTMS in maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?**

No trials were identified that specifically examined longer-term efficacy of rTMS, such as maintaining remission. This could be due to the uncertainty around the short-term effectiveness of this treatment. One study did assess remission at six months reporting that the effects of ECT were not sustained after six months.

### **3. In what setting, inpatient or outpatient, is rTMS most effective in treating acute-phase depressive symptoms OR maintaining response or remission?**

There is insufficient evidence identifying the optimal setting for administering rTMS. The studies included in this review had either inpatient or mixed inpatient and outpatient settings. None of the studies indicated a trend in results according to setting and no studies compared the effect of rTMS in inpatient and outpatient settings.

### **4. What rTMS protocols i.e., what number of treatments over what time period, are effective in treating acute-phase depressive symptoms OR maintaining response or remission?**

The different rTMS treatment protocols and parameters across studies indicate that there is insufficient evidence to determine which rTMS protocol is most effective.

## **CONCLUSION**

Overall, comparative clinical research on rTMS in MDD is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. An optimal protocol for rTMS needs to be defined and tested using high-quality, adequately powered head-to-head clinical trials. Overall there is insufficient evidence to determine whether rTMS is as effective as standard treatment (i.e., ECT), and for which patients (i.e., level of treatment resistance) rTMS may be most effective.

## SUMMARY OF SYNTHESISED STUDIES

**Table 5. Synthesised studies of rTMS vs. sham for depression**

STUDY	Aare 2003 <sup>13</sup>	Allan 2011 <sup>14</sup>	Coutourier 2005 <sup>15</sup>	Gaynes 2011 <sup>4</sup>	Gross 2007 <sup>16</sup>
PATIENTS	Depressive disorders	Depression	MDD	TRD	MDD
INPATIENT OR OUTPATIENT SETTING	Not stated	Not stated	Not stated	Not stated	Not stated
COMPARATORS	Sham rTMS (or ECT)	Sham rTMS	Sham rTMS	Sham rTMS (or ECT)	Sham rTMS
TREATMENT OR REMISSION MAINTENANCE?	Not stated	Not stated	Not stated	Both	Not stated
ON ANTIDEPRESSANTS OR DRUG FREE?	Mixed	Mixed	Mixed	Mixed	Mixed
SEARCH DATE	February 2001	2008	July 2003	November 2010	November 2006
INCLUDED STUDIES (n)	8 studies of rTMS vs. sham, unclear if they are RCTs or CCTs	31 RCTs of rTMS vs. sham	6 RCTs of rTMS vs. sham	23 RCTs of rTMS vs. sham	5 RCTs of rTMS vs. sham
PRIMARY OUTCOMES	Efficacy	Efficacy	Efficacy	Efficacy, remission maintenance	Comparison of efficacy between late and early studies of rTMS
ADVERSE EVENTS	Not reported	Not reported	Not reported	Significantly more scalp pain at stimulation site in rTMS group. Insufficient evidence to draw conclusions on differences in cognitive functioning and withdrawals due to adverse events for rTMS vs. sham.	Not reported
RESULTS	Modest but clinically insignificant result on efficacy. No lasting improvement past two weeks after cessation of treatment.	Moderately sized effect in favour of rTMS. No mean change in depression severity between the end of treatment and follow-up.	Improvements using rTMS compared with sham therapy not clinically significant.	rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate)	The pool effect size was significantly larger than that of earlier meta-analysis
CONCLUSIONS	rTMS not recommended as a standard treatment for	Optimum treatment protocol yet to be discovered.	No significant difference between rTMS and sham	rTMS more effective than sham for TRD	Recent clinical trials of rTMS on depression induced a larger

	depression.	No evidence for lasting treatment effects beyond 12 weeks.	treatment. Most effective combination of parameters for rTMS not yet established.		effect size when compared with the initial studies from Martin et al.
DIRECTION OF FINDINGS	-	?	=	+	+
AMSTAR RATING	3/9	2/11	5/11	11/11	5/11

ECT = electroconvulsive therapy; MDD = major depressive disorder; RCTs = randomised controlled trials; rTMS = repetitive transcranial magnetic stimulation; TRD = treatment resistant depression; - rTMS inferior to comparator; ? no conclusions drawn; = no difference between rTMS and comparator; + rTMS superior to comparator

**Table 5. Synthesised studies of rTMS vs. sham for depression (continued)**

STUDY	Herrmann 2006 <sup>17</sup>	Herrmann 2009 <sup>18</sup>	Holtzheimer 2001 <sup>19</sup>	Kennedy 2009 <sup>20</sup>	Kozel 2002 <sup>21</sup>
PATIENTS	MDD or bipolar	MDD or bipolar	MDD	MDD	depression or depressive disorder
INPATIENT OR OUTPATIENT SETTING	Not stated	Not stated	Not stated	Not stated	Not stated
COMPARATORS	Sham TMS	Sham TMS	Sham TMS	Sham TMS	Sham rTMS
TREATMENT OR REMISSION MAINTENANCE?	Not stated	Not stated	Not stated	Not stated	Not stated
ON ANTIDEPRESSANTS OR DRUG FREE?	Mixed	Mixed	Mixed	Mixed	Not stated
SEARCH DATE	Not reported	2007	Not reported	Dec 2008	April 2002
INCLUDED STUDIES (n)	31 RCTs of rTMS vs. sham	24 RCTs of rTMS vs. sham	12 studies of rTMS vs. sham, unclear if they are RCTs or CCTs	Not Reported	12 RCTs of rTMS vs. sham
PRIMARY OUTCOMES	Efficacy	Efficacy	Efficacy	Efficacy	Efficacy
ADVERSE EVENTS	Not reported	Small risk of seizure	Headaches, discomfort at stimulation site during procedure.	Headaches, scalp pain	Not reported
RESULTS	Clinically significant effect of rTMS	Significantly larger proportion of 'responders' in active rTMS group (35.3%) vs. sham rTMS group (13.1%). 5 patients need to be treated with rTMS to obtain a clinical response.	Overall weighted mean effect size of 0.81 was found for 12 sham-controlled studies of rTMS in the treatment of depression.	Not reported	Significant cumulative effect size of 0.53 (95%CI: 0.24-0.82).
CONCLUSIONS	rTMS is more effective in	Patients treated with rTMS	rTMS has real antidepressant	Some studies to suggest that	Double blind published rTMS

	treating depression than sham rTMS, however, studies are heterogeneous and therefore difficult to accurately determine effectiveness.	more likely to show a clinical response than patients treated with sham; differences disappear at follow-up.	effects that can be large at times but are generally modest.	rTMS is better than sham treatment	literature to date supports the use of left prefrontal rTMS to improve depressive symptoms.
DIRECTION OF FINDINGS	+	+ initially, = at follow-up	+	+	+
AMSTAR RATING	1/11	3/11	3/11	1/9	4/11

CCTs = controlled clinical trials; MDD = major depressive disorder; RCTs = randomised controlled trials; rTMS = repetitive transcranial magnetic stimulation

- rTMS inferior to comparator; ? no conclusions drawn; = no difference between rTMS and comparator; + rTMS superior to comparator

**Table 5. Synthesised studies of rTMS vs. sham for depression (continued)**

STUDY	Lam 2008 <sup>22</sup>	Martin 2003 <sup>23</sup>	McNamara 2001 <sup>24</sup>	Ontario Ministry of Health 2004 <sup>27</sup>
PATIENTS	TRD	Any diagnosis of depression	Major depressive episode	Mixed
INPATIENT OR OUTPATIENT SETTING	Not stated	Not stated	Not stated	Not stated
COMPARATORS	Sham rTMS	Sham rTMS	Sham rTMS	Sham rTMS (or ECT)
TREATMENT OR REMISSION MAINTENANCE?	Not stated	Not stated	Not stated	Not stated
ON ANTIDEPRESSANTS OR DRUG FREE?	Not stated	Mixed	Mixed	Mixed
SEARCH DATE	May 2008	January 2002	January 2000	March 2004
INCLUDED STUDIES (n)	23 RCTs of rTMS vs. sham	14 RCTs of rTMS vs. sham	5 RCTs of rTMS vs. sham	7 SR/MA of rTMS vs. sham
PRIMARY OUTCOMES	Efficacy	Efficacy	Efficacy	Efficacy and cost effectiveness.
ADVERSE EVENTS	Not reported	Not reported	Transient headaches. Discomfort at the site of treatment.	Not reported
RESULTS	rTMS had significantly greater clinical response than sham.	rTMS more effective than sham after two weeks of treatment, but no significant difference at the two week follow-up	Statistically significant benefit of rTMS. 43% difference in the rate of improvement in the treated group and the control group.	Not reported
CONCLUSIONS	rTMS for 1-4 weeks has clear antidepressant effects and is well tolerated, but response and remission rates are low and it is unclear whether	Insufficient evidence to suggest that rTMS is more effective than sham. Any difference between the two groups has disappeared two weeks post-	rTMS is an effective treatment for depression.	Early meta-analyses suggested rTMS may be effective for the treatment of MDD



	the effects are sustained.	intervention.		
DIRECTION OF FINDINGS	+ initially, ? long-term	?	+	+
AMSTAR RATING	8/11	7/11	4/11	6/9

ECT = electroconvulsive therapy; MDD = major depressive disorder; RCTs = randomised controlled trials; rTMS = repetitive transcranial magnetic stimulation; SR/MA = systematic reviews/meta-analyses; TRD = treatment resistant depression; - rTMS inferior to comparator; ? no conclusions drawn; = no difference between rTMS and comparator; + rTMS superior to comparator

**Table 5. Synthesised studies of rTMS vs. sham for depression (continued)**

STUDY	NICE 2007 <sup>26</sup>	Rodriguez-Martin 2009 <sup>28</sup>	Schutter 2010 <sup>30</sup>	Schutter 2009 <sup>29</sup>	Slotema 2010 <sup>31</sup>
PATIENTS	MDD	Depression	Major depressive episode	Major depressive episode	Depression
INPATIENT OR OUTPATIENT SETTING	Not stated	Not stated	Not stated	Not stated	Not stated
INTERVENTION & COMPARATORS	Sham rTMS (or ECT)	Sham rTMS (or ECT or psychotherapy or pharmacotherapy)	Sham rTMS	Sham rTMS	Sham rTMS (or ECT)
TREATMENT OR REMISSION MAINTENANCE?	Not stated	Not stated	Not stated	Not stated	Not stated
ON ANTIDEPRESSANTS OR DRUG FREE?	Mixed	Mixed	Not stated	Not stated	Mixed
SEARCH DATE	October 2006	June 2001	2009	November 2007	October 2008
INCLUDED STUDIES (n)	3 SR/MA & 8 RCTs of rTMS vs. sham	13 RCTs of rTMS vs. sham	9 RCTs of rTMS vs. sham (slow frequency rTMS only)	30 RCTs of rTMS vs. sham	34 RCTs of rTMS vs. sham
PRIMARY OUTCOMES	Efficacy	Efficacy and Safety	Efficacy	Efficacy	Efficacy
ADVERSE EVENTS	Seizures, nausea, scalp discomfort, headache, migraine, neck stiffness, hearing loss, mania.	No significant adverse effects in the short term	Not reported	Headaches, dizziness, nausea, and painful local sensation.	Headache, nausea, scalp discomfort, drowsiness, facial muscle twitching, tearfulness, dizziness.
RESULTS	Not reported	Benefits shown in favour of rTMS versus sham at two weeks.	No significant difference between fast and slow TMS. Cumulative effect size for treatment was 0.63 (95% CI 0.03-1.24).	rTMS has significantly more antidepressant efficacy than sham treatment.	rTMS vs. sham; significant mean weighted effect size (0.55) in favour of rTMS.
CONCLUSIONS	rTMS is a novel treatment with uncertainty around its efficacy	No strong evidence for possible efficacy of rTMS for	rTMS can improve MDD and additional clinical trials aimed	rTMS is superior to sham and may be as effective as at least	rTMS is more effective than sham for depression and

	and safety.	the treatment of depression.	at optimising the treatment are worthwhile.	a subset of antidepressant medications.	appears to be more effective as a monotherapy.
DIRECTION OF FINDINGS	?	?	+	+	+
AMSTAR RATING	4/9	10/11	6/11	4/11	3/11

ECT = electroconvulsive therapy; MDD = major depressive disorder; RCTs = randomised controlled trials; rTMS = repetitive transcranial magnetic stimulation; SR/MA = systematic reviews/meta-analyses; - rTMS inferior to comparator; ? no conclusions drawn; = no difference between rTMS and comparator; + rTMS superior to comparator

**Table 6. Synthesised studies of rTMS vs. ECT for depression**

STUDY	Aare 2003 <sup>13</sup>	Gaynes 2011 <sup>4</sup>	Ontario Ministry of Health 2004 <sup>27</sup>	MSAC 2008 <sup>8</sup>
PATIENTS	Depressive disorders	TRD	Mixed	MDD
INPATIENT OR OUTPATIENT SETTING	Not stated	Not stated	Not stated	Not stated
INTERVENTION & COMPARATORS	ECT (or sham rTMS)	ECT (or sham rTMS)	ECT (or sham rTMS)	ECT (or sham rTMS)
TREATMENT OR REMISSION MAINTENANCE?	Not stated	Both	Not stated	Not stated
ON ANTIDEPRESSANTS OR DRUG FREE?	Mixed	Mixed	Mixed	Mixed
SEARCH DATE	February 2001	November 2010	March 2004	2006
INCLUDED STUDIES (n)	2 Studies (1RCT)	4 RCTs	3 RCTs	7 Studies (2 confirmed RCTs)
PRIMARY OUTCOMES	Efficacy	Efficacy, remission maintenance	Efficacy and cost effectiveness.	Efficacy
ADVERSE EVENTS	Not reported	A small study indicated no difference in withdrawals due to adverse events between the ECT and rTMS groups but did not report on the significance of this result (low strength of evidence).	Not reported	Not reported
RESULTS	Modest but clinically insignificant result on efficacy. No lasting improvement past two weeks after cessation of treatment.	1 fair trial of ECT vs. rTMS in a treatment resistant MDD population showed with low strength of evidence, no difference between treatment options for depressive severity, response rate and remission rate.	Not reported.	No significant difference between the response rates of the rTMS group and the ECT group. Overall rTMS appeared to be less effective than ECT in the treatment of major depression, although this was not statistically significant.
CONCLUSIONS	rTMS not recommended as a standard treatment for depression.	No difference between rTMS and ECT (low strength of evidence)	Early meta-analyses suggested that rTMS may be effective for the treatment of MDD	ECT appears to be as effective as rTMS for the treatment of depression in patients without psychosis
DIRECTION OF FINDINGS	-	=	+	=
AMSTAR RATING	<b>3/9</b>	<b>11/11</b>	<b>6/9</b>	<b>9/11</b>

**Table 6. Synthesised studies of rTMS vs. ECT for depression (continued)**

STUDY	Minichino 2012 <sup>25</sup>	NICE 2007 <sup>26</sup>	Rodriguez-Martin 2009 <sup>28</sup>	Slotema 2010 <sup>31</sup>
PATIENTS	TRD, MDD	MDD	Depression	Depression
INPATIENT OR OUTPATIENT SETTING	Not stated	Not stated	Not stated	Not stated
INTERVENTION & COMPARATORS	ECT	ECT (or sham rTMS)	ECT (or sham rTMS or psychotherapy or pharmacotherapy)	ECT (or sham rTMS)
TREATMENT OR REMISSION MAINTENANCE?	Not stated	Not stated	Not stated	Not stated
ANTIDEPRESSANT TREATMENT?	Drug free	Mixed	Mixed	Mixed
SEARCH DATE	NR	October 2006	June 2001	October 2008
INCLUDED STUDIES (n)	4 Studies (2RCTs)	8 RCTs	1 RCT of rTMS vs. ECT	6 RCTs
PRIMARY OUTCOMES	Efficacy and tolerability	Efficacy	Efficacy	Efficacy
ADVERSE EVENTS	None reported, tolerability measured by the number of “drop-outs”	Seizures, local scalp discomfort, headache, migraine, nausea, neck stiffness, hearing loss and induction of mania.	Not reported	Transient and mild side effects include headache, scalp discomfort, drowsiness, facial muscle twitching, tearfulness, dizziness and nausea.
RESULTS	rTMS more tolerable than ECT. ECT more effective than rTMS.	Not reported	No significant difference between techniques when patients had no psychotic symptoms. ECT was more effective when patients had psychotic symptoms.	ECT was superior to rTMS in the treatment of depression (mean weighted effect size -0.47, p=.004)
CONCLUSIONS	rTMS provides better tolerability than ECT but its therapeutic efficacy is lower.	rTMS is a novel treatment with uncertainty around its efficacy and safety.	No strong evidence for possible efficacy of rTMS for the treatment of depression.	rTMS is less effective than ECT in the treatment of depression.
DIRECTION OF FINDINGS	-	?	?	-
AMSTAR RATING	<b>2/11</b>	<b>4/9</b>	<b>10/11</b>	<b>3/11</b>

ECT = electroconvulsive therapy; MDD = major depressive disorder; RCTs = randomised controlled trials; rTMS = repetitive transcranial magnetic stimulation; SR/MA = systematic reviews/meta-analyses; TRD = treatment resistant depression; - rTMS inferior to comparator; ? no conclusions drawn; = no difference between rTMS and comparator; + rTMS superior to comparator

## DISCLAIMER

The information in this report is a summary of that available and is primarily designed to give readers a starting point to consider currently available research evidence. Whilst appreciable care has been taken in the preparation of the materials included in this publication, the authors and the National Trauma Research Institute do not warrant the accuracy of this document and deny any representation, implied or expressed, concerning the efficacy, appropriateness or suitability of any treatment or product. In view of the possibility of human error or advances of medical knowledge the authors and the National Trauma Research Institute cannot and do not warrant that the information contained in these pages is in every aspect accurate or complete. Accordingly, they are not and will not be held responsible or liable for any errors or omissions that may be found in this publication. You are therefore encouraged to consult other sources in order to confirm the information contained in this publication and, in the event that medical treatment is required, to take professional expert advice from a legally qualified and appropriately experienced medical practitioner.

## CONFLICT OF INTEREST

The TAC/WSV Evidence Service is provided by the National Trauma Research Institute. The NTRI does not accept funding from pharmaceutical or biotechnology companies or other commercial entities with potential vested interest in the outcomes of systematic reviews.

The TAC/WSV Health Services Group has engaged the NTRI for their objectivity and independence and recognise that any materials developed must be free of influence from parties with vested interests. The Evidence Service has full editorial control.

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112. Wang XM, Yang DB, Yu YF, Huang H, Zhao XQ. A controlled study of the treatment of repetitive transcranial magnetic stimulation in patients with major depression. *Chin J Clin Rehab.* 2004;8(9):1770-1.

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113. Zheng H, Zhang L, Li L, Liu P, Gao J, Liu X, et al. High-frequency rTMS treatment increases left prefrontal myo-inositol in young patients with treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(7):1189-95.
114. McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. *HTA*. 2007(3).

## Evidence Service

# Repetitive Transcranial Magnetic Stimulation (rTMS) for Depression

## Technical Report: Appendices 1-7

March 2013

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## INTRODUCTION

This technical report is a companion document to “Repetitive Transcranial Magnetic Stimulation (rTMS) for Depression: Evidence Review”. It contains detailed information about the methods used in the development of the Evidence Review, summaries of the studies included in the review, and quality appraisal results for the most recent and/or most relevant included studies.

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## APPENDIX 1: METHODS

A two-staged approach was undertaken.

### STAGE 1

#### Identify evidence available for each intervention

- Run search in health databases, websites and on the internet, limit to evidence based guidelines (EBGs), health technology assessments (HTAs), systematic reviews (SRs,) randomised controlled trials (RCTs) and controlled clinical trials (CCTs)
- Apply inclusion and exclusion criteria

#### Critically appraise synthesised research

- Start with most recent review, apply standard appraisal criteria
- If found to be of high quality, cross check to ensure references from all other synthesised research are included and check for consistency of findings
- If not high quality, appraise next most recent and repeat process
- If there are inconsistent findings across the existing reviews, investigate the possibility of synthesis of this information or whether a new systematic review is required

#### Decide on actions for Stage 2

- Map available evidence (as per Table A1.1)
- Identify whether sufficient high level evidence exists to answer questions or identify what further action needs to be taken (see algorithm in Table A1.2).

