NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of repetitive transcranial magnetic stimulation for depression

Depression can have a debilitating effect on a person's life, causing low mood or sadness, and may lead to suicide. People with depression often feel hopeless and lose interest in things they used to enjoy. Other symptoms include sleeping badly, and having no appetite or sex drive. Transcranial magnetic stimulation is a possible treatment for depression that uses a powerful electromagnet, placed on the scalp, to produce electric currents in the brain.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in February 2015 and updated in August 2015.

Procedure name

- Repetitive transcranial magnetic stimulation for depression

Specialist societies

- British Psychological Society
- Royal College of Psychiatrists

Description

Indications and current treatment

Depression is a common disorder which can have a debilitating effect on a person's life. It is characterised by persistent sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep, appetite and libido, feelings of tiredness and poor concentration. It is also often accompanied by feelings of hopelessness, suicidal thoughts and can lead to suicide. Depression can last from weeks to years, and can be recurrent. It can substantially impair an individual's ability to function at work or cope with daily life. Treatments for depression include a range of psychological therapies and antidepressant medications. In severe depression that has not responded to other treatments, electroconvulsive therapy is sometimes used.

What the procedure involves

Repetitive transcranial magnetic stimulation (rTMS) does not need anaesthesia and can be done on an outpatient basis. A purpose-made electromagnetic coil is held against the scalp with the intention of inducing electric currents in the cerebral cortex. Imaging may be used to help target specific areas of the brain. Treatment is usually considered for patients with depression that has not responded to antidepressant medication or patients for whom antidepressants are not suitable.

In rTMS, repetitive pulses of electromagnetic energy are delivered at various frequencies or stimulus intensities. Conventional rTMS is a repetition of individual pulses at a pre-set interval (train of pulses), whereas theta-burst rTMS is a repetition of short bursts of pulses at a pre-set interval (train of bursts). Stimulation can either be delivered unilaterally, over the left or right dorso-lateral prefrontal cortex (DLPFC), or bilaterally over both cortices. Bilateral stimulation may be done sequentially or simultaneously. Treatment with rTMS usually comprises daily sessions lasting about 30 minutes, for example, typically for 2 to 6 weeks.

Outcome measures

There are several scales used to measure depression severity. The Montgomery–Åsberg Depression Rating Scale (MADRS) measures 10 items (including apparent sadness, reported sadness and suicidal thoughts) on a scale of 0 to 6 with lower values indicating less depression. The Hamilton Depression Rating Scale (annotated as either HDRS or HAM-D) uses a semi-structured interview to assess several variables (including depressed mood, insomnia, agitation, anxiety and weight loss) measured on 5-point or 3-point scales, with lower scores indicating less depression.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to repetitive transcranial magnetic stimulation for depression. The following databases were searched, covering the period from their start to 28 August 2015: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with depression.
Intervention/test	Repetitive transcranial magnetic stimulation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 6327 patients from 4 systematic reviews, 1 non-randomised comparative study, 1 case series and 1 case report; however there may be considerable overlap between studies

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on repetitive transcranial magnetic stimulation for depression

Study 1 Slotema CW (2010)

Details

Study type	**Systematic review of randomised controlled trials**
Country	Netherlands
Recruitment period	1990 to 2008
Study population and number	Patients with depression (type unspecified) **n=1592 patients from 40 randomised controlled trials (751 rTMS versus 632 sham stimulation; 113 rTMS versus 102 Electroconvulsive therapy [ECT])**
Age and sex	Not reported
Study selection criteria	Inclusion criteria: randomised controlled trials that compared rTMS against sham or ECT were included. All included studies were written in English. When various studies described overlapping samples, the article with the largest sample size was included. Exclusion criteria: studies that included patients with vascular depression, employed single-arm or crossover designs, evaluated single-pulse transcranial magnetic stimulation, or performed rTMS as an add-on to ECT were excluded.
Technique	Patients received between 5 and 25 treatments of rTMS, delivered unilaterally or bilaterally (not simultaneously). Stimulation was performed using frequencies ranging from 1 Hz to 20 Hz and delivered at 80% to120% of motor thresholds.
Follow-up	**Not reported**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: Patients received between 5 and 25 sessions of rTMS.

