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*[1]

In Australia, mental health disorders are the largest cause of nonfatal disease burden.[2] 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.[3]

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).[4] 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.[5]

Although ECT has been shown to be effective, it is associated with cognitive side effects and risks associated with repeated anaesthesia,[5] 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 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.[6]

The rTMS technique can vary in many different ways, such as:[7, 8]

- 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.[8]

Regulatory status

Although rTMS is seen 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)?"[9]

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.[10]

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).[8] The Medical Services Advisory Committee is currently reconsidering funding for this technology.[11]

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')[12] (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[4]).

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[4,8,13-31] synthesised studies (SRs, MA, or EBGs)
- 84[32-113] 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,[25] Gaynes 2011,[4] and Allan 2011.[14] The most up to date search was conducted by Gaynes 2011[4] 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[4] 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.[4, 13, 26-28, 31] Thirteen reviews exclusively compared the effect of rTMS with sham rTMS[14-24, 29, 30] and two exclusively compared rTMS to ECT.[8, 25]

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,[4] 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.[4] An update of this review is presented in this report.

UPDATE OF MOST RECENT, HIGH QUALITY, SYNTHESISED STUDY

The SR by Gaynes 2011[4] 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;[32, 51, 67, 70, 108] four comparing rTMS with sham rTMS and one comparing rTMS to ECT. Overall, including the studies reviewed by Gaynes 2011,[4] 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[4] with the addition of four new studies (Fitzgerald 2012,[51] Aguirre 2011,[32] Triggs 2010[108] and Jakob 2008[67]). 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 [100] and Keshtkar 2011[70] recruited patients with two or more prior treatment failures and one study[58] recruited patients with one or more prior treatment failures. Two studies[46, 73] 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.[58, 100, 114] One did not report the frequency used. The motor threshold was 90% in two studies,[58, 70] 100% in one study[100] and 110% in one study.[114] 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[58, 114] and HAM-D24[70]) to assess improvements in depression. Other scales used to assess response included Clinical Global Impression Scale[100] and the Beck Depression Inventory (BDI).[70] Definition of response and remission differed between studies. For example Rosa 2006[100] defined response as HAM-D17 ≤ 7 while Grunhaus 2003[58] defined response as a decrease of 50% or more, or HAM-D17 ≤ 10 and a final Global Assessment of Function Scale rating ≥ 60. In terms of remission Rosa 2006[100] defined it as HAM-D17 ≤ 7, while McLoughlin 2007[114] and Grunhaus 2003[58] defined remission as HAM-D17 ≤ 8. The majority of studies exclusively assessed outcomes at end of treatment, only McLoughlin 2007[114] assessed outcomes at six months.

Results

With regards to the effectiveness of rTMS compared to ECT, two studies found no significant difference[100,58] and two studies[114,70] 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[58] and Clinical Global Impression Scale.[100] In addition, for those studies reporting response rates[58, 100] no signficant difference between rTMS and ECT was observed. Keshtkar 2011[70] and McLoughlin 2007[114] 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[100,58] found no signficant difference between rTMS and ECT. One other[114] 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[70] found ECT to be more effective in reducing post-treatment BDI and HAM-D suicide scores compared to rTMS.

Neurological functioning

Two studies[100, 114] conducted neurological assesments 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.[70, 100] Overall the main side effects reported for rTMS included localised pain or mild headache. The study by Keshtkar 2011[70] withdrew two patients in the ECT group due to a loss of conciousness. Adverse events were not compared between groups for two studies, as Grunhaus

2003[58] did not report adverse events for the ECT group, and McLoughlin 2007[114] 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,[65, 69, 82, 94, 96] and 11 studies had between 21 and 68 patients. Among these studies there were two large trials, with sample sizes of 199,[55] and 325[92] 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),[82] medication-resistant depression of psychotic subtype (DSM-III),[96] moderate to severe TRD (HAM-D17), and unipolar depression (DSM-IV).[52]

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,[54, 67, 95] different locations[51, 94, 108] or different frequencies in different locations[106] 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,[69] in varying locations,[54, 96] or to an unspecified location.[67]

- 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).[95]

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[55] did not report the rating scale used, reporting only remission rates. One study measured improvements in depressive symptoms using the MADRS.[92]