### STAGE 2

Address further actions identified.

**Table A1.1. Template for map of available evidence**

Synthesised studies		Primary studies	TOTAL
EBGs	SRs & HTAs		

**Table A1.2. Further action required to answer clinical questions**

Is there any synthesised research available? (e.g., EBGs, HTAs, SRs)				
Yes			No	
Is this good quality research?			Are RCTs available?	
Yes		No	Yes	No
Is it current (within 2 years)?			Undertake new SR	Consider looking for lower levels of evidence
Yes	No	Undertake new SR		
No further action	Update existing SR			

## APPENDIX 2: SEARCH DETAILS

TAC/WSV staff assisted in the development of search terms and inclusion and exclusion.

### Inclusion and exclusion criteria

Inclusion and exclusion criteria were established a priori (Table A2.1). The two authors independently screened the search results according to the inclusion and exclusion criteria. Any discrepancies in findings were discussed and resolved.

**Table A2.1 Inclusion and Exclusion criteria**

<b>Patient/ population</b>	<b>Inclusion:</b> Adults, including geriatrics. Male and Female. Depression, acute or chronic, new onset, relapsed, treatment resistant or in remission.
	<b>Exclusion:</b> Children, bipolar depression
<b>Intervention/ indicator</b>	<b>Inclusion:</b> Repetitive transcranial magnetic stimulation. Any dose.
	<b>Exclusion:</b> Non-repetitive transcranial magnetic stimulation.
<b>Comparison/ control</b>	<b>Inclusion:</b> Standard care which may include admission, antidepressants, psychological counselling, electroconvulsive therapy (ECT) or comparison to placebo.
	<b>Exclusion:</b> Nil
<b>Outcomes</b>	<b>Inclusion:</b> Remission of depression, prevention of depression relapse, medication use, healthcare use, function in daily activities, quality of life, social functioning, return to work, adverse events.
	<b>Exclusion:</b> Nil
<b>Setting</b>	<b>Inclusion:</b> in or outpatient.
	<b>Exclusion:</b> Patients in a long term care facility.
<b>Study Design</b>	<b>Inclusion:</b> Evidence-based guidelines (EBG's), systematic reviews (SR), health technology assessments (HTA) and controlled trials.
	<b>Exclusion:</b> Non-evidence-based guidelines, non-systematic reviews, cohort studies, case control studies, case series, editorials, letters and commentaries.
<b>Publication details</b>	<b>Inclusion:</b> All English language studies conducted on humans.
	<b>Exclusion:</b> Non-English language papers or studies conducted on animals.
<b>Time period</b>	<b>Inclusion:</b> Any time
	<b>Exclusion:</b> Nil

## Searches undertaken

### Search methods

Evidence Based Guidelines (EBGs) are generally published as electronic ‘stand alone’ documents on the internet rather than papers in peer reviewed journals. We searched first in standard health databases, then in websites which are known to publish high-quality research and guidelines and finally in a general search engine, as follows;

### Search strategies in electronic databases

Standard systematic review strategies, as outlined below in the Medline search example, were used to identify existing reviews and trials. Additional reviewing of the references from the searches identified EBGs.

### Internet searches to identify relevant websites

The reviewers were aware of websites of guideline clearinghouses, guideline developers, centres of evidence-based practice, Australian government health services and websites of specific relevance (egg. accident compensation groups) known to contain evidence-based resources.

### Website searches to identify relevant EBGs

The reviewers were aware of websites of guideline clearinghouses, guideline developers, centres of evidence-based practice, Australian government health services and websites of specific relevance (eg. accident compensation groups) known to contain evidence-based resources.

The 43 websites listed below were searched for relevant EBGs (see Table A2.4).

Where an internal search engine was available, websites were searched using the search strings detailed in the table below. If no search engine was available, lists of EBGs, publications or other resources identified on the site were scanned for relevant documents.

### Internet searches to identify relevant references

An internet search strategy was conducted using the Google ‘Advanced Search’ function. The search string was limited to documents in English:

The first 100 Google search results were screened and yielded no new studies. As Google search results are presented in order of relevance, we did not screen further.

### Databases accessed

A highly sensitive search in Cochrane library, Medline, Embase, Compendex (Engineering), Pedro and Sportsdiscus (sporting) as detailed below was undertaken for the review terms.

**Table A2.2 Databases accessed**

Database name	Dates covered	Date searched	Refs
Medline (Ovid)	1980 to July Week 2 2012	20 <sup>th</sup> July 2012	877
PreMedline (Ovid)	- July 13, 2012	16 <sup>th</sup> July 2012	71
All EBM (Ovid) *	Complete databases – July 2012	20 <sup>th</sup> July 2012	130
CINAHL (Ovid)	1980 - date	20 <sup>th</sup> July 2012	116
EMBASE	1980 to 2012 Week 28	20 <sup>th</sup> July 2012	1204
WoK	Complete databases – July 2012	21 <sup>st</sup> July 2012	97

\*including The Cochrane Database of Systematic Reviews, DARE, CENTRAL, NHSEED, HTA and ACP Journal Club

The following searches were conducted and adapted for use in other databases.

**Table A2.3 Medline Search Strategy**

1	Depression/
2	exp depressive disorder/
3	(depression or depressive or melanchol*).ti,ab.
4	or/1-3
5	Transcranial Magnetic Stimulation/
6	(transcranial adj2 stimulat*).ti,ab.
7	or/5-6
8	(repeat* or repetitive or repetition or (high adj frequency) or high-frequency).ti,ab.
9	and/7-8
10	RTMS.ti,ab.
11	or/9-10
12	and/4,11
13	(ae or co).fs.
14	and/11,13
15	14 not 12
16	transcranial magnetic stimulation for treating depression.m_titl.
17	Antidepressant efficacy of high frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in.m_titl.
18	(Repetitive transcranial magnetic stimulation for treatment resistant depression a systematic review and metaanalysis).m_titl.

**Table A2.4 Website searches to identify relevant EBGs**

Search 1: Identification of relevant guidelines for Repetitive Transcranial Magnetic Stimulation (rTMS) for Depression using specific guideline-related websites		
Guideline Services	Results	Search
National Health and Medical Research Council (NHMRC)	<a href="http://www.nhmrc.gov.au">http://www.nhmrc.gov.au</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation  Australian Guidelines for the Treatment of Adults with Acute Stress Disorder and Posttraumatic Stress Disorder  <a href="http://www.nhmrc.gov.au/guidelines/publications/mh13-mh14-mh15-mh16">http://www.nhmrc.gov.au/guidelines/publications/mh13-mh14-mh15-mh16</a>
National Institute for Health and Clinical Excellence UK (NICE)	<a href="http://www.nice.org.uk">http://www.nice.org.uk</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation 1 reference from scanned search results  IPG242 Transcranial magnetic stimulation for severe depression <a href="http://publications.nice.org.uk/transcranial-magnetic-stimulation-for-severe-depression-ipg242">http://publications.nice.org.uk/transcranial-magnetic-stimulation-for-severe-depression-ipg242</a>
New Zealand Guideline Group (NZGG)	<a href="http://www.nzgg.org.nz/search">http://www.nzgg.org.nz/search</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Scottish Intercollegiate Guidelines Network (SIGN)	<a href="http://www.sign.ac.uk/search.html">http://www.sign.ac.uk/search.html</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Joanna Briggs Institute	<a href="http://www.joannabriggs.edu.au/">http://www.joannabriggs.edu.au/</a> Subscription service Login to CONNECT+   Subscribe to CONNECT+	Terms used: RTMS , Repetitive transcranial magnetic stimulation 1 of 3 references scanned  Depression: Assessment and Treatment Date: 03/02/2012 Version: 1.2 Lisa Kunde BA, BPsych (Hons)
Guidelines International Network	<a href="http://www.g-i-n.net">http://www.g-i-n.net</a>	Much cheaper, almost as good: decrementally cost-effective medical innovation <a href="http://www.ncbi.nlm.nih.gov/pubmed/19884627">http://www.ncbi.nlm.nih.gov/pubmed/19884627</a>
Guidelines Advisory Committee	<a href="http://www.gacguidelines.ca/">http://www.gacguidelines.ca/</a>	Scanned their list of Endorsed guidelines. 2 references Depression: Management of Mild Depression –  Depression: Management of Moderate to Severe Depression –
National Guideline Clearinghouse US (NGC)	<a href="http://guideline.gov/">guideline.gov/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation  5 references chosen <a href="#">Practice guideline for the treatment of patients with major depressive disorder, third edition. 1993 (revised 2010 Oct). NGC:008093</a> American Psychiatric Association -

		<p><u>Depression. The treatment and management of depression in adults.</u> 2004 (revised 2009 Oct). NGC:007598 National Collaborating Centre for Mental Health - National Government Agency [Non-U.S.].</p> <p><u>Major depression in adults in primary care.</u> 1996 Jan (revised 2011 May). [NGC Update Pending] NGC:008573 Institute for Clinical Systems Improvement -</p> <p>Expert Commentary:<u>Primary Care Depression Guidelines and Treatment Resistant Depression: Variations on an Important but Understudied Theme</u></p> <p><u>Practice parameters for the assessment and treatment of children and adolescents with depressive disorders.</u> 1998 (revised 2007). NGC:005924 American Academy of Child and Adolescent Psychiatry -</p>
TRIP Database	www.tripdatabase.com/	<p>Terms used: RTMS , Repetitive transcranial magnetic stimulation</p> <p>141 references downloaded to the Endnote database</p>
<b>Australian Government Websites containing Guidelines</b>		
Australian Institute of Health and Welfare	www.aihw.gov.au	<p>Terms used: RTMS , Repetitive transcranial magnetic stimulation</p> <p>4 references scanned</p> <p><a href="#">Prevention and management of depression (NHPA report on ... evaluation of Transcranial Magnetic Stimulation (TMS) as a possible alternative to electroconvulsive therapy (ECT).</a> Australian researchers have also played a ...</p>
Health Insite	www.healthinsite.gov.au/	<p>Terms used: RTMS , Repetitive transcranial magnetic stimulation</p> <p>Systematic Reviews of Treatments for Depression Links to summaries of systematic reviews of the evidence for the effectiveness of treatments for depression.</p> <p>Transcranial magnetic stimulation (TMS) for depression John Wiley and Sons~ Ltd. for The Cochrane Collaboration Jul 2001 Transcranial magnetic stimulation can either excite or inhibit cortical areas of the brain, depending on whether</p>
ACT Health	www.health.act.gov.au/	<p>Terms used: RTMS , Repetitive transcranial magnetic stimulation</p> <p>N/A</p>
NSW Health	www.health.nsw.gov.au/	<p>Terms used: RTMS , Repetitive transcranial magnetic stimulation</p>

		N/A
NT Department of Health and Community Services	<a href="http://www.health.nt.gov.au/">www.health.nt.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Queensland Health	<a href="http://www.health.qld.gov.au/">www.health.qld.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
SA Department of Health and Human Services	<a href="http://www.health.sa.gov.au/">www.health.sa.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Tasmanian Department of Health and Human Services	<a href="http://www.dhhs.tas.gov.au/">www.dhhs.tas.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Victorian Department of Human Services	<a href="http://www.dhs.vic.gov.au/">www.dhs.vic.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
WA Department of Health	<a href="http://www.jobs.health.wa.gov.au/">www.jobs.health.wa.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation <a href="#">CCRN News April 2011</a> rTMS: Potential new clinical applications
<b>Centres of Evidence Based Practice Websites</b>		
Western Australian Centre for Evidence Informed Healthcare Practice	<a href="http://wacebnm.curtin.edu.au">http://wacebnm.curtin.edu.au</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
<b>TAC/WSV relevant sites</b>		
Transport Accident Commission	<a href="http://www.tac.vic.gov.au/">www.tac.vic.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation:1 reference <a href="#">Traumatic Brain Injury Projects: Transcranial Magnetic Stimulation (TMS) Treatment in Depression ...</a>
Australian Transport Safety Bureau	<a href="http://www.atsb.gov.au/">http://www.atsb.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Road Safety Victoria (TAC)	<a href="http://www.tacsafety.com.au">http://www.tacsafety.com.au</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
WorkSafe Victoria	<a href="http://www.worksafe.vic.gov.au/">www.worksafe.vic.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Traffic Injury Research Foundation	<a href="http://www.trafficinjuryresearch.com/">www.trafficinjuryresearch.com/</a>	Projects scanned N/A

Motor Accidents Authority NSW	<a href="http://www.maa.nsw.gov.au">http://www.maa.nsw.gov.au</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
WorkSafe British Columbia	<a href="http://www.worksafebc.com/">http://www.worksafebc.com/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation <a href="#">Chronic Pain Treatments: What is the Evidence?</a> WorkSafeBC Evidence-Based Practice Group <a href="http://www.worksafebc.com/health_care_providers/Assets/PDF/poster-presentations/ChronicPainTreatmentsEvidence.pdf">http://www.worksafebc.com/health_care_providers/Assets/PDF/poster-presentations/ChronicPainTreatmentsEvidence.pdf</a>
Accident Compensation Corporation	<a href="http://www.acc.co.nz/">www.acc.co.nz/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Pain Treatment Topics	<a href="http://pain-topics.org/">http://pain-topics.org/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
The George Institute	<a href="http://www.georgeinstitute.org.au/">www.georgeinstitute.org.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Injury Research and Prevention Unit	<a href="http://www.injuryresearch.bc.ca/">www.injuryresearch.bc.ca/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
The Brain Trauma Foundation	<a href="http://www.braintrauma.org/">www.braintrauma.org/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Safer Roads	<a href="http://www.rta.nsw.gov.au/">http://www.rta.nsw.gov.au/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Rail Accident Investigation Branch	<a href="http://www.raib.gov.uk/">www.raib.gov.uk/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Oslo Sports Trauma Research Centre	<a href="http://www.klokavskade.no/en/">www.klokavskade.no/en/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
Oregon Evidence-Based Practice Centre	<a href="http://www.ohsu.edu/epc/">www.ohsu.edu/epc/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation 11 references retrieved N/A
Injury Prevention Network of Aotearoa New Zealand	<a href="http://ipnanz.org.nz/">ipnanz.org.nz/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A



Trauma Centre at Justice Resource Centre	<a href="http://www.traumacenter.org/">www.traumacenter.org/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
The DANA Foundation	<a href="http://www.dana.org/">www.dana.org/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation 11 references retrieved. 2 to review <a href="#">Study Supports Transcranial Magnetic Stimulation to Treat Depression</a>  <a href="http://www.dana.org/news/features/detail.aspx?id=28882">http://www.dana.org/news/features/detail.aspx?id=28882</a>  Biomarkers and the Future of Treatment for Depression  <a href="http://www.dana.org/news/cerebrum/detail.aspx?id=38554">http://www.dana.org/news/cerebrum/detail.aspx?id=38554</a>
European Association for Injury Prevention and Safety Promotion	<a href="http://www.eurosafe.eu.com/">http://www.eurosafe.eu.com/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation 2 references retrieved N/A
New Zealand Injury Prevention strategy	<a href="http://www.nzips.govt.nz/">www.nzips.govt.nz/</a>	Search Resources/ Publications 0
NHS Health at Work	<a href="http://www.nhshealthatwork.co.uk/">www.nhshealthatwork.co.uk/</a>	Terms used: RTMS , Repetitive transcranial magnetic stimulation N/A
The Canadian Association of Road Safety Professionals	<a href="http://www.carsp.ca/">www.carsp.ca/</a>	Search Publications
<b>Search 2: Identification of relevant studies for rTMS for Depression using Google</b>		
Find web pages that have <b>all these words</b>	depression	
Find web pages that have this <b>exact wording or phrase</b>	repetitive transcranial magnetic stimulation	
Find web pages that have <b>any of these words</b>	guideline random	
Find web pages that are in the <b>site or domain</b>	.edu; .org; .gov; .net	
Limits	English	

## Appraisal

Appraisal was undertaken in steps:

1. The most recent review (evidence-based guideline, systematic review or HTA) was assessed for quality using standard appraisal criteria.
2. If found to be of high quality, it was cross checked against the other available reviews to compare scope and consistency of findings.
3. If found not to be of high quality, the next most recent was appraised and the above process repeated.

## Quality

Evidence-based guidelines and systematic reviews were appraised using standard criteria by a single reviewer in consultation with colleagues as required. RCTs were also appraised using standard criteria by a single reviewer in consultation with colleagues as required. Details of quality appraisals are included in Appendix 5.

## Data Extraction

Data on characteristics of the studies were extracted and summarised.

## APPENDIX 3: LIST OF INCLUDED STUDIES

### Primary Studies

#### Randomised Controlled Trials

1. Aguirre I, Carretero B, Ibarra O, Kuhalainen J, Martinez J, Ferrer A, et al. Age predicts low-frequency transcranial magnetic stimulation efficacy in major depression. *J Affect Disord*. 2011;130(3):466-9.
2. Anderson IM, Delvai NA, Ashim B, Ashim S, Lewin C, Singh V, et al. Adjunctive fast repetitive transcranial magnetic stimulation in depression. *Br J Psychiatry*. 2007;190:533-4.
3. Avery DH, Claypoole K, Robinson L, Neumaier JF, Dunner DL, Scheele L, et al. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *J Nerv Ment Dis*. 1999;187(2):114-7.
4. Avery DH, Holtzheimer IPE, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry*. 2006;59(2):187-94.
5. Avery DH, Holtzheimer IPE, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. Transcranial magnetic stimulation reduces pain in patients with major depression: A sham-controlled study. *J Nerv Men Dis*. 2007;195(5):378-81.
6. Bares M, Kopecek M, Novak T, Stopkova P, Sos P, Kozeny J, et al. Low frequency (1-Hz), right prefrontal repetitive transcranial magnetic stimulation (rTMS) compared with venlafaxine ER in the treatment of resistant depression: a double-blind, single-centre, randomized study. *J Affect Disord*. 2009;118(1-3):94-100.
7. Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biol Psychiatry*. 2000;47(4):332-7.
8. Bortolomasi M, Minelli A, Fuggetta G, Perini M, Comencini S, Fiaschi A, et al. Long-lasting effects of high frequency repetitive transcranial magnetic stimulation in major depressed patients. *Psychiatry Res*. 2007;150(2):181-6.
9. Boutros NN, Gueorguieva R, Hoffman RE, Oren DA, Feingold A, Berman RM. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. *Psychiatry Res*. 2002;113(3):245-54.
10. Bretlau LG, Lunde M, Lindberg L, Unden M, Dissing S, Bech P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry*. 2008;41(2):41-7.
11. Chistyakov AV, Kaplan B, Rubichek O, Kreinin I, Koren D, Feinsod M, et al. Antidepressant effects of different schedules of repetitive transcranial magnetic stimulation vs. clomipramine in patients with major depression: relationship to changes in cortical excitability. *Int J Neuropsychopharmacol*. 2005;8(2):223-33.
12. Chistyakov AV, Kaplan B, Rubichek O, Kreinin I, Koren D, Hafner H, et al. Effect of electroconvulsive therapy on cortical excitability in patients with major depression: a transcranial magnetic stimulation study. *Clin Neurophysiol*. 2005;116(2):386-92.
13. Dannon PN, Dolberg OT, Schreiber S, Grunhaus L. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals - Preliminary report. *Biol Psychiatry*. 2002;51(8):687-90.