Study design issues: Systematic review included studies in which rTMS was delivered at different cranial sites, stimulus intensities and motor thresholds. Patients were free of antidepressants in 7 studies; antidepressants were continued during rTMS in 17 studies; rTMS was started simultaneously with antidepressants in 5 studies. The remaining studies did not report if patients were taking antidepressants.

Study population issues: it is unclear what proportions of patients had different types of depression.

Other issues:

- Hedges' g effect sizes were calculated for the mean differences between pre-treatment and post-treatment values of unspecified depression rating scales. No details were provided on which rating scales were used to calculate the mean differences.
- For the overall rTMS versus sham stimulation comparison, the I^2 value was 81%, indicating substantial heterogeneity between studies. For the overall rTMS versus ECT comparison, the I^2 value was 28%, indicating moderate heterogeneity between studies.
- No parameters for low- or high-frequency rTMS were defined.

Efficacy

Number of patients analysed: **1592 patients (751 rTMS versus 632 sham stimulation; 113 rTMS versus 102 ECT. Numbers varied according to outcome measure assessed.**

Meta-analyses of rTMS versus sham stimulation

Outcome measure	Effect size (Hedges g)	Direction of effect	p value	I^2 (%)
All types of stimulation (overall) [a]	0.55	Favours rTMS	<0.001	54
Delivered at the left DLPFC [a]	0.53	Favours rTMS	<0.001	NR
Delivered at the right DLPFC [a]	0.82	Favours rTMS	<0.001	NR
Delivered at both left and right DLPFCs (not simultaneously)	0.47	Favours rTMS	0.3	NR
rTMS monotherapy [a]	0.96	Favours rTMS	<0.001	81
rTMS with continuation of previous antidepressant treatment [a]	0.51	Favours rTMS	<0.001	32
rTMS started simultaneously with antidepressant treatment	0.37	Favours rTMS	0.3	13

[a] Significant differences were observed between groups

- No significant difference was reported when the effect sizes for studies that assessed rTMS monotherapy were compared against studies that assessed rTMS with continuation of antidepressant treatment (p=0.06).
- No significant difference was reported when the effect sizes for studies that assessed rTMS monotherapy were compared against studies that assessed rTMS started simultaneously with antidepressant treatment (p=0.09).

Meta-analysis of rTMS versus ECT

- The meta-analysis of rTMS compared against ECT revealed a Hedges' g value of -0.47, in favour of ECT (p=0.004, I^2=28%)

Safety

	% (n/N)		
Adverse event	High-frequency rTMS	Low-frequency rTMS	Sham
Headache	9.7 (46/472)	3.7 (4/109)	2.5 (12/461)
Scalp discomfort	9.3 (45/472)	1.8 (2/109)	1.9 (9/461)
Facial twitching	1.9 (9/472)	4.6 (5/109)	0
Eye watering	1.5 (7/472)	0	0
Local erythema	1.3 (6/472)	0	0
Drowsiness	2.5 (12/472)	0	0
Other (not specified)	4.7 (22/472)	0.9 (1/109)	2.4 (11/461)
Total	30.7 (145/472)	11 (12/109)	6.9 (32/461)

Abbreviations used: DLPFC, dorso-lateral prefrontal cortex; ECT, electroconvulsive therapy; NR, not reported; rTMS, repetitive transcranial magnetic stimulation

Study 2 Lepping P (2014)

Details

Study type	**Systematic review**
Country	United Kingdom
Recruitment period	Not reported
Study population and number	Patients with patients with depression **n=3236 patients from 63 studies (2330 rTMS versus 806 sham stimulation; 100 patients were treated by ECT)**
Age and sex	Not reported
Study selection criteria	Inclusion criteria: case series and comparative studies that assessed the efficacy of rTMS (as monotherapy or add-on therapy) in patients with depression, irrespective of subtype of depression and diagnostic criteria used, were included. All included studies reported HDRS scores. Exclusion criteria: studies in which depression was not the primary diagnosis or which evaluated adolescents or children were excluded.
Technique	rTMS was delivered unilaterally or bilaterally (sequentially or simultaneously). Stimulation was performed using frequencies ranging from 1 Hz to 20 Hz and delivered at 80% to120% of motor thresholds.
Follow-up	**Treatment periods ranged from 1 week to 12 weeks; however, only week 4 results analysed**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: None identified

Study design issues: Systematic review included studies that assessed rTMS as monotherapy or add-on therapy. For crossover studies, only data from the first crossover sequence were used. Meta-analyses that pooled outcomes from case, series, non-randomised comparative studies and randomised controlled trials may be prone to bias as some of the single-arm studies may have overestimated the treatment effect.