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	1st 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.[35, 52, 54, 55, 92, 96] Of these studies, George 2010[55] and O'Reardon 2007[92] 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[52] 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.[52, 54, 55] Two studies[35, 96] 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.[92]

Nine studies found no significant difference between rTMS and sham rTMS for the treatment of depression.[32, 40, 65, 67, 69, 82, 94, 108, 113] 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 assesments at one week,[65, 82] four weeks,[32] and six months.[40]

Three studies reported mixed results. One study found that unilateral but not bilateral rTMS was more effective than sham treatment.[95] 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.[106] One study reported unilateral left sided rTMS was more effective than sham or bilateral rTMS.[51] All three of the studies measured the primary outcome at the end of active treatment. One study had an additional two week follow-up[106] and one study had a cross-over of patients.[51]

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 occured more frequently in the active group that the sham treatment group.[52, 54, 55, 82, 92, 94-96] None of the studies reported any signifcant differences between groups. Two studies reported on testing for neurophysiological adverse events and found that there was no significant difference between the groups.[35, 82]

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.	
Study design	Systematic review
Scope	**Patient/population:** Patients with TRD. **Intervention and comparators:** nonpharmacologic treatments including rTMS, sham rTMS, ECT, VNS, and evidence-based psychological treatments. **Outcomes assessed:** ECT vs. rTMS: change in depressive severity, response and remission rate, adverse events, withdrawals due to adverse events, cognitive functioning. rTMS vs. sham: change in depressive severity, response and remission rates, adverse events, withdrawals due to adverse events, cognitive functioning, health-related outcomes.
1. What is the effectiveness of rTMS in treating acute-phase depressive symptoms (e.g., response and remission)?	**Effectiveness in treating acute-phase depressive symptoms** **rTMS vs. ECT (n = 4 studies)** 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. **rTMS vs. sham rTMS (n = 18 studies)** Only one good quality study[92] was sufficiently powered to detect a significant difference between treatment arms. This study reported that rTMS was more effective than sham. 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. 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.

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?	**rTMS vs. ECT:** There is no evidence to answer this question. **rTMS vs. sham rTMS:** There is no evidence to draw conclusions on the effectiveness of rTMS on maintaining remission or preventing relapse when compared to sham rTMS.
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 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.
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?	There is insufficient evidence to determine the most effective rTMS protocols. rTMS location, frequency, motor thresholds, and duration of treatment varied across studies.
5. What is the safety of rTMS for depression?	None of the studies reported any significant differences between groups. **rTMS vs. ECT** *Cognitive functioning:* In some cases ECT can have an adverse impact on cognitive functioning. *Withdrawals due to adverse events:* there was no difference in withdrawals due to adverse effects between rTMS and ECT. **rTMS vs. sham rTMS** *Cognitive functioning:* the evidence on the effects of rTMS versus sham on cognitive functioning is insufficient to draw a conclusion. *Specific adverse events:* rTMS groups reported significantly more scalp pain at the stimulation site (low strength of evidence). *Withdrawals due to adverse events:* Findings were mixed as to whether rTMS groups had greater rates of withdrawals due to adverse events than groups receiving sham procedures.
Quality assessment results	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.

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[92], 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[51, 54, 67, 94, 95, 106, 108] 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[13]	Allan 2011[14]	Coutourier 2005[15]	Gaynes 2011[4]	Gross 2007[16]
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[17]	Herrmann 2009[18]	Holtzheimer 2001[19]	Kennedy 2009[20]	Kozel 2002[21]
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[22]	Martin 2003[23]	McNamara 2001[24]	Ontario Ministry of Health 2004[27]
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[26]	Rodriguez-Martin 2009[28]	Schutter 2010[30]	Schutter 2009[29]	Slotema 2010[31]
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[13]	Gaynes 2011[4]	Ontario Ministry of Health 2004[27]	MSAC 2008[8]
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	**3/9**	**11/11**	**6/9**	**9/11**

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

STUDY	Minichino 2012[25]	NICE 2007[26]	Rodriguez-Martin 2009[28]	Slotema 2010[31]
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	**2/11**	**4/9**	**10/11**	**3/11**

ECT = electroconvulsive therapy; MDD = major depressive disorder; RCTs = randomised controlled trials; rTMS = repetitive transcranial magnetic stimulation; SR/MA = systematic reviews/meta-analyses; 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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