14. Eichhammer P, Kharraz A, Wiegand R, Langguth B, Frick U, Aigner JM, et al. Sleep deprivation in depression - Stabilizing antidepressant effects by repetitive transcranial magnetic stimulation. *Life Sci.* 2002;70(15):1741-9.
15. Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *Am J Psychiatry.* 2007;164(1):73-81.
16. Eschweiler GW, Wegerer C, Schlotter W, Spandl C, Stevens A, Bartels M, et al. Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychiatry Res.* 2000;99(3):161-72.
17. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry.* 2006;163(1):88-94.
18. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arc Gen Psychiatry.* 2003;60(10):1002-8.
19. Fitzgerald PB, Hoy K, McQueen S, Herring S, Segrave R, Been G, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol.* 2008;28(1):52-8.
20. Fitzgerald PB, Hoy KE, Herring SE, McQueen S, Peachey AVJ, Segrave RA, et al. A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. *J Affect Disord.* 2012;139(2):193-8.
21. Garcia-Toro M, Mayol A, Arnillas H, Capllonch I, Ibarra O, Crespi M, et al. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *J Affect Disord.* 2001;64(2-3):271-5.
22. Garcia-Toro M, Pascual-Leone A, Romera M, Gonzalez A, Mico J, Ibarra O, et al. Prefrontal repetitive transcranial magnetic stimulation as add on treatment in depression. *J Neurol Neurosurg Psychiatry.* 2001;71(4):546-8.
23. Garcia-Toro M, Salva J, Daumal J, Andres J, Romera M, Lafau O, et al. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. *Psychiatry Res.* 2006;146(1):53-7.
24. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: A sham-controlled randomized trial. *Arch Gen Psychiatry.* 2010;67(5):507-16.
25. George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry.* 1997;154(12):1752-6.
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## Controlled Clinical Trials

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## Synthesised Studies

### Systematic Reviews and Meta Analyses

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### Evidence-Based Guidelines

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## APPENDIX 4: SUMMARY OF SYNTHESISED STUDIES

Table A4.1 summary of included studies

1 <sup>st</sup> author, year, title	Inclusion, Exclusion criteria ( for P.I.C.O)	Study design	Conclusion/Recommendation	Recommendation category
<b>Aare 2003</b> Efficacy of repetitive transcranial magnetic stimulation in depression: a review of the evidence	<b>POPULATION/CLINICAL INDICATION</b> Patients with depressive disorders	SR	rTMS not recommended as a standard treatment for depression.	<i>Negative, rTMS less effective than ECT.</i>
	<b>INTERVENTION and COMPARATORS</b> Sham TMS or ECT			
	<b>OUTCOMES:</b> Efficacy			
<b>Allan 2011</b> Transcranial Magnetic Stimulation in the Management of Mood Disorders.	<b>POPULATION/CLINICAL INDICATION</b> Mood Disorders	SR	Optimum treatment protocol yet to be discovered. No evidence for lasting treatment effects beyond 12 weeks.	<i>Inconclusive</i>
	<b>INTERVENTION and COMPARATORS</b> Sham TMS or ECT			
	<b>OUTCOMES:</b> Efficacy			
<b>Coutourier 2005</b> Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis	<b>POPULATION/CLINICAL INDICATION</b> MDD	SR	No significant difference between rTMS and sham treatment. May be due to differences in study protocol. Most effective combination of parameters for rTMS not yet established.	<i>Neutral -no difference between rTMS and Sham rTMS</i>
	<b>INTERVENTION and COMPARATORS</b> Sham TMS			
	<b>OUTCOMES:</b> Efficacy			
<b>Gaynes 2011</b> Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33	<b>POPULATION/CLINICAL INDICATION</b> TRD	SR	rTMS more effective than sham for treatment resistant depression	<i>Positive for rTMS vs Sham Inconclusive evidence for the efficacy of rTMS compared with ECT.</i>
	<b>INTERVENTION and COMPARATORS</b> Sham rTMS or ECT			
	<b>OUTCOMES:</b>			
<b>Gross 2007</b>	<b>POPULATION/CLINICAL INDICATION</b> MDD	SR	Recent clinical trials of rTMS on depression induced a larger	<i>Positive</i>

Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies.	<b>INTERVENTION and COMPARATORS</b> Various frequency of TMS or Sham  <b>OUTCOMES:</b> Comparison of efficacy between late and early studies of rTMS		effect size when compared with the initial studies from Martin et al.	
<b>Herrmann 2006</b> Transcranial magnetic stimulation.	<b>POPULATION/CLINICAL INDICATION</b> MDD or bipolar  <b>INTERVENTION and COMPARATORS</b> Sham TMS  <b>OUTCOMES:</b> Efficacy	SR	rTMS is more effective in the treatment of depression than sham rTMS, with a medium-sized effect size. Studies are heterogeneous and therefore difficult to determine accurately the effect of rTMS compared to sham rTMS. No compelling evidence of the most effective parameters.	<i>Positive – rTMS more effective than Sham rTMS</i>
<b>Herrmann 2009</b> Transcranial magnetic stimulation.	<b>POPULATION/CLINICAL INDICATION</b> MDD or Bipolar  <b>INTERVENTION and COMPARATORS</b> Sham TMS  <b>OUTCOMES:</b> Efficacy and NNTS	SR	Patients treated with rTMS more likely to show a clinical response than patients treated with sham treatment. Differences between rTMS and Sham disappear at follow up.	<i>Positive – rTMS more effective than Sham rTMS Neutral for long term efficacy</i>
<b>Holtzheimer 2001</b> A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. Psychopharmacology bulletin.	<b>POPULATION/CLINICAL INDICATION</b> MDD  <b>INTERVENTION and COMPARATORS</b> SHAM TMS  <b>OUTCOMES:</b> Efficacy	SR	Results of meta analysis support the conclusion that rTMS has real antidepressant effects that can be large at times but are generally modest. There is variability in the study outcomes that cannot be explained by sampling error alone.	<i>Positive- rTMS more effective than Sham rTMS</i>
<b>Kennedy 2009</b> Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major	<b>POPULATION/CLINICAL INDICATION</b> MDD  <b>INTERVENTION and COMPARATORS</b> Sham TMS  <b>OUTCOMES:</b>	EBG	There are some studies to suggest that rTMS is better than sham treatment but there is little evidence to suggest that rTMS is more effective than ECT.	<i>Positive - rTMS compared to Sham. Insufficient evidence to suggest rTMS is more effective than ECT.</i>

depressive disorder in adults.	Efficacy			
<b>Kozel 2002</b> Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression.	<b>POPULATION/CLINICAL INDICATION</b> Depression or depressive disorder <b>INTERVENTION and COMPARATORS</b> rTMS of left prefrontal cortex vs sham <b>OUTCOMES:</b> Efficacy	SR	Double blind published rTMS literature to date supports the use of left prefrontal rTMS to improve depressive symptoms.	<i>Positive- Left prefrontal rTMS more effective than sham</i>
<b>Lam 2008</b> Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis.	<b>POPULATION/CLINICAL INDICATION</b> TRD <b>INTERVENTION and COMPARATORS</b> rTMS vs Sham <b>OUTCOMES:</b> Efficacy and NNT	SR	rTMS with short treatment duration (1-4) weeks has clear AD effects and is well-tolerated, but the overall response and remission rates are low and it is unclear whether the effects are sustained.	<i>Insufficient evidence to show rTMS is more effective than sham long term.</i> <i>Positive for short term efficacy</i>
<b>Martin 2003</b> Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis.	<b>POPULATION/CLINICAL INDICATION</b> Any diagnosis of depression <b>INTERVENTION and COMPARATORS</b> rTMS vs Sham <b>OUTCOMES:</b> Efficacy	SR	Insufficient evidence to suggest that rTMS is effective in the treatment of depression. Studies that tested patients two weeks post intervention showed that any difference between the two groups has disappeared.	<i>Insufficient evidence to draw conclusions</i>
<b>McNamara 2001</b> Transcranial magnetic stimulation for depression and other psychiatric disorders	<b>POPULATION/CLINICAL INDICATION</b> MDD <b>INTERVENTION and COMPARATORS</b> rTMS various methods vs Placebo <b>OUTCOMES:</b> Efficacy and NNT	SR	rTMS effective treatment for depression but further studies are needed to determine if rTMS is as effective as ECT.	<i>Neutral /Insufficient-rTMS is effective for depression but more evidence is needed to determine its effectiveness compared with ECT.</i>
<b>Medical Advisory 2004</b> Repetitive transcranial magnetic stimulation for	<b>POPULATION/CLINICAL INDICATION</b> MDD <b>INTERVENTION and COMPARATORS</b>	SR	Some early meta-analyses suggested that rTMS may be effective for the treatment of MDD (for treatment resistant MDD or as an add-on to pharmacotherapy for patients who are not specifically	<i>Positive</i>

the treatment of major depressive disorder: an evidence-based analysis	rTMS vs sham, rTMS vs ECT, rTMS vs drugs, rTMS vs psychotherapy		defined as treatment resistant). There are however several crucial methodological considerations and limitations in the included studies that were not critically assessed.	
	<b>OUTCOMES:</b> Efficacy and cost effectiveness			
<b>MSAC 2008</b> Repetitive transcranial magnetic stimulation as a treatment for major depression.	<b>POPULATION/CLINICAL INDICATION</b> MDD		ECT vs rTMS; No significant difference between the response rates of the rTMS group and the ECT group. Overall rTMS appeared to be less effective than ECT in the treatment of major depression, although this was not statistically significant.	<i>Inconclusive evidence to determine long term effect</i>
	<b>INTERVENTION and COMPARATORS</b> rTMS vs ECT, rTMS vs Sham.		rTMS vs Sham; In the studies that had a follow-up period, the response rate was not maintained by most patients (>75%) after 3 months.	
	<b>OUTCOMES:</b> Efficacy			
<b>Minichino 2012</b> ECT, rTMS, and deep TMS in pharmacoresistant drug-free patients with unipolar depression: A comparative review	<b>POPULATION/CLINICAL INDICATION</b> TRD and MDD	SR	Deep TMS is the only therapy that provides substantial improvement in both depressive symptoms and cognitive performances but it has poor tolerability. rTMS provides better tolerability than ECT but its therapeutic efficacy is lower.	<i>Negative-Therapeutic efficacy of rTMS lower than ECT.</i>
	<b>INTERVENTION and COMPARATORS</b> rTMS vs deepTMS vs ECT			
	<b>OUTCOMES:</b> Efficacy and tolerability			
<b>NICE 2007</b> Transcranial magnetic stimulation for severe depression.	<b>POPULATION/CLINICAL INDICATION</b> MDD	SR	rTMS is a novel treatment with uncertainty around its efficacy and safety.	<i>Inconclusive</i>
	<b>INTERVENTION and COMPARATORS</b> Sham TMS and ECT			
	<b>OUTCOMES:</b> Efficacy			
<b>Rodriguez-Martin 2009</b> Transcranial magnetic stimulation for treating depression.	<b>POPULATION/CLINICAL INDICATION</b> depression diagnosed by recognised criteria	SR	Overall the analysis showed that there was no strong evidence for possible efficacy of rTMS for the treatment of depression.	<i>Inconclusive- no strong evidence for the use of rTMS for the treatment of depression.</i>
	<b>INTERVENTION and COMPARATORS</b> rTMS vs nothing rTMS v sham rTMS vs psychotherapy rTMS vs psychotropic drugs rTMS vs any other treatment			

	<b>OUTCOMES:</b> Efficacy and safety			
<b>Schutter 2010</b> Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder	<b>POPULATION/CLINICAL INDICATION</b> MDD <b>INTERVENTION and COMPARATORS</b> slow frequency rTMS vs sham <b>OUTCOMES:</b> Efficacy		Findings suggest that slow frequency rTMS can improve MDD and additional clinical trials aimed at optimising the treatment are worthwhile.	<i>Positive for rTMS compared to sham rTMS for the treatment of depression.</i>
<b>Schutter 2009</b> Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis	<b>POPULATION/CLINICAL INDICATION</b> MDD without psychotic features <b>INTERVENTION and COMPARATORS</b> High Frequency rTMS vs Sham <b>OUTCOMES:</b> Efficacy	SR	Fast frequency rTMS over the left DLPFC is superior to sham and may be as effective as at least a subset of antidepressant medications. It is well tolerated by patients with few side effects. Limitations to trials due to insufficient blinding.	<i>Positive – rTMS (left DLPFC) more effective than sham treatment.</i>
<b>Slotema 2010</b> Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders.	<b>POPULATION/CLINICAL INDICATION</b> mixed psych disorders with subgroup of 'depression' <b>INTERVENTION and COMPARATORS</b> rTMS vs sham rTMS vs ECT <b>OUTCOMES:</b> Efficacy	SR	Repetitive TMS is more effective than sham treatment in the treatment of depression but less effective than ECT. rTMS appears to be more effective when given as a monotherapy.	<i>Positive- rTMS more effective than Sham. Negative –rTMS compared to ECT.</i>

**Table A4.2 AMSTAR Rating of Included Synthesized Studies**

AMSTAR checklist items	Aare 2003	Allan 2011	Coutourier 2005	Gaynes 2011	Gross 2007	Herrmann 2006	Herrmann 2009	Holtzheimer 2001	Kennedy 2009	Kozel 2002	Lam 2008
1. Was an 'a priori' design provided?	X	X	X	✓	X	X	X	X	X	X	X
2. Was there duplicate study selection and data extraction?	X	X	X	✓	X	X	X	X	X	X	✓
3. Was a comprehensive literature search performed?	✓	X	✓	✓	X	X	✓	X	✓	✓	✓
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	✓	X	✓	✓	X	X	X	✓	X	X	X
5. Was a list of studies (included and excluded) provided?	✓	X	✓	✓	X	X	X	X	X	X	✓
6. Were the characteristics of the included studies provided?	X	X	✓	✓	✓	X	X	✓	X	✓	✓
7. Was the scientific quality of the included studies assessed and documented?	X	X	X	✓	✓	X	X	X	X	X	✓
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	X	X	X	✓	✓	X	X	X	X	X	✓
9. Were the methods used to combine the findings of studies appropriate?	NA	✓	✓	✓	✓	✓	✓	✓	NA	✓	✓
10. Was the likelihood of publication bias assessed?	NA	✓	X	✓	✓	X	✓	X	NA	✓	✓
11. Was the conflict of interest included?	X	X	X	✓	X	X	X	X	X	X	X
<b>AMSTAR score</b>	<b>3/9</b>	<b>2/11</b>	<b>5/11</b>	<b>11/11</b>	<b>5/11</b>	<b>1/11</b>	<b>3/11</b>	<b>3/11</b>	<b>1/9</b>	<b>4/11</b>	<b>8/11</b>



**Table A4.3 AMSTAR rating of included systematic Reviews - Continued.**

AMSTAR checklist items	Martin 2003	McNamara 2001	Medical Advisory 2004	MSAC 2008	Minichino 2012	NICE 2007	Rodriguez-Martin 2009	Schutter 2009	Schutter 2010	Slotema 2010
1. Was an 'a priori' design provided?	X	X	✓	✓	X	✓	✓	X	X	X
2. Was there duplicate study selection and data extraction?	X	X	X	✓	X	X	✓	X	X	X
3. Was a comprehensive literature search performed?	✓	✓	✓	✓	X	✓	✓	✓	X	✓
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	✓	✓	✓	✓	X	✓	✓	X	X	X
5. Was a list of studies (included and excluded) provided?	✓	X	X	✓	X	X	✓	X	X	X
6. Were the characteristics of the included studies provided?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
7. Was the scientific quality of the included studies assessed and documented?	✓	X	✓	✓	X	X	✓	✓	✓	X
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	✓	X	✓	✓	X	X	✓	✓	✓	✓
9. Were the methods used to combine the findings of studies appropriate?	✓	✓	NA	✓	✓	NA	✓	✓	✓	✓
10. Was the likelihood of publication bias assessed?	X	X	NA	X	X	NA	✓	✓	X	X
11. Was the conflict of interest included?	X	X	X	X	X	X	X	X	X	X
<b>AMSTAR score</b>	<b>7/11</b>	<b>4/11</b>	<b>6/9</b>	<b>9/11</b>	<b>2/11</b>	<b>4/9</b>	<b>10/11</b>	<b>6/11</b>	<b>4/11</b>	<b>3/11</b>

## APPENDIX 5: SUMMARY OF PRIMARY STUDIES

**Table A5.1 Primary studies of ECT vs rTMS for depression (studies included in Gaynes)**

STUDY	Rosa 2006	Grunhaus 2003	McLoughlin 2007, Eranti 2007, and Knapp 2008
<b>PATIENTS</b>	N=42 Adult population with TRD. Unipolar depressive disorder (Ham-D $\geq 22$ ) w/o psychotic symptoms	N= 40 Adult population. Unipolar major depression (DSM IV). HAM-D $\geq 18$	N= 46 Adults referred for ECT due to major depressive episode.
<b>TREATMENT FAILURE</b>	Patients specifically had two or more prior treatment failures with medications	Patients had one or more treatment failures with medications	Prior treatment failure not specified but clinical situation suggests high probability of patients having two or more prior treatment failures with antidepressants
<b>INPATIENT OR OUTPATIENT SETTING</b>	Inpatient and outpatient	Inpatient and outpatient	Inpatient
<b>INTERVENTION &amp; COMPARATORS</b>	<p>rTMS vs. ECT</p> <p><u>Duration</u> Active txt 2-4wks (rTMS pts not responding after 2 wks switched over to ECT).</p> <p>rTMS: <u>Parameters:</u> Frequency (Hz):10 Motor threshold (%): 100 <u>Duration:</u> Number of trains: 25 Length of train (seconds): 10 Inter-train interval: 20 Pulses per session: 2500 Total number of sessions: 20 over 4 wks</p> <p>ECT: % receiving bilateral: NR Intensity: 4.5 times threshold Number of sessions (range, mean, SD): 10(1.5)</p>	<p>rTMS vs. ECT</p> <p><u>Duration</u> 4 weeks of treatment</p> <p>rTMS: <u>Parameters:</u> Frequency (Hz): 10 Motor threshold (%):90 <u>Duration:</u> Number of trains: 20 Length of train (seconds): 6 Inter-train interval:60 Pulses per session:1200 Total number of sessions: 5/ wk over 4 wks</p> <p>ECT: % receiving bilateral: 35 Intensity: 2.5 times seizure threshold Number of sessions (range, mean, SD): 10.25 (3.1)</p>	<p>rTMS vs. ECT</p> <p><b>rTMS</b> <u>Parameters:</u> Frequency (Hz): 10 Motor threshold (%):110 Number of trains: 20 <u>Duration:</u> Length of train (seconds): 5 Inter-train interval: 55 Pulses per session: 1000 Total number of sessions:15</p> <p><b>ECT:</b> • % receiving bilateral: 82 Intensity: 1.5 <math>\times</math> ST for bilateral frontotemporal ECT and 2.5 <math>\times</math> ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5</p> <p><u>Duration</u> Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow up at 6 months</p>
<b>TREATMENT OR REMISSION MAINTENANCE?</b>	Treatment	Treatment	Treatment
<b>ON ANTIDEPRESSANTS OR DRUG FREE?</b>	ADs, antipsychotics, mood stabilizers were discontinued while anti anxiety meds were allowed/initiated as	Patients in both groups required to taper psychotropic medications. Only lorazepam allowed regularly,	Patients continued their usual medical care and stable psychotropic medications were allowed.

	needed	benzodiazepine allowed only for sleep induction	
<b>PRIMARY OUTCOMES</b>	Depression Improvement. HAMD-17 endpoint score, mean (SD) at four weeks. Clinical Global Impression	Improvement in depression. HAMD-17 end point score, mean (SD).	Improvement in depression measured by HAMD.
<b>ADVERSE EVENTS</b>	Suicidality, % ECT: 10.0 rTMS: 9.1 rTMS: 2 pts developed new psychological symptoms (i.e., 1 = dissociative state, 1 = hypomanic symptoms) and were removed from study. Withdrawals due to adverse events, % ECT: NR rTMS: 9.1	Overall, % ECT: NR "the ECT group was handled clinically and no special recording of side effects was done rTMS: NR Headache, % ECT: NR rTMS: 15.0 Sleep disturbance: ECT: NR rTMS: 10%	No adverse events were reported.
<b>RESULTS</b>	<p><b>Responders, n (%)</b> ECT: 6 (20) rTMS: 10 (45) P = 0.35</p> <p><b>Remitters, n (%)</b> Ham-D17 ≤ 7 ECT: 3 (15) rTMS: 2 (9) P = 0.65</p> <p>Instrument CGI Endpoint score, mean (SD) 2wk ECT: 4.0 (1.0) rTMS: 3.7 (1.1) 4wk ECT: 3.2 (1.5) rTMS: 3.1 (1.3)</p>	<p>HAM-D 17 <b>Endpoint score, mean (SD):</b> At week 2 ECT: 15.9 (6.6) rTMS: 14.7 (8.8) At week 4 ECT: 13.2 (6.6) rTMS: 13.3 (9.2)</p> <p><b>Change, mean (SD)</b> At week 2 ECT: -9.6 rTMS: -9.7 At week 4 ECT: -12.3 rTMS: -11.1</p> <p><b>Responders, n</b> Response defined as a decrease ≥ 50% or HAM-D17 score ≤ 10 and a GAF rating ≥ 60 ECT: 12 (60%) rTMS: 11 (55%) P = NS</p> <p><b>Remitters, n</b> HAM-D17 ≤ 8 ECT: 6 (30%)</p>	<p>HAM-D 17 <b>Analyzed n</b> ECT: 22 rTMS: 23 Endpoint score, mean (SD) End of treatment ECT: 10.7 rTMS: 18.5 P = 0.002, effect size of 1.44</p> <p><b>Follow-up at 6 months</b> ECT: NR rTMS: NR P = 0.93</p> <p>Change, mean (SD) End of treatment ECT: -14.1 rTMS: -5.4 P = 0.017</p> <p><b>Responders, n</b> <b>End of treatment</b> ECT: 13 (59.1%) rTMS: 4 (17.4%)</p>

		rTMS: 6 (30%) P = NS	<p>P = 0.005</p> <p><b>Remitters, n</b> <b>HAM-D ≤ 8</b> <b>End of treatment</b> ECT: 13 (59.1%) rTMS: 4 (17.4%) P = 0.005</p> <p>Follow-up at 6 months* ECT: 6 (27.4%) rTMS: 2 (8.7%)</p> <p>*only 12 ECT remitters followed after End of txt</p>
<b>CONCLUSIONS</b>	Efficacy for rTMS is similar to that of ECT. No statistical difference between rTMS and ECT.	The overall response rate was 58% (23 out of 40 patients responded to treatment). In the ECT group, 12 responded and eight did not; in the rTMS group, 11 responded and nine did not. Thus, patients responded as well to either ECT or rTMS.	rTMS is less effective than ECT for the treatment of depression.
<b>COMMENTS</b>	Country =Brazil	Country= Israel	Country = United Kingdom