Study population issues: Studies included patients who had different types of depression, such as major depressive disorder and treatment resistant depression.

Other issues:

- Authors pooled percentage changes in HDRS-17 (17 item), HDRS-21 (21-item) and HDRS-24 (24-item) scores reported in all included studies. When it was unclear what version of the HDRS was used, authors assumed that the HDRS-17 questionnaire was used. Percentage changes were converted into Clinical Global Impressions - improvement (CGI-I) scale scores. The CGI-I scale is a widely used psychiatric assessment tool that measures perceived improvements in a patient's mental illness. Percentage changes in HDRS scores were converted into CGI-I scores as follows:

Percentage change in HDRS scores (%)	Clinical Global Impression – Improvement scale equivalent	Interpretation
-84	1	Very much improved
-59	2	Much improved
-33	3	Minimally improved
-9	4	No change
8	5	Minimally worse
27.5	6	Much worse
60	7	Very much worse

Efficacy

n=**3236 patients from 63 studies (2330 rTMS versus 806 sham stimulation; 100 patients were treated by ECT)**

Meta-analyses of rTMS versus sham stimulation in patients with depression

	rTMS		Sham		
Grouping	Mean percentage **reduction** in HDRS scores (SD)	CGI-I score equivalent	Mean percentage **reduction** in HDRS scores (SD)	CGI-I score equivalent	p value
Randomised controlled trials - only	35.63 (16.51)	2.9	23.33 (16.51)	3.4	<0.05
All included studies	37.18 (15.13)	2.8	22.14 (16.55)	3.4	<0.05

Meta-analyses of rTMS versus sham stimulation in patients with treatment resistant depression

	rTMS		Sham		
Grouping	Mean percentage **reduction** in HDRS scores (SD)	CGI-I score equivalent	Mean percentage **reduction** in HDRS scores (SD)	CGI-I score equivalent	p value
Randomised controlled trials - only	45.21 (10.94)	2.55	25.04 (17.55)	3.3	<0.05
All included studies	47.77 (12.80)	2.4	23.03 (16.00)	3.4	<0.05

Other meta-analyses

- When rTMS was compared against ECT in patients with any type of depression, the mean percentage reduction in HDRS scores was 33.7% (CGI-I score equivalent not reported) in the rTMS group and 46.4% (CGI-I 2.45) in the ECT group (p<0.05)
- When low-frequency rTMS (below 1Hz) was compared against high-frequency rTMS (above 1Hz), the mean percentage reduction in HDRS scores was 46.6% in the low-frequency group and 40.9% in the high-frequency group (p<0.05). CGI-I score equivalents were not reported

Abbreviations used: CGI-, Clinical global impressions-improvement; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; NR, not reported; rTMS, repetitive transcranial magnetic stimulation; TRD; treatment resistant depression

Study 3 Zhang YQ (2015)

Details

Study type	**Systematic review of randomised controlled trials**
Country	China
Recruitment period	Up to January 2014
Study population and number	Patients with treatment resistant depression **n=634 patients from 10 randomised controlled trials (Total numbers in each study arm not specified)**
Age and sex	Not reported
Study selection criteria	Inclusion criteria: randomised controlled trials that compared bilateral rTMS against unilateral or sham rTMS were included. All studies included patients who were diagnosed with major depressive disorder and met the treatment resistant depression criteria of not responding to at least 1 course of adequate medication during their current depressive episode. Exclusion criteria: studies that assessed patients who had treatment resistant depression with comorbid neurological disorders or psychotic disorders were excluded. Studies that assessed patients with child, adolescent or postpartum depression were also excluded.
Technique	Patients received rTMS, delivered unilaterally or bilaterally over a period of 1 to 6 weeks. Stimulation was performed using frequencies ranging from 1 Hz to 20 Hz and delivered at 90% to120% of motor thresholds.
Follow-up	**Treatment periods ranged from 1 week to 6 weeks**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: None identified

Study design issues: All included studies adopted single- or double blinded designs. Half of the included studies described the methods of randomisation.

Study population issues: Some studies included patients with major depressive disorder or bipolar depression. Studies also included patients with varying severities of treatment resistant depression.

Other issues:

- A clinical response was classified as more than a 50% improvement in pre-treatment Hamilton Depression Rating Scale (HDRS) or Montgomery–Åsberg Depression Rating Scale (MADRS) scores, or a score of 1 (very improved) or 2 (much improved) on the Clinical Global Impression scale (CGI).
- Remission was classified as a post-treatment depression rating scale score within a predefined normal range: ≤8 on the 21-item HDRS scale, ≤7 on the 17-item HDRS scale, ≤12 on the MADRS scale, or a global rating of 'not depressed' or 'equivalent' on the CGI scale.
- If more than 1 scale was used to evaluate response or remission within a study, HDRS was preferentially selected followed by the MADRS and CGI scales.
- The effect sizes were summarised using risk ratios.
- I^2 ranged from 0% to 40%, indicating very low to moderate heterogeneity between included studies.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **n=634 patients. Numbers varied according to outcome measure assessed.**

Meta-analyses of bilateral rTMS against sham stimulation

Outcome measure	Effect size (Risk ratio)	95% CI	Direction of effect	p value	I^2 (%)
Response	3.29	1.69 to 6.38	Favours bilateral	0.0004	0
Remission	0.5	0.19 to 1.31	Favours bilateral	0.16	0

Meta-analyses of bilateral rTMS against unilateral rTMS

Outcome measure	Effect size (Risk ratio)	95% CI	Direction of effect	p value	I^2 (%)
Response	1.01	0.81 to 1.26	Bilateral=unilateral	0.93	40
Remission	0.77	0.52 to 1.16	Favours bilateral	0.22	9

- No significant differences in response or remission rates were observed between groups.

Abbreviations used: rTMS, repetitive transcranial magnetic stimulation

Study 4 Ren J (2014)

Details

Study type	**Systematic review of randomised controlled trials**
Country	China
Recruitment period	Up to November 2013
Study population and number	Patients with primary major depressive episode **n=429 patients from 10 randomised controlled trials (217 rTMS versus 212 ECT)**
Age and sex	Mean age: rTMS group, 47.6 years; ECT group, 49.8 years Sex: rTMS group, 57.1% female; ECT group, 61.8% female
Study selection criteria	Inclusion criteria: randomised controlled trials that compared rTMS against ECT were included. All studies included patients who were diagnosed with a primary major depressive episode (unipolar or bipolar) with or without psychotic symptoms. Exclusion criteria: quasi-randomised studies, where treatment allocation was performed using alternate days of week, or where allocation was performed on the basis of surname were excluded Studies that evaluated single-pulse rTMS or rTMS given for less than 1 week were excluded
Technique	rTMS was delivered unilaterally over the left or right DLPFC. Stimulation was performed using frequencies ranging from 1 Hz to 20 Hz and delivered at various stimulus intensities. ECT was delivered unilaterally and bilaterally at different intensities.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: None identified

Study design issues: Four of the included studies were open-label trials, 4 studies were either single- or double blinded trials, and 2 studies did not report if patients or assessors were blinded to group allocations. The intervention was delivered over the right or left DLPFC; however, no subgroup analysis was performed to distinguish between the 2 treatment sites. Meta-analyses were stratified according to stimulation intensity; however, only 1 of the included studies evaluated the efficacy of low-frequency rTMS.

Study population issues: 93% (202/217) of patients in the rTMS group were diagnosed with major depressive disorder whereas 95% (201/212) of patients in the ECT group were diagnosed with the major depressive disorder. The remaining patients in each group were diagnosed with bipolar depression. Results were not stratified according to type of depression. Only 1 study compared the efficacy of rTMS against ECT in patients who were not taking antidepressants, antipsychotics or mood stabilizers during treatment.