**Table A5.2 Primary studies of ECT vs rTMS for depression (studies NOT included in Gaynes)**

STUDY		Keshtkar 2011	
<b>PATIENTS</b>		n = 73 patients with refractory major depressive disorder (DSM-IV) Patients had already received 2 full courses of drug therapy during the current episode. They were all diagnosed as refractory cases.	
<b>TREATMENT FAILURE</b>		Patients specifically had two or more prior treatment failures with medications	
<b>INPATIENT OR OUTPATIENT SETTING</b>		Inpatient/outpatient status not clearly reported	
<b>INTERVENTION &amp; COMPARATORS</b>		rTMS vs ECT  Parameters: 90% MT Location: LDPC Duration: 10 days, 10 min sessions, 408 stimulations per session.  ECT bilateral for 10 sessions (3 per week), seizure duration at least 20 seconds	
<b>TREATMENT OR REMISSION MAINTENANCE?</b>		Treatment	
<b>ON ANTIDEPRESSANTS OR DRUG FREE?</b>		All patients on medication	
<b>PRIMARY OUTCOMES</b>		BDI & HDRS	
<b>ADVERSE EVENTS</b>		No significant adverse effects (i.e., seizure, mania) observed. Headache (n=1 rTMS group) decreased levels of consciousness and withdrawal from study (n=2 ECT group)	
<b>RESULTS</b>		Both ECT and rTMS significantly improved depression and suicidal behavior scores. However, ECT reduced depression and suicidal behavior scores more than rTMS.	
		ECT Mean (SD)	rTMS Mean (SD)
BDI	pre	34.8 (9.9)	34.0 (9.6)
	post	17.9 (8.3)	26.5 (9.2)
HDRS	pre	25.8 (6.1)	21.0 (7.5)
	post	8.4 (6.1)	15.1 (5.6)
BDI suicide	pre	1.4 (1.0)	1.5 (0.8)
	post	0.5 (0.7)	1.2 (0.9)
HDRS suicide	pre	2.3 (1.1)	1.9 (1.3)
	Post	0.3 (0.5)	1.4 (1.2)
<b>CONCLUSIONS</b>		Both treatments improved MDD in the short term, but the antidepressant efficacy of ECT was greater than rTMS. Moreover, ECT led to greater reductions in suicidal behavior than rTMS. Until strong evidence for the safety and efficacy of rTMS is available, further studies are needed to compare ECT and rTMS in terms of the long-term relapse rate and quality of life.	
<b>COMMENTS</b>		Country = Iran	

**Table A5.3 Primary studies of rTMS vs Sham rTMS for depression (Studies included in Gaynes)**

STUDY	Boutros 2002	Garcia-Toro 2001	Garcia-Toro 2006
<b>PATIENTS</b>	N=21 Major Depression (HAM-D25 $\geq$ 20)	N=40 Unipolar depression (DSM IV)	N=30 MDD, unipolar
<b>TREATMENT FAILURE</b>	Patients specifically had two or more prior treatment failures with medications	Patients specifically had two or more prior treatment failures with medications	Patients specifically had two or more prior treatment failures with medications
<b>INPATIENT OR OUTPATIENT SETTING</b>	Outpatient	Inpatient/outpatient status not clearly reported	Outpatient
<b>INTERVENTION &amp; COMPARATORS</b>	<p>rTMS:</p> <ul style="list-style-type: none"> <li>• Frequency (Hz):20</li> <li>• Motor threshold (%):80</li> <li>• Number of trains: 20</li> <li>• Length of train (seconds): 2</li> <li>• Inter-train interval: 58</li> <li>• Pulses per session:800</li> <li>• Total number of sessions: 10 over 10 days</li> </ul> <p>Sham:</p> <ul style="list-style-type: none"> <li>• Coil angled 90 degrees to scalp</li> <li>• 1 wing of figure 8 touching scalp</li> </ul>	<p>rTMS:</p> <ul style="list-style-type: none"> <li>• Frequency (Hz): 20</li> <li>• Motor threshold (%):90</li> <li>• Number of trains: 30</li> <li>• Length of train (seconds): 2</li> <li>• Inter-train interval: 20-40</li> <li>• Pulses per session:1200</li> <li>• Total number of sessions: 10 in 10 days</li> </ul> <p>Sham:</p> <ul style="list-style-type: none"> <li>• Edge was placed at 90 degrees</li> </ul>	<p>rTMS:</p> <ul style="list-style-type: none"> <li>• Frequency (Hz):1</li> <li>• Motor threshold (%): 110</li> <li>• Number of trains: 30</li> <li>• Length of train (seconds): 60</li> <li>• Inter-train interval:</li> <li>• Pulses per session:1800</li> <li>• Total number of sessions: 10 in 2 wks</li> </ul> <p>High</p> <ul style="list-style-type: none"> <li>• Frequency (Hz):20</li> <li>• Motor threshold (%):110</li> <li>• Number of trains: 30</li> <li>• Length of train (seconds): 2</li> <li>• Inter-train interval: 20+5</li> <li>• Pulses per session: 1200</li> <li>• Total number of sessions: 10 in 2 wks</li> </ul> <p>Sham</p> <ul style="list-style-type: none"> <li>• Same but with coil angling 45 degrees away from scalp</li> </ul>
<b>TREATMENT OR REMISSION MAINTENANCE?</b>	Treatment (augment current therapies)	Treatment (augment current therapies)	Treatment (augment current therapies)
<b>ON ANTIDEPRESSANTS OR DRUG FREE?</b>	Pts allowed to continue all current psychotropic meds	<p><i>Medications allowed</i></p> <ul style="list-style-type: none"> <li>• stable treatment with antidepressants</li> <li>• most pts taking benzodiazepines</li> </ul>	All pts continued (failed) AD medication and other psychotropic meds
<b>PRIMARY OUTCOMES</b>	HAM-D25	HAM-D 17 BDI CGI-S	HAM-D 21 CGI-S
<b>ADVERSE EVENTS</b>	Adverse Events Overall, %	Additional Comments:	Not reported

	<p>G1: (% of pts reporting AEs) 66.7 G2: 55.6 Cognitive impairment, % Difficulty concentrating (phase 1 only) G1: 25 G2: NR Headache, % "most frequent complaint" % NR Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhoea: 8.3%, NR</p>	<p>"most frequency side effects were scalp discomfort and slight and transitory headaches in approximately a third of cases, nearly all from stimulation group"</p>	
<b>RESULTS</b>	<p><i>HAM-D 25</i> Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11 Change, mean (SD) G1: -11.75 G2: -6.22 <i>P</i> = NS Responders, n Defined as 30% improvement on Ham-D 25 G1: 7 G2: 2 Responders, n (%) Defined as 50% improvement on Ham-D 25 G1: 3 G2: 2 <i>Relapse</i> Defined as ≥ baseline</p>	<p><i>HAM-D 17</i> N analyzed G1: 17 G2: 18  Change, mean (SD) At week 1 G1: -4.52(4.66) G2: -2.87(4.27) <i>P</i> = 0.297  At week 2 G1: -7.05 (5.66) G2: -1.77(3.78) <i>P</i> = 0.003  2 week follow up G1: -8.17(7.69) G2: -2.05(6.07) <i>P</i> = 0.013  Responders, n (%) G1: 5 (25)</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD)  At week 1 G1: 23.6 (7.04) G2: 24.1 (7.91) G3: 21.6 (3.10)  At week 2 G1: 23.6 (7.79) G2: 20.10 (8.18) G3: 18.10 (6.15)  Follow up 2 weeks post treatment G1: 23.67 (5.55) G2: 20.88 (7.26) G3: 16.9 (7.0)  Change, mean (% change) At 1 week G1: -1.5 (-5.9%) G2: -3.2 (-13.27%) G3: -3.4 (-13.6%)</p>

	<p>score <math>\pm</math> 10%</p> <p>Of 6 active treatment responders included in 20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in the 20-week follow-up, 1 relapsed.</p>	<p>G2: 1 (5) P=NR</p> <p><i>BDI</i> Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) At 2 weeks G1: -1.35(4.44) G2: -2.75(4.28) P = 0.299</p> <p><i>CGI-S</i> Change, mean (SD)</p> <p>At week 2 G1: -0.82(0.80) G2: -0.27(0.66) P = 0.04</p> <p>2 week follow up G1: -1.00(1.17) G2: +0.27(0.95) P = 0.037</p>	<p>At 2 weeks G1: -1.5 (-5.9%) G2: -7.2 (-26.37%) G3: -6.9 (-27.6%) G1: vs. G2+G3 (mean = 7.05), P = 0.048</p> <p>Follow up at week 4 G1: -1.43 (-5.6%) G2: -6.42 (-23.51%) G3: -8.1 (-32.4%) G1: vs. G2+G3, P = 0.121</p> <p>Responders, n (%) G1: 0 (0) G2: 2 (20) G3: 2 (20) P = NR</p> <p><i>CGI-S</i> Endpoint score, mean(SD) At 2 weeks G1: 4.6 (0.97) G2: 3.8 (1.48) G3: 3.9 (0.99)</p> <p>2 week follow up G1: 4.75 (1.16) G2: 4.00 (1.15) G3: 3.7 (1.57)</p>
<b>CONCLUSIONS</b>	<p>rTMS administered utilizing subthreshold stimulation, a 2-week course of treatment, or a total small number of stimuli (800y session as in the current study) may not be a clinically effective approach and support the recent reports suggesting that stronger stimulation parameters or longer periods of stimulation are necessary.</p>	<p>Real, but not sham HF-rTMS, was associated with a significant decrease in the Hamilton Depression Rating Scale, but only twelve patients decreased more than 50%. Left prefrontal HF-rTMS was effectively associated with antidepressant treatment, although the size effect was small</p>	<p>Comparison of the sham rTMS group with the overall group that received active rTMS revealed statistically significant changes on the Hamilton Rating Scale for Depression after 10 sessions. This study demonstrated that combined 20+1-Hz rTMS was effective, but no additional advantages were obtained by focusing rTMS on areas identified by single photon emission tomography as showing high versus low levels of functional activity.</p>
<b>COMMENTS</b>			



**Table A5.3 Primary studies of rTMS vs Sham rTMS for depression (Studies included in Gaynes) *Continued.***

STUDY	Kauffmann 2004	Padberg 1999	Pallanti 2010
<b>PATIENTS</b>	N=12 Major Depression (DSM-IV)	N=18 Major Depression (DSM-IV)	N=60 Major Depression (DSM-IV)
<b>TREATMENT FAILURE</b>	Patients specifically had two or more prior treatment failures with medications	Patients specifically had two or more prior treatment failures with medications	Patients specifically had two or more prior treatment failures with medications
<b>INPATIENT OR OUTPATIENT SETTING</b>	Inpatient/outpatient status not clearly reported	Inpatient/outpatient status not clearly reported	Inpatient/outpatient status not clearly reported
<b>INTERVENTION &amp; COMPARATORS</b>	<p>rTMS</p> <ul style="list-style-type: none"> <li>• Frequency (Hz):1</li> <li>• Motor threshold (%): 110</li> <li>• Number of trains: 2</li> <li>• Length of train (seconds): 60</li> <li>• Inter-train interval: 180</li> <li>• Pulses per session: 120</li> <li>• Total number of sessions: 10 in 10 days</li> </ul> <p>Sham</p> <ul style="list-style-type: none"> <li>• Same as above but coil was held at a 45 degree angle from skull</li> </ul>	<p>G1: Bilateral:</p> <p>Location of Stimuli: 1<sup>st</sup> applied of right DLPFC then left DLPFC</p> <p>Right DLPFC</p> <p>Frequency: 3 140s trains at 1 Hz</p> <p>Intensity: 110% RMT</p> <p>Interval: 30s inter-train interval</p> <p>Total 420 stimuli per session</p> <p>Left DLPFC</p> <p>Frequency: 20 5s trains at 10 Hz</p> <p>Intensity: 100% RMT</p> <p>Interval: 25 s inter-train interval</p> <p>Total 1000 stimuli per session</p> <p>G2: Unilateral:</p> <p>Location of Stimuli: Right DLPFC</p> <p>Frequency: 3 140s trains at 1 Hz</p> <p>Intensity: 110% RMT</p> <p>Interval: 30s inter-train interval</p> <p>Total 420 stimuli per session</p> <p>Sham: Left DLPFC</p> <p>Same length of time as the 420 stimuli per session.</p>	<p>rTMS High</p> <ul style="list-style-type: none"> <li>• Frequency (Hz):10</li> <li>• Motor threshold (%): 90</li> <li>• Number of trains: 5</li> <li>• Length of train (seconds): 5</li> <li>• Inter-train interval: 30</li> <li>• Pulses per session: 250</li> <li>• Total number of sessions: 5/wk</li> </ul> <p>rTMS Low</p> <ul style="list-style-type: none"> <li>• Frequency (Hz):0.3</li> <li>• Motor threshold (%): 90</li> <li>• Number of trains: 10</li> <li>• Length of train (seconds): 25</li> <li>• Inter-train interval: NR</li> <li>• Pulses per session: 75</li> <li>• Total number of sessions: 5/wk</li> </ul> <p>Sham:</p> <ul style="list-style-type: none"> <li>• Same as high rTMS except coil angled at 90 degrees with 1 wing resting on skull</li> </ul>
<b>TREATMENT OR REMISSION MAINTENANCE?</b>	Treatment (augment current therapies)	Treatment (augment current therapies)	
<b>ON ANTIDEPRESSANTS OR</b>	Allowed to continue antidepressants but	83.3% of pts continued on their current [failed] AD	Current [failed] antidepressant regime continued

<b>DRUG FREE?</b>	advised to discontinue benzodiazepines & mood stabilizers	medication, others were not on a med and did not start one prior to trial	
<b>PRIMARY OUTCOMES</b>	HAM-D 21	HAM-D 21 MADRS	HAM-D17
<b>ADVERSE EVENTS</b>	Not reported	<p>Headache, % G1: 16.7 G2: 16.7 G3: NR Focal Pain at rTMS site during stimulations: 50%, 33.3%, &amp; 0%. There were no serious AE.</p> <p><i>Neuropsychological or executive functioning</i> Verbal Memory Tests (included 3 learning trials and a consecutive, delayed recall task after distraction):</p> <p>Verbal memory performance improved significantly after fast rTMS</p> <p>Learning 1. <math>P = 0.006</math> 2. NA 3. Fast rTMS improvement <math>P = 0.032</math>, Slow rTMS <math>P = NS</math>, Sham decrease in performance <math>P = 0.09</math></p>	<p>Cognitive impairment, % Week 0 G1: 25 G2: 20 G3: 35 Week 3 G1: 15 G2: 10 G3: 30</p> <p>Headache, % Week 0 G1: 40 G2: 30 G3: 20 Week 3 G1: 5 G2: 5 G3: 5</p> <p>Pain/burning in the scalp: Week 0 G1: 50 G2: 40 G3: 15 Week 3 G1: 5 G2: 0 G3: 10 Anxiety Week 0 G1: 20 G2: 15 G3: 15 Week 3</p>

			<p>G1: 0 G2: 0 G3: 5</p>
<b>RESULTS</b>	<p><i>HAM-D 21</i> Endpoint score, mean (SEM) G1: 11.29 (3.17) G2: 11.80 (1.93) Change, mean (SD) G1: -10.57 G2: -6.31 <i>P</i> = NR (ns)</p> <p>Responders, n G1: 4 (57%) G2: 2 (40%)</p> <p>Response2, n HAM-D21 &lt;10 G1: 4 (57%) G2: 1 (20%)</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD) G1: 28.5 (9.4) G2: 21.5 (21.5) G3: 23.5 (10.4)</p> <p>Change, mean (SD) G1: -1.7 G2: -5.2 G3: -1.3 <i>P</i> &gt; 0.05</p> <p><i>MADRS</i> Endpoint score, mean (SD) graph only Group x time, <i>P</i> &lt; 0.1</p>	<p>HAM-D reduction up to 10% G1: 5 G2: 4 G3: 15 <math>\chi^2</math> 19.17, df 6, Sig. = 0.04 HAM-D reduction up to 25% G1: 5 G2: 6 G3: 3 HAM-D reduction up to 50% G1: 6 G2: 3 G3: 0 HAM-D reduction over 50% G1: 4 G2: 7 G3: 2</p> <p>NNT (Response) rTMS1 vs. sham 10.00 (95%CI: 3.13 to -8.39)</p> <p>rTMS2 vs. sham 4.00 (95%CI: 2.01 to 328.11)</p>
<b>CONCLUSIONS</b>	<p>This study supports the therapeutic potential of rTMS in the low-frequency range of 1 Hz on right prefrontal cortex for the treatment of refractory major depression.</p>	<p>This study further supported the safety of rTMS but does not show any clinically meaningful antidepressant efficacy of rTMS at 250 daily stimuli over 5 days in pharmacotherapy-refractory major depression.</p>	<p>Low frequency right-sided and sequential bilateral stimulation showed different antidepressant efficacy at 3 weeks and across the full duration of the study, only the unilateral method appearing significantly more effective than sham at the end of the trial, and correlated to the higher percent of remitters (30% of the group vs. 10% -bilateral- and 5% -sham). Unilateral stimulation, but not bilateral, showed higher antidepressant efficacy compared to sham stimulation. The data suggest that right sided low frequency stimulation may be a first line treatment alternative in resistant depression.</p>