Other issues:

- A clinical response was defined as more than a 50% improvement in HDRS scores.
- Remission was classified according to predefined criteria in each included study.
- Acceptability was assessed by using trial discontinuation rates as a proxy measure.
- Psychological wellbeing was evaluated by pooling Brief Psychiatric Rating scale scores. The questionnaire assesses 18 symptom domains; including, hostility, suspiciousness, hallucinations, emotional withdrawal and grandiosity. Total scores range from 18 to 126 with higher scores indicating worse mental health.
- Cognitive function was evaluated by pooling MMSE scores across included studies. MMSE is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment
- Frequencies of less than 1 Hz were classified as low-frequency whereas frequencies above 1 Hz her classified as high-frequency.
- The effect sizes of continuous variables were summarised using weighted mean differences. The effect sizes of dichotomous variables were summarised using risk ratios.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **429 patients (212 ECT versus 217 rTMS). Numbers varied according to outcome measure assessed.**

Meta-analyses

Outcome measure	Effect	Effect size	95% CI	Direction of effect	p value	I^2 (%)
Clinical response						
High-frequency [a]	RR	1.41	1.04 to 1.90	Favours ECT	0.03	36
Low-frequency [a]	RR	1.85	1.18 to 2.89	Favours ECT	0.007	NA
Overall [a]	RR	1.52	1.18 to 1.95	Favours ECT	0.001	34
Remission						
High-frequency [a]	RR	1.38	1.10 to 1.74	Favours ECT	0.006	43
Low-frequency [a]	RR	1.57	1.01 to 2.44	Favours ECT	0.04	NA
Overall [a]	RR	1.42	1.16 to 1.75	Favours ECT	0.0007	38
Acceptability						
High-frequency	RR	1.11	0.49 to 2.53	Favours ECT	0.8	0
Low-frequency	RR	1.25	0.57 to 2.73	Favours ECT	0.57	NA
Overall	RR	1.17	0.66 to 2.08	Favours ECT	0.58	0
Changes in HDRS scores						
High-frequency	MD	2.15	-0.50 to 4.81	Favours ECT	0.11	50
Low-frequency [a]	MD	5.50	2.64 to 8.36	Favours ECT	0.0002	NA
Overall [a]	MD	2.81	0.17 to 5.46	Favours ECT	0.04	64
Other outcome measures						
Changes in BPRS scores	MD	2.66	0.08 to 5.24	Favours ECT	0.04	NR
Cognitive function (changes in MMSE)	MD	0.65	-0.51 to 1.82	Favours ECT	0.27	NR

[a] Significant differences were observed between groups

- No I^2 results were reported in the low-frequency meta-analyses because only 1 study utilised low-frequency rTMS.
- Authors state that high-frequency rTMS was more effective than ECT in patients who had psychotic symptoms. The response rates were 52.5% in the rTMS group and 51.4% in the ECT group. No numerators or denominators were reported.

Abbreviations used:, BPRS, Brief Psychiatric Rating scale; CI, confidence interval; DLPFC, dorso-lateral prefrontal cortex; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MD, mean difference; MMSE, Mini-mental State Examination scores; NA, Not applicable; NR, Not reported; rTMS, repetitive transcranial magnetic stimulation; RR, risk ratio

Study 5 Bakker N (2015)

Details

Study type	**Non-randomised comparative study**
Country	United states
Recruitment period	April 2011 to February 2014
Study population and number	Patients with treatment resistant depression **n=185 (98 conventional rTMS versus 87 Theta-burst rTMS)**
Age and sex	Mean age: rTMS group, 38.4 years; Theta-burst rTMS group, 45.9 years Sex: rTMS group, 71.4% female; Theta-burst rTMS group, 65.5% female
Patient selection criteria	Inclusion criteria: patients with a major depressive episode who had unipolar or bipolar symptoms were included. All patients had a history of treatment resistant depression; defined as, not responding to at least 2 courses of adequate medication. All included patients had not responded to at least one course of medication during their current depressive episode. Patients with comorbidities were also included Exclusion criteria: not reported.
Technique	Conventional rTMS group: stimulation was performed using a frequency of 10Hz by applying 3000 pulses to each hemisphere. Stimulation trains were cycled at 5 seconds on, then 10 seconds off. Treatment duration was 30 minutes. Intermittent theta-burst rTMS group: the procedure was performed by delivering 50Hz triplet-bursts of stimulation, 5 times per second. Stimulation was delivered by applying 600 pulses to each hemisphere. The treatment duration was 30 minutes. Stimulation was delivered to the left and then right DLPFC. All patients initially received 20 sessions of treatment. Those who achieved response but did not achieve remission were offered an additional 10 sessions.
Follow-up	**1 month**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: There was no significant difference in the mean number of treatments given to patients in each group.

Study design issue: Authors assessed the effectiveness of rTMS and theta-burst rTMS by retrospectively evaluating the clinical records of patients who received therapy at a depression clinic. Included patients were required to take unspecified psychoactive medications for 4 weeks before rTMS therapy, and continue with medications throughout the treatment course. Treatment was offered to all patients with depression severe enough for them to want to receive at least 20 sessions of rTMS. Patients who had a response, after 20 sessions, but who were not classified as having remission were offered an additional 10 treatment sessions. Stimulation was delivered at different cranial sites.

Study population issues: Study included patients with unipolar and bipolar depression. Authors state that no comorbidities were used as exclusion criteria in order to maximise the generalisability of results. There were no significant differences in the length of current depressive episodes, the number of previous depressive episodes and the number of treatment sessions between groups. Patients with missing pre-treatment depression rating scores were excluded from response rate calculations.

Other issues:

- A response was defined as more than a 50% reduction in HDRS or Beck Depressive Inventory II (BDI-II) scores.
- BDI-II scores range from 0 to 63 with lower scores indicating less depression.
- Remission was defined as a post-treatment depression rating score of ≤7 for HDRS and ≤12 for BDI-II.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **(98 conventional rTMS versus 87 TB-rTMS)**

Depression rating scales

	rTMS		TB-rTMS		
Outcome measure	Baseline	1 month	Baseline	1 month	p value for post-treatment score comparisons
HDRS (All patients)	22.1±6.9	12.3±8.9	21.1±5.1	12.7±7.9	0.750
HDRS (Responders only)	20.8±6.9	5.7±3.8	21.3±4.9	6.0±3.9	0.740
BDI-II (All patients)	35.4±10.8	22.4±15.5	35.9±9.9	20.2±13.3	0.307
BDI-II (Responders only)	32.0±11.2	14.1±10.9	36.5±8.0	11.3±7.6	0.200

- Significant improvements in HDRS and BDI-II scores were reported within each groups.

Response

	Response rates (%)		
Outcome	rTMS (n/N)	TB-rTMS (n/N)	p value
HDRS scores	50.6 (42/83)	48.5 (32/66)	0.869
BDI-II scores	40.6 (39/96)	43.0 (37/86)	0.765

- No significant difference in response rates were observed between groups.

Remission

	Remission rates (%)		
Outcome	rTMS (n/N)	TB-rTMS (n/N)	p value
HDRS scores	38.5 (37/96)	27.9 (24/86)	0.157
BDI-II scores	29.2 (28/96)	31.0 (27/87)	0.872

- No significant difference in response rates were observed between groups

Safety

Incidence of Seizures

- No seizures or other serious adverse events were reported.

Premature discontinuation of Treatment

- Discontinuation of therapy was reported in 6.1% (6/98) of patients in the conventional rTMS group: 1 patient stopped therapy due to intolerable headaches, 4 patients stopped due to lack of response and 1 patient stopped due to the excessive commute to the clinic.
- Discontinuation of therapy was reported in 13.8% (12/87) of patients in the TB-rTMS group: 4 patients stopped therapy due to intolerable headaches, 1 patient stopped due to vertigo, 4 patients stopped due to a lack of response and 1 patient stopped due to increasingly hostile thoughts.