**Table A5.3 Primary studies of rTMS vs Sham rTMS for depression (Studies included in Gaynes) *Continued.***

STUDY	Zheng 2010	Holtzheimer 2004	Avery 2006
<b>PATIENTS</b>	N=34 Major Depression (DSM-IV)	N = 15 Patients with treatment resistant depression (must have failed at least two previous antidepressant trials due to lack of response to an adequate trial (defined by ATHF) or medication intolerance)  Meet DSM-IV criteria for a major depressive episode due to MDD (HAM-D17 $\geq$ 18)	N = 68 patients with treatment resistant depression (Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score $\geq$ 3 on ATHF)  Meet DSM-IV criteria for current major depressive disorder (MDD) HAM-D 17 $\geq$ 17 and a decrease of no more than 20% between screening and 1st txt day
<b>TREATMENT FAILURE</b>	Patients specifically had two or more prior treatment failures with medications	Patients specifically had two or more prior treatment failures with medications	Patients specifically had two or more prior treatment failures with medications
<b>INPATIENT OR OUTPATIENT SETTING</b>	Inpatient/outpatient status not clearly reported	Inpatient/outpatient status not clearly reported	Outpatient
<b>INTERVENTION &amp; COMPARATORS</b>	rTMS 20 sessions of over the left DLPFC within four weeks, at 110% stimulation intensity related to resting motor threshold  15 Hz, 50 trains of 4 s duration 3000 stimuli/day, 28 min per session, 20 sessions of stimulation over a 4-week period	<i>rTMS vs sham rTMS</i>  Primary endpoint following 2 weeks of treatment and follow up  <i>Parameters</i> rTMS <ul style="list-style-type: none"> <li>• Frequency (Hz): 10</li> <li>• Motor threshold (%): 110</li> <li>• Number of trains:32</li> <li>• Length of train (seconds): 5</li> <li>• Inter-train interval: 30-60</li> <li>• Pulses per session: 1600</li> <li>• Total number of sessions: 10 over 2 wks</li> </ul> Sham rTMS <ul style="list-style-type: none"> <li>• Delivered in same anatomical location with identical stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp</li> </ul>	<i>rTMS vs sham rTMS</i>  4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint  <i>Parameters</i> rTMS <ul style="list-style-type: none"> <li>• Frequency (Hz):10</li> <li>• Motor threshold (%): 110</li> <li>• Number of trains: 32</li> <li>• Length of train (seconds): 5</li> <li>• Inter-train interval: 25-30</li> <li>• Pulses per session: 1600</li> <li>• Total number of sessions: 15 in 4 wks</li> </ul>
<b>TREATMENT OR REMISSION MAINTENANCE?</b>	TRD	Treatment	Treatment
<b>ON ANTIDEPRESSANTS OR DRUG FREE?</b>	Augment – all patients taking escitalopram from 2+ weeks before trial	All patients discontinued (failed) AD medication – switch study*	Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing

			<p>benzodiazapines G1: 26% vs. G2: 24%)</p> <ul style="list-style-type: none"> <li>• Those stopping medications had to be medication-free for at least 2 weeks</li> <li>• All responders given AD post rTMS treatment (active or sham)</li> </ul>
<b>PRIMARY OUTCOMES</b>	HAM-D (17) BDI	Effectiveness (antidepressant effects) – HDRS, BDI Safety Tolerability	Response, remission (HAM-D-17, BDI) cognitive functioning, adverse effects (discomfort pain scale, SAFTEE, GOAT, RAVLT, WAIS-R, COWAT)
<b>ADVERSE EVENTS</b>		<p>No major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated.</p> <p><i>Neuropsychological or executive functioning</i> Both groups performed equally well with exception of one measure of verbal memory, Trial 7 of Rey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); <math>P &lt; 0.05</math>).</p> <p>No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions.</p> <p>There were no major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated.</p>	<p>Site pain first session sham none (0/33) vs. TMS group, 41% (14/35) 15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased in TMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (<math>t = 4.24</math>, <math>P &lt; 0.001</math>).</p> <p>Changes from baseline in 128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any of emerging symptoms.</p> <p><i>Neuropsychological or executive functioning</i> No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS11: At 15<sup>th</sup> session pain TMS 33% vs, sham 3% (<math>P &lt; 0.05</math>) no statistically significant (<math>P &gt; 0.05</math>) time by treatment group interactions for any of neuropsychological test measures. models were refit without interaction term, there was no significant treatment group main effect (<math>P &gt; 0.05</math>) evident for any of neuropsychological tests, indicating groups had similar levels of neuropsychological performance collapsed over time. Several measures showed significant main effects of time, that is, collapsed over groups, there was significant improvement in individual neuropsychological test performances for both groups.</p> <p>No confusion was associated with TMS treatments. GOAT assessments were well within normal range and ranged from 98 to 100. No significant (<math>P &gt; 0.05</math>) differences between groups for any session.</p>

<p><b>RESULTS</b></p>	<p>HAM-D (17) Endpoint score, mean (SD) G1: 13.5 (5.1) G2: 22.9 (3.4) Change, mean (SD) G1: -11.1 G2: -1.7 P = NR Responders, n G1: 12 G2: 1</p> <p>BDI Yes G1: rTMS G2: Sham</p> <p>Endpoint score, mean (SD) G1: 13.5 (5.1) G2: 19.8 (5.1)</p> <p>Change, mean (SD) G1: -7.6 G2: -1.2</p>	<p>“Treatment (rTMS vs. sham) did not significantly predict changes in depression severity. Shorter duration of episode and more lifetime treatment trials significantly predicted improvements in BDI but not HDRS scores. Data from all subjects who received active rTMS (n=14) showed that those with a depressive episode duration of shorter than 4 years had a mean HDRS decrease of 52% compared to 6% in those with an episode duration longer than 10 years. Active rTMS was well tolerated and was not associated with neuropsychological decrements when compared to sham.”</p> <p>HAM-D 17 Endpoint score, mean (SD) At week 1 G1: 18.0 (1.2) G2: 18.0 (2.7) At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0) 1 week follow-up G1: 18.8 (2.5) G2: 17.6 (2.1) Change, mean (SD) At week 1 G1: 4.7 G2: 2.8 At week 2 G1: 8.1 G2: 5.5 1 week follow-up G1: 3.9 G2: 3.2 All endpoints, P = NS Responders, n (%) At week 1</p>	<p>The response rate for the TMS group was 30.6% (11/35), significantly (p = .008) greater than the 6.1% (2/33) rate in the sham group. The remission rate for the TMS group was 20% (7/35), significantly (p = .033) greater than the 3% (1/33) rate in the sham group. The HDRS scores showed a significantly (p &lt; .002) greater decrease over time in the TMS group compared with the sham group.</p> <p>HAM-D 17 Endpoint score, mean (SD) G1: 15.7 G2: 19.8 Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time P = 0.002 Responders, n G1: 11 (31.4%) G2: 2 (6.1%) P = 0.008 Remitters, n HAM-D21 &lt; 10 G1: 7 (20.0%) G2: 1 (3.0%) P = 0.033 No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse) BDI Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5)</p>
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		<p>G1: 0 G2: 0 At week 2 G1: 2 (28.6) G2: 1 (12.5) 1 week follow-up G1: 0 G2: 0 BDI Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7)</p>	
<b>CONCLUSIONS</b>	Our results support the notion that major depressive disorder is accompanied by state dependent metabolic alterations, especially in myo-inositol metabolism, which can be partly reversed by successful rTMS.	<p>“No significant antidepressant effects were found for 2 weeks of rTMS compared to sham. Among all subjects receiving rTMS those with a shorter duration of the current episode showed a greater response. Patients may need more than 10 treatments to obtain full benefit from rTMS.”</p>	Transcranial magnetic stimulation can produce statistically and clinically significant antidepressant effects in patients with medication-resistant major depression.
<b>COMMENTS</b>		<i>Quality Rating: Fair</i>	<p><i>Quality Rating: Good</i> Fair for KQ2 and subgroups<sup>11</sup> (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)</p>

Table A5.3 Primary studies of rTMS vs Sham rTMS for depression (Studies included in Gaynes) *Continued.*

STUDY	Pascual-Leone 1996	George 2010	Manes 2001 and Moser 2002
<b>PATIENTS</b>	17 patients with medication-resistant depression of psychotic subtype (DSM-III-R) <i>TRD definition:</i> At least three episodes of depression that had been resistant to multiple medications despite combinations and high doses	199 patients with treatment resistant depression. "All patients had either one failed antidepressant failure, or multiple intolerance to antidepressant medications." DSM-IV MDD, single or recurrent; HAM-D24 $\geq$ 20; Stable during 2wk medication-free lead-in	20 patients with Major/Minor Depression (DSM IV)
<b>TREATMENT FAILURE</b>	Patients specifically had two or more prior treatment failures with medications	Patients specifically had two or more prior treatment failures with medications	Patients specifically had two or more prior treatment failures with medications
<b>INPATIENT OR OUTPATIENT SETTING</b>	Inpatients and outpatients	Outpatient	Outpatient
<b>INTERVENTION &amp; COMPARATORS</b>	G1: High Frequency rTMS G2: High frequency right rTMS (control) G3: Sham left rTMS G4: Sham right rTMS G5: Real vertex stimulation (control)  "The study was designed as a multiple cross-over, randomised placebo-controlled trial. Sham rTMS and stimulation of different cortical areas were used as controls"  Primary endpoint after 1 week of treatment. Total study duration 5 months (3 week washout between treatments)  Strategy Mixed-within group differences  Parameters • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 10	rTMS vs sham rTMS  rTMS Parameters Location: Left prefrontal cortex Frequency: 10 Hz Intensity 120% MT Pulses: 10 pulses per second for 4 seconds; 3000 per session Inter-train interval: 26 seconds Length of Session: 37.5 minutes (75 trains) Fixed Active Treatment 2 Number of sessions: daily weekday sessions (15 sessions)	<i>Duration</i> 2 weeks (1 week of treatment, 1 wk follow-up following last treatment) <i>Interventions</i> G1: rTMS (N=10) G2: Sham rTMS (N=10)  <i>Parameters</i> rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk



	<ul style="list-style-type: none"> <li>• Inter-train interval: 60</li> <li>• Pulses per session: 2000</li> <li>• Total number of sessions: 5 in 5 days</li> <li>• Left Sham Coil angled at 45 degrees with edge of coil resting on scalp</li> <li>• Right Sham Coil angled at 45 degrees with edge of coil resting on scalp</li> </ul>		
<b>TREATMENT OR REMISSION MAINTENANCE?</b>	Treatment	treatment	treatment
<b>ON ANTIDEPRESSANTS OR DRUG FREE?</b>	Attempts were made to taper medications. Nine patients continued AD medication and only 4 patients were AD free at the end of the study. All pts given nimodipine at a constant dose of 30mg/3x daily	Antidepressant medication-free (2-week washout)	No antidepressant medication
<b>PRIMARY OUTCOMES</b>	Reduction in depressive symptoms (HAMD-21, BDI)	Remission rates	Primary outcomes HAMD at end of treatment and at 1 week follow-up
<b>ADVERSE EVENTS</b>	<p>No patients experienced any significant undesirable side effects</p> <p>"All patients tolerated rTMS without complications...complications were not related to stimulation condition and did not prompt pts to request discontinuation of study."</p>	<p>Minimal adverse effects did not differ by treatment arm</p> <p>"Many patients receiving sham rTMS also reported headache, site discomfort, and facial twitching, common adverse effects associated with active rTMS that have raised concerns in Five patients discontinued study participation because of adverse events, all of whom were receiving active TMS (5.4% dropout rate owing to adverse events in the active group). Four of the 5 patients dropped out because of pain or headache and received only a single TMS treatment. One patient received 14 treatments and then dropped out because of syncope. No seizures or suicides occurred...There were 2 serious adverse events without long-term sequelae: 1 patient had syncope (active rTMS) that the investigator deemed unlikely related to the study and 1 patient had paranoid ideation (sham TMS), possibly related to the study."</p>	<p><i>Adverse Events</i></p> <p>Headache, %</p> <p>G1: 40%</p> <p>G2: 0%</p> <p>Other:</p> <p>Local pain/local discomfort: 10%/40% vs. 0%/40%; anxiety: 0 vs 10%</p> <p><i>Neuropsychological or executive functioning</i></p> <p>**some variation in pts included in two samples but reported as same study by authors. #1564 includes at least 1 participant &lt;50 years old, n=19</p> <p>Other neuropsychological tests showing no statistical significance in either group: Trail Making Test-A, Stroop Test, WAIS-R digit symbol, Controlled Oral Word Association, Boston naming test, sentence repetition, Rey Auditory Verbal Learning test, &amp; Judgement of Line Orientation</p>
<b>RESULTS</b>	Left dorsolateral prefrontal cortex rTMS resulted in a significant decrease in scores on	"Primary efficacy analysis revealed a significant effect of treatment on the proportion of remitters	"There were no significant differences in HDRS scores either before or after treatment at 7 days follow-up. There were 3 responders to

	<p>the Hamilton depression rating scale HDRS (from 25.2 to 13.8) and the Beck Questionnaire BQ (from 47.9 to 25.7). 11 of the 17 patients showed pronounced improvement that lasted for about 2 weeks after 5 days of daily rTMS sessions.</p>	<p>(14.1% active rTMS and 5.1% sham) (<math>P=.02</math>). The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95% confidence interval, 1.32- 13.24). The number needed to treat was 12. Most remitters had low antidepressant treatment resistance. Almost 30% of patients remitted in the open-label follow-up (30.2% originally active and 29.6% sham)."</p> <p>G1: rTMS G2: sham stimulation Change, mean (SD) At 2 weeks G1: -5.25 G2: +3.33 <math>P &lt; 0.03</math></p>	<p>active treatment and three to sham treatment and responders had significantly greater frontal lobe volume than nonresponders (<math>p=.03</math>)"</p> <p>HAM-D Endpoint score, mean (SD) At 1 week G1: 13.7 (5.4) G2: 16.2 (8.5) 1 week Follow-up G1: 14.4 (6.4) G2: 15.5 (9.1) Change, mean (SD) At week 1 G1: -9 G2: -6.5 1 week follow-up G1: -8.3 G2: -7.2 All time points <math>P &gt; 0.66</math>; pts with MDD only - <math>P = 0.3919</math> Responders, n (%) G1: 3 (30) G2: 3 (30) <math>P = NS</math> Remitters, n G1: 2 G2: 2 <math>P = NR</math></p>
<b>CONCLUSIONS</b>	<p>"Our findings emphasise the role of the left dorsolateral prefrontal cortex in depression, and suggest that rTMS of the left dorsolateral prefrontal cortex might become a safe, non-convulsive alternative to electroconvulsive treatment in depression"</p>	<p>"Daily left prefrontal rTMS as monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects greater than sham."</p>	<p>"These findings suggest that the stimulation parameters used in this study were probably insufficient to produce treatment response and that frontal atrophy may interfere with the effectiveness of rTMS"</p>
<b>COMMENTS</b>	<p><i>Quality Rating</i> Fair</p>	<p><i>Quality Rating</i> Good</p>	<p><i>Quality Rating</i> Fair</p>

**Table A5.3 Primary studies of rTMS vs Sham rTMS for depression (Studies included in Gaynes) *Continued.***

STUDY	Stern 2007	O'Reardon 2007
<b>PATIENTS</b>	N=45 patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score $\geq 20$ All patients were referred for ECT having failed an adequate course of antidepressant med	N=325 patients with DSM-IV diagnosis of MDD Single episode or recurrent, with a current episode duration $\leq 3$ CGI-S score $\geq 4$ , HAM-D17 $\geq 20$
<b>TREATMENT FAILURE</b>	Patients specifically had one or more prior treatment failures with medications	Patients specifically had one or more prior treatment failures with medications
<b>INPATIENT OR OUTPATIENT SETTING</b>	Outpatient	Outpatient/inpatient status not clearly reported
<b>INTERVENTION &amp; COMPARATORS</b>	<p>High frequency left rTMS vs low frequency left rTMS vs low frequency right rTMS vs sham rTMS</p> <p>Duration</p> <ul style="list-style-type: none"> <li>• 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps</li> <li>• An additional 2 wk of unblinded f/u with gp 1 &amp; 3 to assess for relapse.</li> </ul> <p>rTMS parameters</p> <p>High Frequency:</p> <ul style="list-style-type: none"> <li>• Frequency (Hz):10</li> <li>• Motor threshold (%): 110</li> <li>• Number of trains: 20</li> <li>• Length of train (seconds): 8</li> <li>• Inter-train interval: 52</li> <li>• Pulses per session: 1600</li> <li>• Total number of sessions: 10 days</li> </ul> <p>Low Frequency LDLPFC:</p> <ul style="list-style-type: none"> <li>• Frequency (Hz):1</li> <li>• Motor threshold (%): 110</li> <li>• Number of trains: 1</li> <li>• Length of train (seconds): 1600</li> <li>• Inter-train interval: 1</li> <li>• Pulses per session: 1600</li> <li>• Total number of sessions: 10 days</li> </ul> <p>Low Frequency RDLFPFC:</p> <ul style="list-style-type: none"> <li>• Frequency (Hz): 1</li> <li>• Motor threshold (%): 110</li> </ul>	<p>rTMS (n=165) vs sham rTMS (n=160)</p> <p>Duration: 6 weeks; Sham patients could cross over after 4 weeks if not responding.</p> <p>Parameters rTMS</p> <ul style="list-style-type: none"> <li>• Frequency (Hz): 10</li> <li>• Motor threshold (%): 120</li> <li>• Number of trains: 75</li> <li>• Length of train (seconds): 4</li> <li>• Inter-train interval: 26</li> <li>• Pulses per session: 3000</li> <li>• Total number of sessions: 5/week for 4-6 wks</li> </ul>

	<ul style="list-style-type: none"> <li>• Number of trains: 1</li> <li>• Length of train (seconds): 1600</li> <li>• Inter-train interval: 1</li> <li>• Pulses per session: 1600</li> <li>• Total number of sessions: 10 days</li> </ul>	
<b>TREATMENT OR REMISSION MAINTENANCE?</b>	Treatment	treatment
<b>ON ANTIDEPRESSANTS OR DRUG FREE?</b>	No psychotropic medications were allowed	All patients were free of ADs and other psychotropic medications directed at treating depression. Pts allowed only limited use of hypnotics, anxiolytics for txt emergent insomnia or anxiety
<b>PRIMARY OUTCOMES</b>	HAMD-21	Change in MADRS score
<b>ADVERSE EVENTS</b>	<p>Adverse Events</p> <p>9/45 pts reported severe headaches (pts by group NR); no seizures</p> <p>Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period.</p> <p>Reported in text as dropped out following week 2.</p>	There were no deaths in this study, and no seizures were reported. During the acute treatment phase, 16 serious adverse events were reported, 9 in the active TMS group and 7 in the sham TMS group. Events reflecting disease-related exacerbation were the most common serious adverse events. These included suicidality (1.9% with sham vs. .6% with active TMS), exacerbation of depression (1.9% with sham vs. .6% with active), and a single suspected suicide gesture (in the sham group).
<b>RESULTS</b>	<p>None of the patients in Group 2 (left-sided, low frequency rTMS) or Group 4 (sham rTMS) met the criteria for a clinical response. However, at the end of the 10 days of stimulation, 60% of the patients in Group 1 (leftsided, high frequency rTMS) and 60% in Group 3 (rightsided, low frequency rTMS) showed a clinical response.</p> <p>Similarly, while none of the patients in Group 2 or Group 4 met the criteria for remission, 33.3% of the patients in Group 1 and 10% of the patients in Group 3 showed this level of improvement</p> <p>HAM-D 21</p> <p>Endpoint score, mean (SD)</p> <p>At week 1</p> <p>G1: 22.2 (5.6)</p> <p>G2: 27.6 (5.9)</p> <p>G3: 20.9 (4.1)</p> <p>G4: 25.6 (4.5)</p> <p>At week 2</p> <p>G1: 15.1 (6)</p> <p>G2: 27.6 (5.9)</p> <p>G3: 15.8 (4.8)</p>	<p>Active TMS was significantly superior to sham TMS on the MADRS at week 4 (with a post hoc correction for inequality in symptom severity between groups at baseline), as well as on the HAMD17 and HAMD24 scales at weeks 4 and 6. Response rates were significantly higher with active TMS on all three scales at weeks 4 and 6. Remission rates were approximately twofold higher with active TMS at week 6 and significant on the MADRS and HAMD24 scales (but not the HAMD17 scale). Active TMS was well tolerated with a low dropout rate for adverse events (4.5%) that were generally mild and limited to transient scalp discomfort or pain.</p> <p>HAM-D 17</p> <p>Analyzed n</p> <p>G1: 155</p> <p>G2: 146</p> <p>Endpoint score, mean (SD)</p> <p>At week 4</p> <p>G1: 17.4 (6.5)</p> <p>G2: 19.4 (6.5)</p> <p>At week 6</p> <p>G1: 17.1 (7.7)</p> <p>G2: 19.6 (7.0)</p>

<p>G4: 26.7 (3.6)</p> <p>Week 1 Follow-up</p> <p>G1: 12.8 (5.7)</p> <p>G2: 26.4 (2.3)</p> <p>G3: 15.3 (6.4)</p> <p>G4: 26.5 (2.3)</p> <p>Week 2 Follow-up</p> <p>G1: 13.4 (5.6)</p> <p>G2: 26.6 (3.0)</p> <p>G3: 14.9 (5.9)</p> <p>G4: 26.8 (2.3)</p> <p>Change, mean (SD)</p> <p>At week 2</p> <p>G1: -12.7</p> <p>G2: 0.0</p> <p>G3: -12.1</p> <p>G4: -0.7</p> <p>% change, P = 0.001</p> <p>2 week follow-up</p> <p>G1: 0</p> <p>G2: 1.0</p> <p>G3: 13.0</p> <p>G4: 0.6</p> <p>% change, P = 0.00001</p> <p>Responders, n</p> <p>At week 1</p> <p>G1: 0</p> <p>G2: 0</p> <p>G3: 0</p> <p>G4: 0</p> <p>At week 2</p> <p>G1: 2 (50%)</p> <p>G2: 0 (0%)</p> <p>G3: 5 (50%)</p> <p>G4: 0 (0%)</p> <p>G1/G3 vs. G2/G4</p> <p>(P &lt; 0.0005)</p> <p>1 week follow-up</p> <p>G1: 6 (60%)</p>	<p>Change, mean (SD)</p> <p>At week 2</p> <p>G1: -5.2</p> <p>G2: -3.5</p> <p>At week 6</p> <p>G1: -5.5</p> <p>G2: -3.3</p> <p>P = 0.005</p> <p>Responders, n (%)</p> <p>At week 2</p> <p>G1: 18 (11.6)</p> <p>G2: 13 (8.9)</p> <p>P &gt; 0.10</p> <p>At week 4</p> <p>G1: 32 (20.6)</p> <p>G2: 17 (11.5)</p> <p>P &lt; 0.05</p> <p>At week 6</p> <p>G1: 38 (24.5)</p> <p>G2: 20 (13.7)</p> <p>P &lt; 0.05</p> <p>Remission rate n (%)</p> <p>HAM-D17 &lt; 8</p> <p>At week 2</p> <p>G1: 5 (3.2)</p> <p>G2: 3 (2.1)</p> <p>P &gt; 0.10</p> <p>At week 4</p> <p>G1: 110 (7.1)</p> <p>G2: 9 (6.2)</p> <p>P &gt; 0.10</p> <p>At week 6</p> <p>G1: 24 (15.5)</p> <p>G2: 13 (8.9)</p> <p>P = 0.065</p> <p>MADRS</p> <p>Endpoint score, mean (SD)</p>
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	<p>G2: 0 (0%) G3: 6 (60%) G4: 0 (0%) G1/G3 vs. G2/G4 (<math>P &lt; 0.0005</math>) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 6 (6%) G4: 0 G1/G3 vs. G2/G4 (<math>P &lt; 0.0005</math>)</p>	<p>At 4 weeks G1: 27 (11.1) G2: 29.8 (10.1) At 6 weeks G1: 26.8 (12.8) G2: 30 (10.8) Change, mean (SD) At 4 weeks G1: 5.8 G2: 4.1</p>
<b>CONCLUSIONS</b>	<p>This study demonstrates that high frequency rTMS to the left DLPFC and low frequency rTMS to the right DLPFC are both effective in the treatment of depression, while sham TMS and low frequency rTMS to the left DLPFC are ineffective.</p>	<p>Transcranial magnetic stimulation was effective in treating major depression with minimal side effects reported. It offers clinicians a novel alternative for the treatment of this disorder.</p>
<b>COMMENTS</b>	<p><i>Quality Rating: Fair</i></p>	<p><i>Quality Rating: Good</i></p>

**Table A5.4 Primary studies of rTMS vs Sham rTMS for depression (studies NOT included in Gaynes)**

STUDY	Aguirre 2011	Fitzgerald 2012
<b>PATIENTS</b>	n = 34 Major Depression patients	n = 67 patients with TRD diagnosis of moderate to severe depression (>15 17-item HAMD) + failure to respond to at least 2 courses of antidepressant meds for at least 6 weeks
<b>TREATMENT FAILURE</b>	Prior treatment failure not specified but clinical situation suggests high probability of patients having two or more prior treatment failures with antidepressants	Patients specifically had two or more prior treatment failures with medications
<b>INPATIENT OR OUTPATIENT SETTING</b>	Outpatient	Inpatient/outpatient status not clearly reported
<b>INTERVENTION &amp; COMPARATORS</b>	LF-TMS vs sham LF-TMS  <u>Parameters:</u> 1Hz, 110% MT <u>Location:</u> RDPC <u>Duration:</u> 20 sessions of 20 x 60s trains, 4wks treatment + 4wks followup	SB-rTMS vs standard high-frequency left sided rTMS vs sham rTMS  <u>Parameters:</u> RS: 15 min train at 1 Hz (120% RMT) LS: 30 trains at 10 Hz for 5 s (120% RMT) <u>Location:</u> Bilateral <u>Duration:</u> treatment over a 3-week period (5 Sessions per week) with a further 3 week comparison of the two active treatments
<b>TREATMENT OR REMISSION MAINTENANCE?</b>	Not stated	Treatment
<b>ON ANTIDEPRESSANTS OR DRUG FREE?</b>	As adjuvant treatment to pharmacotherapy	Mixed
<b>PRIMARY OUTCOMES</b>	Decrease in scores on the Hamilton Depression Rating Scale.	Scores on the 17-item Hamilton Depression Rating Scale (HAMD).
<b>ADVERSE EVENTS</b>	Mild headache pain discomfort increase in anxiety one patient had a mild and short hypomanic episode after the sessions (had not had one before)	No serious adverse events. No evidence of cognitive deterioration in rTMS groups from baseline to week 3.
<b>RESULTS</b>	Both groups significantly improved, but no statistical differences between them. In the real TMS group patients age inversely correlated with improvement of depressive symptoms at the end of the study ( $r=-0.683$ $p=0.002$ ). Percentage of decrease in Hamilton scores was greater in subjects younger than 45 years old vs. others ( $41.3 \pm 22.6$ vs. $15.1 \pm 15.8$ ; $t=2.8$ $df=16$ , $p=0.011$ ).	In the three-week double-blind phase of the trial there was a greater antidepressant response to unilateral left sided rTMS compared with sham or bilateral rTMS. Across the full six weeks of active rTMS, there was also a consistent pattern of improved response in unilateral left compared to bilateral treatment. Response rates were low in both active groups.
<b>CONCLUSIONS</b>	Only younger patients benefited from LF-rTMS as adjuvant treatment to antidepressants in this study.	This study does not support the hypothesis that sequential bilateral rTMS is more effective than unilateral high-frequency left-sided rTMS
<b>COMMENTS</b>	Country = Spain	Country = Australia

**Table A5.4 Primary studies of rTMS vs Sham rTMS for depression (studies NOT included in Gaynes) Continued.**

STUDY	Jakob 2008	Triggs 2010
<b>PATIENTS</b>	n = 36 patients diagnosed with major depression moderate to severe unipolar depression (DSM IV) >18 HAM-D17, MADRS or BDI	n = 48 patients with major depressive disorder (DSM-IV, SCID) medication resistant depression
<b>TREATMENT FAILURE</b>	Prior treatment failure not specified but clinical situation suggests high probability of patients having two or more prior treatment failures with antidepressants	Patients specifically had two or more prior treatment failures with medications
<b>INPATIENT OR OUTPATIENT SETTING</b>	Inpatient/outpatient status not clearly reported	Inpatient/outpatient status not clearly reported
<b>INTERVENTION &amp; COMPARATORS</b>	<p>UHF-rTMS (50Hz) vs standard rTMS (20Hz) vs sham 2 week trial</p> <p><u>Parameters:</u> 20Hz, 100% MT <u>Location:</u> not specified <u>Duration:</u> 10 sessions. 2s duration, 18s interval over 2 weeks</p> <p><u>Parameters:</u> 50Hz, 100% MT <u>Location:</u> not specified <u>Duration:</u> 10 sessions. 1s duration, 59s interval over 2 weeks</p>	<p>left frontal rTMS vs right frontal rTMS vs sham rTMS</p> <p><u>Parameters:</u> 5Hz, 100% MT <u>Location:</u> R or L DPFC <u>Duration:</u> 10 sessions over 2 weeks. 50 trains of 40 stim (2000 per session), 8s duration, 22s interval</p>
<b>TREATMENT OR REMISSION MAINTENANCE?</b>	Treatment	Treatment
<b>ON ANTIDEPRESSANTS OR DRUG FREE?</b>	Mixed	On antidepressants
<b>PRIMARY OUTCOMES</b>	Tolerability and efficacy HDRS, MADRS, BDI score reduction	Mood HAMD, BDI, STAI
<b>ADVERSE EVENTS</b>	Treatments in this trial were found to be safe	No subjects experienced any serious adverse events. Adverse events consisted mainly of headache and localized scalp discomfort. These adverse events were reported in both TMS and sham treatment groups
<b>RESULTS</b>	<p>Although we were able to find that 50Hz rTMS is safe, we were not able to find clinical effects with the chosen parameters after 2 weeks of treatment.</p> <p>Although a clinical improvement after real rTMS treatment at 20Hz and 50Hz was observed, this was clinically indistinguishable from that seen in the placebo arm. Furthermore after 2 weeks, high-frequency rTMS with 50Hz did not seem to be superior to the conventional 20 Hz rTMS</p>	no significant group differences in HAMD scores between subjects receiving left rTMS, right rTMS and sham stimulation ( $F_{2,169}=2.02$ ; $P=0.14$ ).
<b>CONCLUSIONS</b>	Because safety data for a 50 Hz rTMS treatment were not available, we decided to restrict the treatment period to duration of 2 weeks. Because we were able to demonstrate that this is safe, further RCTs can be conducted and are needed to clarify whether finding optimal stimulation parameters can help to create a substantial treatment efficacy in patients with major depression	We found no statistically significant effect of 5 Hz dorsolateral prefrontal rTMS, left or right, on depression. Our study suggests that the effects of the rTMS treatment paradigm on depression likely reflect a complex mix of placebo, social, and somatic stimulation effects in which laterality of stimulation may be important. Although we did not find an rTMS effect, we cannot rule it out, particularly when it is applied to the left hemisphere, and future studies need to consider the possible value of rTMS applied at other sites, possibly at different frequencies, and ultimately, tailored to specific patients.
<b>COMMENTS</b>	Country = Germany	Country = USA



## APPENDIX 6: QUALITY APPRAISALS

**Table A6.1 Quality appraisal table (Aquirre, 2011)**

**Study:** Aguirre, I., B. Carretero, et al. (2011). "Age predicts low-frequency transcranial magnetic stimulation efficacy in major depression." *J Affect Disord* 130(3): 466-469

### Description of study: Randomized Control Trial

<b>Patient/population</b>	Patients older than 18 years fulfilling DSM-IV criteria for unipolar major depression.
<b>N</b>	N total = 34. rTMS=19 sham=15
<b>Setting</b>	Outpatients, non-psychotic
<b>Intervention/indicator</b>	LF-rTMS Parameters: 1Hz, 110% MT Location: RDPC Duration: 20 sessions of 20 x 60s trains, 4wks treatment + 4wks follow-up.
<b>Comparison/control</b>	sham LF-rTMS
<b>Outcomes</b>	Decrease of scores in the Hamilton Depression rating scale.
<b>Inclusion Criteria</b>	Patients older than 18 fulfilling DSM-IV criteria for unipolar major depression. Must have followed at least one adequate trial of antidepressant medication (maximum doses tolerated within the therapeutic range, for at least one month). Patients were required to take the same medication for at least one month prior to inclusion and to agree to continue doing so during the entire study.
<b>Exclusion Criteria</b>	Contradictions to rTMS, personal or family history of seizures, past neurosurgical procedures, Implanted pace makers, inner ear prosthesis, medication pumps, and unstable medical conditions. Pregnant women or those of childbearing potential lacking an effective contraceptive method. Patients with high suicidal risk.

### Study Validity.

<b>Is it clear that there were no conflicts of interest in the writing or funding of this study?</b>	Yes	Funding for this study was provided by the IUNICS Research Institute and the Mateu Orfila Foundation. Both institutes had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. All authors declared that they had no conflicts of interest.
<b>Does the study have a clearly- focused question?</b>	Yes	The study aims to analyze the efficacy of LF-rTMS as a co-adjuvant to pharmacological treatment in patients with major depression.

<b>Is a RCT the appropriate method to answer the question?</b>	Yes	
<b>Does the study have specified inclusion/exclusion criteria?</b>	Yes	Contradictions to rTMS, personal or family history of seizures, past neurosurgical procedures, Implanted pace makers, inner ear prosthesis, medication pumps, and unstable medical conditions. Pregnant women or those of childbearing potential lacking an effective contraceptive method. Patients with high suicidal risk.
<b>If there were specified inclusion/ exclusion criteria, were these appropriate?</b>	Yes	
<b>Did the study have an adequate method of randomization?</b>	Not reported	Method of randomisation not reported.
<b>Was allocation to intervention group concealed?</b>	Not reported	
<b>Were patients blind to the intervention group?</b>	Yes	Authors state that patients were blind to the procedure. Sham treatment was performed in a way that meant no magnetic field was produced but so that the apparatus still made sound.
<b>Were investigators and care providers blind to intervention group?</b>	No	The physicians who administered the procedure were not blind to the procedure. Due to the nature of the intervention is difficult to blind the care providers.
<b>Were outcome assessors blind to intervention group?</b>	Yes	An external assessor was used to evaluate the outcomes.
<b>All outcomes were measured in a standard, valid and reliable way?</b>	Yes	The outcome was measured using the 17-item Hamilton Depression Rating Scale for each of the patients in the intervention and control group.
<b>Were outcomes assessed objectively?</b>	Yes	The outcome was measured using the 17-item Hamilton Depression Rating Scale by an external assessor blinded to the intervention.
<b>Were outcomes assessed independently?</b>	Yes	
<b>Were the groups similar at baseline with regards to key prognostic variables?</b>	Yes	The group receiving active and sham treatment did not differ significantly in gender, age baseline, scores or other clinical parameters. Patients comparable in sociodemographic parameters. Most of the patients were taking selective serotonin reuptake inhibitors and most were taking them in combination with benzodiazepines.
<b>Aside from the experimental intervention, were the groups treated the same?</b>	Yes	There was no reported difference in the way the patients were treated aside from the experimental intervention. All subjects were

		outpatients and non-psychotic.
<b>Were the outcomes measured appropriate?</b>	Yes	Outcome measure was a score from the Hamilton Depression Rating Scale.
<b>Was there a sufficient duration of follow-up?</b>	Not reported	
<b>Was there <math>\leq 20\%</math> drop-out?</b>	Yes	34 Patients commenced the study. There were two drop outs. One in the active treatment left in the second week due to the onset of alcohol abuse with irregular attendance at TMS sessions. The other, in the control group left in the fourth week due to the emergence of myeloma. Data from these patients was included in the statistical analysis.
<b>Was the study sufficiently powered to detect any difference between the groups?</b>	No	Lack of statistical power due to a relatively small sample size.
<b>If statistical analysis was undertaken, was this appropriate?</b>	Yes	A two-tailed Students t test was used to compare independent and matched samples after confirming that the distribution was normal. When the application of parametric tests was not possible, the Mann-Whitney test was used. Qualitative variables were compared using the chi-square and fishers exact test.
<b>Were all the subjects analysed in groups to which they were randomly allocated (intention to treat analysis)?</b>	Yes	There were two drop outs in the study who were both analysed in their original group allocation.
<b>Is the paper free of selective outcome reporting?</b>	Yes	<i>Planned outcomes were measured, Hamilton depression scores in LF-rTMS compared to sham treatment.</i>
<b>Other</b>		
<b>What is the overall risk of bias?</b>	Low	

### Results.

Both groups significantly improved, but no statistical differences between them.

In the real TMS group patients age inversely correlated with improvement of depressive symptoms at the end of the study ( $r=-0.683$   $p=0.002$ ). Percentage of decrease in Hamilton scores was greater in subjects younger than 45 years old vs. others (41.3  $\pm$  22.6 vs. 15.1  $\pm$  15.8;  $t=2.8$   $df=16$ ,  $p=0.011$ ).

*See article for relevant tables and figures*

### Author's Conclusions.

Only younger patients benefited from LF-rTMS as adjuvant to treatment to antidepressants in this study.

### Our Comments/Summary.

Low risk of Bias.

Lack of statistical power due to small study population.

It is possible from the study that there is an inverse relationship between age and effectiveness of LF-rTMS, due to the small study population and lack of statistical power these results cannot be generalised to a wider population.

**Table A6.2 Quality appraisal table (Fitzgerald, 2012)**

**Study:** Fitzgerald, P. B., K. E. Hoy, et al. (2012). "A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression." *J Affect Disord* 139(2): 193-198.

**Description of study: Randomized Control Trial**

<b>Patient/population</b>	Patients with treatment resistant depression with a score (>15 17-item HAMD) + failure to respond to at least 2 courses of antidepressant meds for at least 6 weeks
<b>N</b>	N total = 67
<b>Setting</b>	Not stated
<b>Intervention/indicator</b>	SB-rTMS vs standard high-frequency left sided rTMS
<b>Comparison/control</b>	Sham rTMS treatment
<b>Outcomes</b>	scores on the 17-item Hamilton Depression Rating Scale (HAMD).
<b>Inclusion Criteria</b>	A diagnosis of moderate to severe depression (scoring greater than 15 on the 17-item version of the Hamilton Depression rating scale (HAMD).
<b>Exclusion Criteria</b>	Bipolar disorder, a significant active medical/neurological illness, or a contradiction to rTMS. Those with schizophrenia spectrum disorders.

**Study Validity.**

Is it clear that there were no conflicts of interest in the writing or funding of this study?	No	The authors reported that there were no actual or potential conflicts of interest
Does the study have a clearly- focused question?	Yes	
Is a RCT the appropriate method to answer the question?	Yes	
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Did the study have an adequate method of randomization?	Not reported	
Was allocation to intervention group concealed?	Not reported	
Were patients blind to the intervention group?	Yes	
Were investigators and care providers blind to intervention group?	No	Care providers were not blinded to the intervention due to the nature of the treatment.

Were outcome assessors blind to intervention group?	Yes	Raters were blind to the treatment.
All outcomes were measured in a standard, valid and reliable way?	Yes	
Were outcomes assessed objectively?	Yes	
Were outcomes assessed independently?	Not reported	
Were the groups similar at baseline with regards to key prognostic variables?	Yes	
Aside from the experimental intervention, were the groups treated the same?	Yes	
Were the outcomes measured appropriate?	Yes	
Was there a sufficient duration of follow-up?	Not reported	
Was there $\leq 20\%$ drop-out?	No	There was a 22% dropout rate.
Was the study sufficiently powered to detect any difference between the groups?	No	
If statistical analysis was undertaken, was this appropriate?	Yes	
Were all the subjects analysed in groups to which they were randomly allocated (intention to treat analysis)?	Yes	
Is the paper free of selective outcome reporting?	Yes	
Other		
What is the overall risk of bias?	Low	

#### Results.

In the three-week double-blind phase of the trial there was a greater antidepressant response to unilateral left sided rTMS compared with sham or bilateral rTMS. Across the full six weeks of active rTMS, there was also a consistent pattern of improved response in unilateral left compared to bilateral treatment. Response rates were low in both active groups.

*See article for relevant tables and figures*

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#### Author's Conclusions.

This study does not support the hypothesis that sequential bilateral rTMS is more effective than unilateral high-frequency left-sided rTMS

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#### Our Comments/Summary.

Low risk of bias, result generalisable to patients with treatment resistant depression.

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**Table A6.3 Quality appraisal table (Jakob, 2008)**

**Study:** Jakob F, Brakemeier EL, Schommer NC, Quante A, Merkl A, Danker-Hopfe H, et al. *Ultrahigh frequency repetitive transcranial magnetic stimulation in unipolar depression. Journal of Clinical Psychopharmacol.* 2008;28(4):474-6.

**Description of study: Randomized Control Trial**

<b>Patient/population</b>	Inpatients with moderate to severe unipolar depression (DSM-IV criteria)
<b>N</b>	N = 36
<b>Setting</b>	Unknown
<b>Intervention/indicator</b>	Parameters: 20Hz, 2000 stimuli; train duration, 2 seconds; interstimulus interval, 18 seconds, 100% MT or 50Hz, 2000 stimuli; train duration, 1 second; interstimulus interval, 59 seconds; 100% MT Location: DLPFC Duration: daily runs of rTMS for 5 consecutive working days within 1 week
<b>Comparison/control</b>	Sham rTMS
<b>Outcomes</b>	HDRS, MADRS and BDI
<b>Inclusion Criteria</b>	Inpatients with moderate to severe unipolar depression (DSM-IV criteria)
<b>Exclusion Criteria</b>	Refer to a previous study (see citation 9, pg. 476)

**Study Validity.**

<b>Is it clear that there were no conflicts of interest in the writing or funding of this study?</b>	Yes	This study was supported by a grant from the German Ministry of Education and Research and the Charite Research Program.
<b>Does the study have a clearly- focused question?</b>	Yes	"To determine the tolerability and the antidepressive efficacy of an ultrahigh frequency rTMS with 50Hz as compared with a standard intervention (20Hz) and a placebo".
<b>Is a RCT the appropriate method to answer the question?</b>	Yes	
<b>Does the study have specified inclusion/exclusion criteria?</b>	Yes	
<b>If there were specified inclusion/ exclusion criteria, were these appropriate?</b>	Yes	Reference is made to a previous study (see citation 9, pg. 476)
<b>Did the study have an adequate method of randomization?</b>	Not reported	Method of randomisation not reported
<b>Was allocation to intervention group concealed?</b>	Not reported	Method of allocation was not reported



Were patients blind to the intervention group?	Yes	"...patients were blinded to treatment type".
Were investigators and care providers blind to intervention group?	Not reported	
Were outcome assessors blind to intervention group?	Yes	"...clinical raters were blinded to treatment type".
All outcomes were measured in a standard, valid and reliable way?	Yes	See outcomes above
Were outcomes assessed objectively?	Not reported	Outcomes objectively assessed not reported
Were outcomes assessed independently?	Not reported	Outcomes independently assessed not reported
Were the groups similar at baseline with regards to key prognostic variables?	Yes	"At baseline, the three groups receiving real treatment did not differ significantly in sex distribution or antidepressant mediation".
Aside from the experimental intervention, were the groups treated the same?	Not applicable	This was a randomised, crossover, single-blind study.
Were the outcomes measured appropriate?	Yes	Standard objective tools and measures
Was there a sufficient duration of follow-up?	Not Reported	
Was there ≤20% drop-out?	No	.
Was the study sufficiently powered to detect any difference between the groups?	Not applicable	
If statistical analysis was undertaken, was this appropriate?	Yes	
Were all the subjects analysed in groups to which they were randomly allocated (intention to treat analysis)?	Not applicable	This was a randomised, crossover, single-blind study
Is the paper free of selective outcome reporting?	Yes	
Other		

What is the overall risk of bias?

Moderate

## Results.

$\chi^2_2 = 0.9$ ;  $P = 0.6$ ). Furthermore, no differences could be observed concerning the duration of the current episode (sham,  $12.7 \pm 5.4$  month; 20 Hz,  $12.2 \pm 12.3$ ; 50 Hz,  $12.2 \pm 9.8$ ;  $F = 0.013$ ;  $P = 0.9$ ) and the total number of depressive episodes (sham,  $3.7 \pm 2.6$ ; 20 Hz,  $3.8 \pm 3.3$ ; 50 Hz,  $3.7 \pm 1.9$ ;  $F = 0.016$ ;  $P = 0.9$ ). Univariate ANOVAs showed differences neither at baseline between the treatment groups in the 3 outcome scores (HDRS:  $F = 0.5$ ,  $P = 0.6$ ; MADRS:  $F = 0.7$ ,  $P = 0.5$ ; BDI:  $F = 0.8$ ,  $P = 0.5$ ) nor after 2 weeks of treatment (HDRS:  $F = 0.02$ ,  $P > 0.9$ ; MADRS:  $F = 0.1$ ,  $P = 0.9$ ; BDI:  $F = 0.04$ ,  $P > 0.9$ ). In the total group (pooled sample), ANOVAs for repeated measurements revealed significant time effects reflecting reductions in HDRS ( $F = 16.1$ ;  $P < 0.001$ ), MADRS ( $F = 18.8$ ;  $P < 0.001$ ), and BDI ( $F = 17.3$ ;  $P < 0.001$ ). However, as nonsignificant interaction effects time  $\times$  treatment indicate, the placebo stimulation and the 2 verum rTMS did not result in different HDRS ( $F = 0.8$ ;  $P > 0.4$ ), MADRS ( $F = 0.3$ ;  $P > 0.7$ ), or BDI ( $F = 0.8$ ;  $P > 0.4$ ) changes over the 2 weeks (see also Fig. 1). Univariate ANOVAs were also performed for the differences between the scores observed at baseline and after 2 weeks of treatment. All 3 outcome variables did not show significant differences between the 3 treatment groups (all  $F$  values  $< 0.8$ ; all  $P$  values  $> 0.4$ ) concerning the changes of scores.

## Author's Conclusions.

"Although we were able to find that 50Hz rTMS is safe, we were not able to find clinical effects with the chosen parameters after two weeks of treatment"

## Our Comments/Summary.

Moderate risk of bias.

**Table A6.4 Quality appraisal table (*Keshtkar, 2011*)**

**Study:** Keshtkar M, Ghanizadeh A, Firoozabadi A. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for the treatment of major depressive disorder, a randomized controlled clinical trial. J ECT. 2011;27(4):310-4.

**Description of study: Randomized Control Trial**

<b>Patient/population</b>	Patients with major depressive disorder (DSM-IV criteria)
<b>N</b>	N = 73
<b>Setting</b>	Unknown
<b>Intervention/indicator</b>	rTMS; Parameters: 90% MT Location: left DLPFC Duration: 10 minute session for 10 days
<b>Comparison/control</b>	Bilateral ECT (10 sessions, 3 weekly)
<b>Outcomes</b>	BDI and HDRS
<b>Inclusion Criteria</b>	Inpatients with dysthymia or major depressive disorder without psychoactive medication for 7 days
<b>Exclusion Criteria</b>	Exclusion criteria were previous experience with transcranial magnetic stimulation, implanted devices such as a cochlear implant or pacemaker, history of seizures, bipolar disorder, a diagnosis of substance or alcohol abuse, a history of significant head trauma, severe medical conditions such as hypothyroidism, a history of nonresponse to earlier ECT, and pregnancy or planning to become pregnant during the study period. Patients who did not provide written informed consent were excluded in the study.

**Study Validity.**

<b>Is it clear that there were no conflicts of interest in the writing or funding of this study?</b>	Not reported	
<b>Does the study have a clearly- focused question?</b>	Yes	"In the present study of patients with MDD, we hypothesized that the antidepressant effect of bilateral temporal ECT and rTMS would be similar. In addition, we compared the effects of rTMS and ECT on suicidal behavior. To the best of the authors' knowledge, this is the first study that examines the effects of these 2 treatments on suicidal behavior in patients with MDD"
<b>Is a RCT the appropriate method to answer the question?</b>	Yes	
<b>Does the study have specified inclusion/exclusion criteria?</b>	Yes	The study lists an inclusion and exclusion criteria
<b>If there were specified inclusion/ exclusion criteria, were these appropriate?</b>	Yes	See above

<b>Did the study have an adequate method of randomization?</b>	No	"Simple randomization by tossing a coin was used for each trial participant."
<b>Was allocation to intervention group concealed?</b>	Not reported	Method of allocation not stated
<b>Were patients blind to the intervention group?</b>	No	"The participants were not blind to the treatment they received"
<b>Were investigators and care providers blind to intervention group?</b>	Not reported	Method of blinding not stated
<b>Were outcome assessors blind to intervention group?</b>	Not reported	Method of blinding not stated
<b>All outcomes were measured in a standard, valid and reliable way?</b>	Yes	See outcomes above
<b>Were outcomes assessed objectively?</b>	Partial	"The BDI is a self-reporting questionnaire, whereas the HDRS is administered in a structured, face-to-face interview".
<b>Were outcomes assessed independently?</b>	Partial	"Data for the HDRS were provided by the patients themselves and also, in many cases, by their relatives"
<b>Were the groups similar at baseline with regards to key prognostic variables?</b>	Yes	
<b>Aside from the experimental intervention, were the groups treated the same?</b>	Yes	
<b>Were the outcomes measured appropriate?</b>	Yes	Standard objective tools and measures were used
<b>Was there a sufficient duration of follow-up?</b>	Unsure	
<b>Was there ≤20% drop-out?</b>	Yes	."60 patients completed the study"
<b>Was the study sufficiently powered to detect any difference between the groups?</b>	Yes	"The power of this study in the ECT group for the BDI score and HDRS was 0.999 and 0.999, respectively. The power in the rTMS group for the BDI score and HDRS was 0.993 and 0.999, respectively"
<b>If statistical analysis was undertaken, was this appropriate?</b>	Yes	"General linear model, repeated-measures analysis, was conducted to examine the trend for reduction of the scores between the 2 groups. The pre-intervention BDI score, HDRS score, and sex were considered as independent factors".

Were all the subjects analysed in groups to which they were randomly allocated (intention to treat analysis)?	Yes	
Is the paper free of selective outcome reporting?	Yes	
Other		
What is the overall risk of bias?	Moderate	

#### Results.

Both interventions significantly decreased BDI score. However, ECT decreased BDI score more than rTMS. Electroconvulsive therapy and rTMS decreased depression measured by HDRS. Again, ECT decreased HDRS score more than rTMS. Both ECT and rTMS significantly decreased the suicidal subscale score of BDI. Electroconvulsive therapy significantly decreased the score more than rTMS

#### Author's Conclusions.

"In conclusion, in a sample of adult patients with refractory MDD, ECT was more effective than rTMS in reducing symptoms of depression. Moreover, ECT was more effective than rTMS in reducing suicidal behavior in the short term. Until strong evidence for the safety and efficacy of rTMS is available, further studies should be designed to compare ECT and rTMS in terms of the long-term relapse rate and quality of life".

#### Our Comments/Summary.

Moderate risk of bias

**Table A6.5 Quality appraisal table (Triggs, 2010)**

**Study:** Triggs WJ, Ricciuti N, Ward HE, Cheng J, Bowers D, Goodman WK, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. *Psychiatry Res.* 2010;178(3):467-74.

**Description of study: Randomized Control Trial**

<b>Patient/population</b>	Patients between 18 and 75 years of age with medically resistant major depressive disorder (DSM-IV, SCID) over 6 years
<b>N</b>	n = 48: right rTMS (n=16); left rTMS (n=18); right sham rTMS (n=7); left sham rTMS (n=7)
<b>Setting</b>	Not stated, conducted in USA
<b>Intervention/indicator</b>	left vs right frontal rTMS (5Hz, 100% MT; 10 sessions over 2 weeks; 50 trains of 40 stimuli (2000 per session), 8s duration, 22s interval) All patients continued their antidepressant medication throughout the study period
<b>Comparison/control</b>	Right sham rTMS vs left sham rTMS
<b>Outcomes</b>	Mood HAMD, BDI, STAI
<b>Inclusion Criteria</b>	Patients between 18 and 75 yrs of age with medically resistant major depression over 6 years Major Depressive Disorder according to DSM IV criteria and verified by Structured Clinical Interview for DSM Disorders (SCID). All patients had a total score of 18 or higher and a score of at least 3 on item number 1 of the 24-item Hamilton Rating Scale for Depression (HAMD) in two separate screening sessions. All patients had 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). All patients continued their antidepressant medication throughout the study period.
<b>Exclusion Criteria</b>	<p>"Exclusionary criteria for participation included a lifetime history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar illness, alcohol or drug abuse within the past year; a positive urine drug test; axis II diagnosis of Cluster A (paranoid, schizoid, or schizotypal) or Cluster B (antisocial, borderline, histrionic, or narcissistic) personality disorder or mental retardation. Additional exclusionary criteria included:</p> <p>I. Use of medications that may lower seizure threshold (e.g., metronidazole) if the particular medication could not be stopped or altered without affecting the patient's medical care.</p> <p>II. History of neurological illness, epilepsy or seizure disorder, intracranial tumor, or major head trauma leading to loss of consciousness of any duration.</p> <p>III. 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.</p> <p>IV. History of implanted pacemaker or medication pump, metal plate in skull, or metal objects in the eye or skull.</p> <p>VIII. 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).</p> <p>IX. A medical condition that was not well controlled, such as diabetes or hypertension, or concomitant medical or nutritional problems necessitating hospitalization.</p> <p>X. Use of anticonvulsant mood stabilizers (e.g., carbamazepine, valproic acid).</p> <p>XI. Inability to personally grant informed consent.</p>

**Study Validity.**

<b>Is it clear that there were no conflicts of interest in the writing or funding of this study?</b>	Not reported	
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Does the study have a clearly- focused question?	Yes	
Is a RCT the appropriate method to answer the question?	Yes	
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Did the study have an adequate method of randomization?	Not reported	"Subjects were randomized 1:1:1 to receive left frontal rTMS, right frontal rTMS, or sham rTMS. Subjects randomized to receive sham rTMS were further randomized 1:1 to either left or right frontal sham rTMS."
Was allocation to intervention group concealed?	Not reported	
Were patients blind to the intervention group?	Yes	
Were investigators and care providers blind to intervention group?	Partial	"One of the limitations inherent to controlled studies of rTMS is that it is impractical to blind the investigator administering real or sham stimulation. It is therefore possible that some aspect of the proposed treatment other than actual electromagnetic brain stimulation (e.g., psychological interaction with an unblinded treating investigator) might contribute to the therapeutic effect of rTMS. In reviewing controlled trials of ECT, Crow and Johnstone (1986) suggested that the psychological effects of participation in an elaborate physical procedure are underestimated. We attempted to control for this by deliberately limiting interaction between unblinded treating investigators and patients. Instead, a blinded psychiatric research nurse accompanied all patients to all treatment sessions. During each treatment session, the research nurse engaged each patient in conversation about their lives and addressed patient expectations and experience regarding their participation in this clinical trial (i.e., possible discomforts associated with either real or simulated rTMS)."
Were outcome assessors blind to intervention group?	Yes	"The mood assessments were administered by trained psychiatry research nurses unaware of the patient's treatment group (real or sham rTMS)."
All outcomes were measured in a standard, valid and reliable way?	Yes	
Were outcomes assessed objectively?	Yes	"We rated mood using the 24-item Hamilton Rating Scale for Depression (HAM-D) and the long form of the Beck Depression Inventory (BDI). We used the State Trait Anxiety Inventory (STAI) as a secondary measure... The mood assessments were administered by trained psychiatry research nurses unaware of the patient's treatment group (real or sham rTMS)."
Were outcomes assessed independently?	Not reported	
Were the groups similar at baseline with regards to key prognostic variables?	Yes	"We found no significant differences in baseline characteristics among the subjects randomized to receive left rTMS, right rTMS or sham stimulation, or between the subjects in the two sham groups"

<b>Aside from the experimental intervention, were the groups treated the same?</b>	Yes	“It is therefore possible that some aspect of the proposed treatment other than actual electromagnetic brain stimulation (e.g., psychological interaction with an unblinded treating investigator) might contribute to the therapeutic effect of rTMS. In reviewing controlled trials of ECT, Crow and Johnstone, (1986) suggested that the psychological effects of participation in an elaborate physical procedure are underestimated. We attempted to control for this by deliberately limiting interaction between unblinded treating investigators and patients. Instead, a blinded psychiatric research nurse accompanied all patients to all treatment sessions. During each treatment session, the research nurse engaged each patient in conversation about their lives and addressed patient expectations and experience regarding their participation in this clinical trial (i.e., possible discomforts associated with either real or simulated rTMS).”
<b>Were the outcomes measured appropriate?</b>	Yes	
<b>Was there a sufficient duration of follow-up?</b>	Yes	Patients followed up at 1 and 3 months
<b>Was there ≤20% drop-out?</b>	Yes	All 48 enrolled patients completed treatment and post treatment evaluation 3 were lost to follow up at 3 months (the treatment group that these patients belonged to was not specified)
<b>Was the study sufficiently powered to detect any difference between the groups?</b>	No	“not statistically significant because of the lower statistical power of our smaller study” “It can be seen that because there was a larger treatment effect in our study, we would likely have had statistical power to demonstrate significance at one of two endpoints at an alpha level of 0.025 with 80% probability with 22–30 subjects in the left rTMS group and 22–30 subjects in the left sham group.” – there were 18 patients in the left rTMS groups, and 7 in the left sham rTMS group
<b>If statistical analysis was undertaken, was this appropriate?</b>	Yes	“Means and S.D.s were computed for continuous baseline variables and outcomes and percentages were computed for binary variables for the sham, right rTMS and left rTMS groups. The balance of baseline characteristics across three groups was compared using ANOVA for continuous variables and chi-squared and Fisher's exact tests for categorical variables. A linear mixed effect model was used to evaluate the effects of study intervention (left rTMS, right rTMS, or sham) on HAMD scores by controlling the baseline HAMD scores and taking into account the correlation between repeated measurements within subject. The model adequacy was assessed with standard model diagnostics. Analyses were conducted in SAS (SAS Institute, Cary, North Carolina). Posthoc analyses were carried out similarly.”
<b>Were all the subjects analysed in groups to which they were randomly allocated (intention to treat analysis)?</b>	Yes	There should not be any crossovers in a blinded sham controlled study
<b>Is the paper free of selective outcome reporting?</b>	Yes	
<b>Other</b>		
<b>What is the overall risk of bias?</b>	Low	Low - Most of the criteria have been fulfilled and those criteria that have not been fulfilled are unlikely to affect the conclusions of the study.

## Results.



“Mean ( $\pm$ S.D.) reductions in the HAMD-24 from baseline to 3-months were not significantly different between rTMS and sham treatment groups. However, right cranial stimulation (sham or rTMS) was significantly more effective than left cranial stimulation (sham or rTMS) ( $P=0.012$ ). Mean ( $\pm$ S.D.) reductions in the HAMD from baseline to 3 months were: left: 28.1 ( $\pm 5.36$ ) to 19.2 ( $\pm 11.2$ ); and right 27.2 ( $\pm 4.2$ ) to 11.5 ( $\pm 9.4$ ).”

“3. Results We found no significant differences in baseline characteristics among the subjects randomized to receive left rTMS, right rTMS or sham stimulation, or between the subjects in the two sham groups (Table 1). None of our subjects experienced any serious adverse events. All 48 subjects completed the 2-week course of rTMS treatment (Fig. 1). Adverse events consisted mainly of headache and localized scalp discomfort. These adverse events were reported in both TMS and sham treatment groups as presented in Table 2. We did not ask subjects if they thought they were receiving either real or sham stimulation because we did not want subjects to focus their attention on this issue. However, previous studies (Rossi et al., 2007; Mennemeier et al., 2009) in volunteers naïve to TMS suggest that this technique provides effective subject blinding.

Mean results for the HAMD, BDI and STAI are presented in Table 3. The linear mixed model for the HAMD as the dependent measure revealed no significant group differences in HAMD scores between subjects receiving left rTMS, right rTMS and sham stimulation (Fig. 2;  $F_{2,169}=2.02$ ;  $P=0.14$ ).

Fig. 2 and Table 3 suggest that patients receiving right rTMS tended to improve more than patients receiving left rTMS or sham stimulation, but also that patients receiving right-sided sham stimulation improved more than patients receiving left-sided sham stimulation. The difference between the sham groups was statistically significant at 1 month ( $P=0.022$ ) and 3 months ( $P=0.0053$ ) after completion of treatment. These two groups were comparable at baseline (Tables 1 and 3). A post-hoc linear mixed model comparing right-sided and left-sided stimulation collapsed across both rTMS and sham stimulation types also showed a significant difference ( $F_{1,169}=6.45$ ,  $P=0.012$ ), such that on average patients receiving right-sided stimulation (rTMS or sham) achieved HAMD scores about 8 points lower than patients receiving left-sided stimulation (rTMS or sham). This difference is illustrated in Fig. 3. We found that MEP thresholds decreased slightly after rTMS ( $-0.97 \pm 1.30$ ;  $P=0.0001$ ) but not after sham stimulation ( $0.14 \pm 0.55$ ;  $P=0.37$ ). The change in thresholds was significantly different between rTMS and sham ( $P=0.0036$ ).”

*See article for relevant tables and figures*

#### Author’s Conclusions.

“Left rTMS achieved a reduction in HAMD 9.5 points greater than that achieved by left sham, a benefit greater than that reported in a recent multi-center Phase III trial of rTMS (O’Reardon et al., 2007), albeit not statistically significant. These results suggest that somatosensory stimuli that repeatedly engage the left hemisphere may be important to the achievement of therapeutic effect.”

“Our study suggests that the effects of the rTMS treatment paradigm on depression likely reflect a complex mix of placebo, social, and somatic stimulation effects in which laterality of stimulation may be important. Although we did not find an rTMS effect, we cannot rule it out, particularly when it is applied to the left hemisphere, and future studies need to consider the possible value of rTMS applied at other sites, possibly at different frequencies, and ultimately, tailored to specific patients

#### Our Comments/Summary.

This study has a low risk of bias.

Overall this study was conducted well. The lack of information about the method of randomisation used makes it difficult to determine if randomisation was done effectively, however, the similarity of the groups at baseline show that an adequate method may have been used.

Despite the low risk of bias, the small sample size makes this study underpowered to confidently detect a difference in outcomes between groups, therefore the results should not be generalised.

## APPENDIX 7: QUALITY APPRAISAL GAYNES REPORT

**Table A7.1 Critical appraisal table (Gaynes, 2011)**

**Study:** Gaynes, B. N., L. J. Lux, et al. (2011). Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33. AHRQ Publication No. 11-EHC056-EF. Rockville, MD, Agency for Healthcare Research and Quality.

### Description of study: Systematic Review

<b>Patient/population</b>	Patients with Major depressive Disorder.		
<b>N</b>	64 studies Please note all these studies may not have assessed our outcomes of interest.		
<b>Setting</b>	In patient and outpatient		
<b>Intervention/indicator Comparison/control</b>	<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
	Rosa et al., 2006	rTMS	ECT
	Grunhaus et al., 2003		
	Hansen et al., 2010		
	McLoughlin et al., 2007, Eranti et al., 2007, and Knapp et al., 2008		
	Boutros et al., 2002	rTMS	Sham Treatment
	Garcia-Toro et al., 2001		
	Garcia-Toro et al., 2006		
	Kauffmann et al., 2004		
	Padberg et al., 1999		
	Pallanti et al., 2010		
	Zheng et al., 2010		
	Holtzheimer et al., 2004		
	Avery et al., 2006		
	Pascual-Leone et al., 1996		
	George et al., 2010		
	Manes et al., 2001 and Moser et al., 2002		
	Stern et al., 2007		
	O'Reardon, 2007		

	Please note some of these studies may have used comparators not relevant to our question.	
Outcomes	Response and remission, Maintenance of remssion, safety adverse events and adherence, health related outcomes	
Inclusion Criteria	RCTs comparing non-pharmacological treatments, RCTs comparing non-pharmacological treatments to pharmacological treatment. Observational studies.	
Exclusion Criteria	No major exclusion criteria reported.	
Study Validity.		
Is it clear that there were no conflicts of interest in the writing or funding of this review?	Yes	“None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report”
Does the review have a clearly- focused question?	Yes	The report has a set of key questions it wishes to answer.
Is a systematic review the appropriate method to answer the question?	Yes	
Does the review have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Does the review document a comprehensive search strategy?	Yes	
Were reviewers blind to authors, institutions and affiliations?	Not reported	
Were 2 or more independent reviewers used for:	Yes	
1. application of inclusion criteria to assess eligibility of studies?		
2. extraction of data from study reports?	Yes	

<b>3. appraisal of study quality?</b>	Yes	
<b>Were the strengths and limitations of included studies and potential impact on the results discussed?</b>	Yes	
<b>Was the validity of included trials appraised using appropriate criteria?</b>	Yes	
<b>Is there a summary of the results of individual studies?</b>	Yes	
<b>If meta-analyses were conducted, was it reasonable to do so?</b>	Yes	
<b>If meta-analyses were conducted, was it done appropriately?</b>	Yes	
<b>Other</b>		
<b>What is the overall risk of bias?</b>	Low	

#### Results.

From a total of 2,754 citations retrieved, we ultimately identified 79 good-, fair-, or poor-quality articles in this review; they represent 64 studies. Of these studies, there were 17 head-to-head RCTs (19 articles): 7 studies (9 articles) were head-to-head RCTs of a nonpharmacologic intervention versus a nonpharmacologic intervention; 3 were head-to-head RCTs of a nonpharmacologic intervention versus a pharmacologic one; and 7 were head-to-head studies of a pharmacologic versus pharmacologic intervention. Further, there were 38 additional RCTs (50 articles) that were sham- or placebo-controlled, and 2 observational studies (2 articles). We excluded 8 studies (8 articles) because of poor quality. We present evidence that allows comparison of the four nonpharmacologic treatments of interest (ECT, rTMS, VNS, and psychotherapy) stratified by tiers of evidence. Comparative clinical research on nonpharmacologic interventions in a TRD population is in its infancy. Many clinical questions about efficacy and effectiveness remain unanswered. The text below presents our principal results; summary tables (A–J) document Tier 1 TRD findings for major comparisons and outcomes for each key question, give the overall strength of evidence for that comparison, and outline key findings. We report first on direct evidence (head-to-head comparisons) and then on indirect evidence (e.g., trials using controls). If a specific comparison did not involve a Tier 1 population but did have trials conducted in a Tier 2 and/or Tier 3 population, we have listed it in this table, noted “No eligible studies identified,” and added a footnote indicating the presence of at least one such study. The greatest volume of evidence is for ECT and rTMS; however, the direct comparative evidence about even these treatments is quite limited. Available indirect evidence primarily involves rTMS; a little information is available on VNS and psychotherapy (chiefly for efficacy and adverse events), and no available indirect evidence involves ECT. Given the limited number of Tier 1 studies incomplete reporting on the number of failed treatment attempts, we were unable to stratify our outcomes by the number of treatment failures within Tier 1.

*See article for relevant tables and figures*

## **Efficacy of Nonpharmacologic Interventions Against Other Nonpharmacologic Interventions (KQ 1a)**

### **Direct Evidence**

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for Tier 1 TRD is limited to two fair trials (both in MDD-only populations). One compared ECT and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another nonpharmacologic intervention.

### **Indirect Evidence**

We identified trials that compared a nonpharmacologic intervention, generally rTMS, VNS, or psychotherapy, with a control or sham procedure in Tier 1 populations. We identified no eligible ECT versus control studies. The number of these trials with the same or similar control group was very small, so we could not pool them quantitatively. We could, however, assess the potential benefits of nonpharmacologic interventions versus controls by calculating mean changes in depressive severity, relative risks of response, and relative risks of remission. rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate). rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than three times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than six times as likely to achieve remission as those receiving the sham. In the only other Tier 1 comparison, one good-quality VNS versus sham control trial (a mixed MDD/bipolar population) reported no differences between the groups as measured by a change in depressive severity or response rates (low strength of evidence).

## **Efficacy of Nonpharmacologic Interventions Compared With Antidepressant Pharmacotherapies (KQ 1b)**

### **Direct Evidence**

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions compared with pharmacologic treatment (in this case, paroxetine) for Tier 1 trials is limited to one fair trial (a mixed MDD/bipolar population). ECT produced a significantly greater decrease in depressive severity (9 points by HAM-D) and significantly better response rates (71 percent vs. 28 percent) than medications (low strength of evidence).

### **Indirect Evidence**

Indirect evidence about procedures or psychotherapy (vs. sham or nonpharmacologic controls) was presented above as part of KQ 1. We attempted to determine mean changes in depressive severity, relative risks of response, and relative risks of remission for pharmacologic versus control studies to allow a comparison with similar outcomes in the nonpharmacologic versus control trials (KQ 1a, indirect). However, we found no comparable, common control groups (i.e., patients not receiving a mood-related medication) to allow such comparisons. Instead, we determined mean average outcomes for pharmacologic treatments. ¶ For switching strategies, mean pharmacologic response rates averaged 39.8 percent (95% CI, 30.7% to 48.9%) and mean remission rates averaged 22.3 percent (95% CI, 16.2% to 28.4%). For augmentation, mean response rates averaged 38.1 percent (31.0% to 45.3%) and

mean remission rates averaged 27.2 percent (20.4% to 34.0%). For maintenance strategies, mean response rates averaged 27.3 percent (19.8% to 34.8%) and mean remission rates averaged 16.8 percent (13.5% to 20.2%). Although these results provide an idea of the general degree of response seen with next-step pharmacologic treatment in TRD, they serve as an uncontrolled case series and should be compared to nonpharmacologic outcomes only with caution.

### **Maintenance of Remission or Prevention of Relapse (KQ 2)**

#### **Direct Evidence**

With respect to maintaining remission (or preventing relapse), we had no direct comparisons involving ECT, rTMS, VNS, or CBT.

#### **Indirect Evidence**

Three fair trials compared rTMS with a sham procedure and found no significant differences. However, too few patients were followed during the relapse prevention phases in two of the three studies, and patients in the third received a co intervention providing insufficient evidence for a conclusion. We had no eligible studies for ECT, VNS, or psychotherapy.

### **Efficacy of Nonpharmacologic Interventions for Patients With Different Symptomatology (KQ 3)**

#### **Direct Evidence**

We identified no Tier 1 trials that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.

#### **Indirect Evidence**

We identified no studies testing either procedure-based or psychotherapeutic interventions against sham procedures or other controls.

### **Safety, Adverse Events, and Adherence (KQ 4)**

#### **Direct Evidence**

In examining safety, adverse events, and adherence, we found some differences across the interventions in the harms and negative side effects to patients. However, the data were insufficient to reach a conclusive result. For just this set of analyses, we examined both clinical trials and cohort studies, and we focus on cognitive functioning, occurrence of specific adverse events, and withdrawals.

#### **Cognitive Functioning**

For Tier 1 studies on cognitive functioning, some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS (insufficient strength of evidence). No differences between groups on a single-item measure of cognitive functioning were found in a study comparing ECT with ECT and rTMS (insufficient strength of evidence).

#### **Specific Adverse Events**

One Tier 1 study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events (low strength of evidence).

### Withdrawals

We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result (low strength of evidence). Evidence for ECT compared with rTMS indicated higher rates of overall withdrawals in the ECT compared to the rTMS group ( $P = \text{NR}$ ; low strength of evidence).

### Indirect Evidence

We attempted to include data from the same types of studies and for the same outcomes as for direct evidence. We identified no studies comparing ECT versus control.

### Cognitive Functioning

Mixed evidence on cognitive functioning in rTMS versus sham was insufficient evidence to draw a conclusion (insufficient strength of evidence).

### Specific Adverse Events

rTMS groups reported significantly more scalp pain at the stimulation site (low strength of evidence). Some differences in the frequency of specific adverse events were seen when comparing VNS and sham groups, but the significance of the findings was not reported ( $P = \text{NR}$ ) (low strength of evidence).

### Withdrawals

Findings were mixed in Tier 1 studies as to whether rTMS groups had greater rates of withdrawals (overall and due to adverse events) than groups receiving sham procedures (insufficient evidence for both). Withdrawals attributable to adverse events were higher in the VNS group compared with sham (low strength of evidence). No Tier 1 studies reported on withdrawals for CBT groups versus those receiving some form of usual care.

### Efficacy or Harms of Nonpharmacologic Treatments for Selected Patient Subgroups (KQ 5)

#### Direct Evidence

We found no studies (in any tier) directly comparing nonpharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.

#### Indirect Evidence

Two Tier 1 trials compared rTMS with sham. All findings provided low strength of evidence. For young adults (ages 18–37), one trial found that rTMS produced a greater decrease in depressive severity and a greater response rate than sham. A second trial, conducted in older adults with post-stroke depression, found that rTMS produced a greater decrease in depressive severity and a greater response rate but no difference in remission rates compared with a sham control.

### Health-Related Outcomes of Nonpharmacologic Treatments (KQ 6)

#### Direct Evidence

With respect to patient-reported health-related outcomes, we focused on quality of life (various measures) and ability to function in daily life. One Tier 1 study compared ECT with a combination of ECT and rTMS and found no differences between groups in improvement on the Global Assessment of Functioning scale (low strength of evidence).

#### Indirect Evidence

Two trials (both in mixed MDD/bipolar populations) assessed general health status and mental and physical functioning (all health domains related to quality of life). In one fair trial, low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham (as measured by the Global Assessment of Functioning scale; low strength of evidence). In the other fair trial, VNS and sham groups did not differ significantly in daily functioning (as measured by the 36-item Medical Outcomes Study Short Form [MOS SF-36]; low strength of evidence). No studies of psychotherapy were identified.

### **Applicability**

For the limited amount and low strength of evidence available, the data for Tier 1 (TRD) is generally applicable to TRD populations. Populations enrolled in these trials appeared representative of our target population. Studied interventions were comparable to those in routine use, though dose and duration of nonpharmacologic treatment often varied between studies. Measured outcomes on the whole reflected the most important clinical outcomes for depression measures, although reporting was inconsistent; outcomes for the other key questions were much more restricted. Followup periods were generally shorter than desirable, but most were sufficient to measure an initial acute-phase treatment response. Study settings were a mixture of inpatient and outpatient, because ECT is generally an inpatient procedure and the others are generally outpatient. Some evidence highlights the importance of patient acceptability of treatment as some patients refuse particular interventions. An individualized balance between a patient's needs and concerns must be taken into account during selection from a range of nonpharmacologic and pharmacologic antidepressant treatment options. The use of inconsistent definitions of TRD in the trials and the absence of analyses considering the effect of the number of current treatment failures on outcomes hindered interpretation of data, leading to our use of a tiered system for analyses. The evidence base combining data for Tiers 1–3 on the whole produced findings that were consistent with Tier 1 TRD data and also appear applicable to TRD populations.

### **Remaining Issues**

This area of comparative clinical research is in its infancy. Key areas for future research need primarily to lay more robust foundations for an evidence base that can better inform decisions for clinicians and patients.

### **The Field Needs a Standard Definition of TRD That Investigators Should use in Their Clinical Trials Research**

Comparison of any of the potential interventions in the field, nonpharmacologic or otherwise, is hampered by the variability in TRD definitions. Although these definitions appear to be converging on a single meaning—two or more treatment failures in the current episode—very few studies of TRD have applied it. Progress in this area of research requires better standardization of this concept, so that future reviews of the evidence do not need to resort to differentiating, as we did, between “Tier 1” studies (i.e., TRD by this definition based on two or more treatment failures) and “Tier 2 or 3” types of studies. The latter do provide information that helps illuminate likely impacts of these interventions on patients with TRD, but that is not the same thing as having robust studies focused clearly on the patient population of greatest interest. The challenge will be to provide a definition that operationalizes TRD to make it feasible for clinicians while at the same time successfully capturing the complexity of treatment resistance.

**More Clinical Trials, as Well as Other Possible Study Designs, That Compare Nonpharmacologic Interventions With Other Nonpharmacologic Options and With Pharmacologic Treatments are Necessary to Inform Decisionmaking in TRD** Clinicians, patients, and policymakers need additional relevant data to guide difficult treatment decisions about what to do next: try another medication (and should it be an augmentation, switch, or combination strategy?) or add (or switch to) rTMS, ECT, VNS, or psychotherapy? Also, given that treatment options for many TRD patients include medications, trials should directly compare nonpharmacologic interventions with each other and with pharmacologic treatments.



### **The Number of Treatment Failures in the Current Episode Should be Delineated Carefully**

This information, more likely to be accurate than lifetime histories of failures, can help investigators determine whether the particular number of failures, or reaching a particular number of failures in a current episode, can help differentiate between nonpharmacologic treatment choices. For example, for patients with two treatment failures in a current episode, the outcomes may not differ between cognitive therapy and rTMS; however, for patients with a different (higher or lower) number of treatment failures in the current episode, one nonpharmacologic treatment may indeed be better than the other. Currently, we do not know what the proper threshold is for selection of treatment. Clarification of the scientific basis for such a decision would substantially improve decisionmaking.

### **Clarifying Whether Responses Differ for TRD Patients With MDD Compared With Those With Bipolar Disorder Will Help Guide**

#### **Future Clinical Trial Design**

Our decision to include trials with patient populations including up to 20 percent with bipolar disorder (i.e., the “mixed” populations noted earlier) was guided by clinical experience and common sense but not by data. Testing to see whether outcomes differ between the two groups can yield information about inclusion criteria (should the mix be 0 percent, 10 percent, 20 percent, etc.?) that may be useful to investigators in designing TRD trials and may be important to consider as a potential covariate in analyses involving such mixes.

### **Greater Consideration Should be Given to the Role That the Spectrum of Depressive Severity Plays**

Using a finer gradation of depressive severity than investigators now typically employ might identify whether particularly severe degrees of depression, most commonly understood currently as a HAM-D17  $\geq$  20, may respond differently to the available nonpharmacologic interventions than do less severe levels of depression. These gradations may lead clinicians to a better understanding of severe depression and its role in guiding treatment selection in TRD.

### **Direct Comparisons of Treatment Strategies, Holding Consistent any Coexisting or Concomitant Therapies, are Imperative**

Decisionmakers need to know whether outcomes with nonpharmacologic treatments are better when such a treatment augments the current treatment, replaces the current treatment, or replaces the current treatment in combination with another treatment. When ongoing treatment is uncontrolled and reflects a variety of treatments—e.g., some patients continue with atypical antipsychotics, some with mood stabilizers, some with no psychotropic medications—results of such studies are difficult, if not impossible, to interpret.

### **Consistent Reporting of Changes in Depressive Severity, Response Rates, and Remission Rates is Crucial**

To allow for better comparisons of clinical outcomes in this difficult-to-treat population, all three measures offer useful information for clinicians. Thus, for either clinical trials or observational studies, investigators should attempt to collect data on all three routinely.

#### **Application of Consistent, Accepted Protocols in Trials is Necessary**

Making sure that patients receive equivalent doses of different nonpharmacologic interventions is more difficult than making sure of this for pharmacologic interventions. Nevertheless, investigators designing trials of nonpharmacologic therapies can attempt to do so by implementing standard accepted protocols for their trials. Such “dosing” had been difficult to control when that protocol was in the process of being developed, as with rTMS, but given current treatment parameters, this standardization is a goal well worth trying to reach.

### **More Careful and Consistent Assessment of Adverse Events is Required**

Adverse event reporting is quite limited and tends to cover only a short time span; what reporting does exist is variable and inconsistent. Systematic collection and more consistent reporting of data on harms—that is, adverse events and negative side effects—and information about attrition and withdrawal would provide useful information to help balance information now focused on clinical benefits. Use of the CONSORT statement (available at: <http://www.consort-statement.org/home/>), which guides proper reporting of study information (including the presentation of adverse events), would strengthen reporting of both harms and other clinical trial findings; it would also aid in the critical appraisal and interpretation of all study results. Further, a more informative assessment of adverse events would require studies to be able to assess long-term and cumulative outcomes.

#### **Including Key Relevant Measures and Subgroups in Subsequent Research is Desirable**

As indicated by the review, nearly no evidence exists on how the effectiveness of nonpharmacologic treatments differs (or not) as a function of symptom subtypes or for subgroups defined by sociodemographic characteristic (such as age) or coexisting medical conditions (e.g., post-stroke or postmyocardial infarction depression; perinatal depression). Also essentially missing is information about health-related outcomes, especially those reported by patients, that concern their quality of life or levels of functional impairment. Subsequent studies should focus on employing known, reliable, and valid measures of patient-reported outcomes, such as the MOS SF-36, the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LESQ), and the EQ-5D.

#### **Including Comparisons of Newer Nonpharmacologic Interventions Will be Important in Future Research**

As new nonpharmacologic treatments are developed and tested, investigators should try to include them as potential comparators. At the time we started this comparative effectiveness review, clinical trial data on some of the developing nonpharmacologic interventions, such as magnetic seizure therapy or deep brain stimulation, were insufficient (from the published literature) for us to try to include them. As the evidence bases grow to support the efficacy of such additional nonpharmacologic interventions, the newer strategies should be included in comparative effectiveness study designs.

### **Author's Conclusions.**

#### **Conclusion**

Our review suggests that comparative clinical research on nonpharmacologic interventions in a TRD population is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS. However, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for benefits, reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change our confidence in these findings. This finding of low strength is most notable in two cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions with themselves and with pharmacologic treatments, and to delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.

#### **Our Comments/Summary.**

This is a well conducted study with a low risk of bias.