Abbreviations used: BDI, Beck Depressive Inventory; HDRS, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; TB-rTMS, theta-burst transcranial magnetic stimulation

Study 6 Fitzgerald PB (2006)

Details

Study type	**Randomised controlled trial**
Country	Australia
Recruitment period	May 2001 to January 2006
Study population and number	Patients with depression **n=130 patients (67 1 Hz rTMS versus 63 2 Hz rTMS)**
Age and sex	Mean age: 1 Hz group, 50.5 years; 2 Hz group, 48.1years Sex: 1 Hz group 33% (22/67) female; 2 Hz group, 40% (25/63) female
Patient selection criteria	Inclusion criteria: Patients with moderate to severe depression, with a score HDRS-17 score greater than 16, were included. All patients had not responded to a minimum of two courses of appropriate antidepressant medication for at least 6 weeks during the current depressive episode Exclusion criteria: Patients with significant currently active medical illness, current neurological disease or contraindications to rTMS were excluded. Patients diagnosed with alcohol or substance dependence, according to Diagnostic and Statistical Manual of Mental Disorders (4th Edition) criteria, were also excluded.
Technique	1 Hz group: rTMS 900 pulses were delivered over the right DLPFC in 1 train which lasted for 15 minutes. Stimulation was applied at 110% of the motor threshold 2Hz group: rTMS 1800 pulses were delivered over the right DLPFC in 1 train which lasted for 15 minutes. Stimulation was applied at 110% of the motor threshold All patients initially received 10 sessions of rTMS over 2 weeks. Patients classified as 'initial responders' (who had more than a 20% reduction in HDRS scores) were offered a further two weeks of rTMS.
Follow-up	**1 month**
Conflict of interest/source of funding	Two authors had received support for research conducted with the manufacturer

Analysis

Follow-up issues: 2 patients withdrew from the study within 2 weeks of commencing treatment. Authors state that they experienced no change or mild deterioration before withdrawal. 86 patients had an initial response. 68 of these patients elected to continue treatment: all completed the additional 2 week treatment.

Study design issue: The trial was conducted across 3 hospitals. Patients were sequentially randomised using a single computer-generated random number sequence; no stratified random sampling was performed. Patients and assessors were informed that there was a difference in treatment parameters but they were blinded to treatment allocations. Sample size calculations revealed that a sample of 130 patients were required in order to confer >90% power in detecting at least a 5 point difference in HDRS scores between groups.

Study population issues: Study included patients with various types of depression: 43 patients had a single episode of major depressive disorder, 62 had relapse of major depressive disorder, 14 had a depressive episode of bipolar I disorder and 11 had a depressive episode of bipolar II disorder. 117 patients were receiving antidepressant medication during the study whereas 55 were receiving concurrent treatment with a mood stabilizer. There were no significant differences in demographic and baseline clinical characteristics between the groups.

Other issues:

- Results for 'all' patients uses the last observation carried forward method.
- A response was defined as more than a 50% improvement in HDRS-17 scores.
- Remission was defined as a post-treatment HDRS score ≤8.
- Systematic reviews included in this overview assessed the efficacy rTMS delivered over the right DLPFC (Slotema, 2010) or compared different frequencies of rTMS (Lepping, 2014 and Ren 2014). This study was primarily added to highlight the occurrence of an adverse event (hypomania) in a large group of patients.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: n=128 (66 1 Hz rTMS versus 62 2 Hz rTMS); however numbers analysed varied according to follow-up assessment.

Response rates (%) for all patients using the last observation carried forward method
<table>
<tr><td></td><td colspan="2">Follow-up</td></tr>
<tr><td>Group</td><td>2 weeks</td><td>4 weeks</td></tr>
<tr><td>1 Hz</td><td>27 (18/67)</td><td>42 (28/67)</td></tr>
<tr><td>2 Hz</td><td>32 (20/63)</td><td>52 (33/63)</td></tr>
</table>
• No significant difference in response rates were observed between groups

Response rates (%) of patients who completed each follow-up assessments
<table>
<tr><td></td><td colspan="2">Follow-up</td></tr>
<tr><td>Group</td><td>2 weeks</td><td>4 weeks</td></tr>
<tr><td>1 Hz</td><td>27 (18/67)</td><td>77 (24/31)</td></tr>
<tr><td>2 Hz</td><td>32 (20/63)</td><td>81 (30/37)</td></tr>
</table>
• No significant difference in response rates were observed between groups

Remission rates (%) for all patients using the last observation carried forward method
<table>
<tr><td></td><td colspan="2">Follow-up</td></tr>
<tr><td>Group</td><td>2 weeks</td><td>4 weeks</td></tr>
<tr><td>1 Hz</td><td>7 (5/67)</td><td>19 (13/67)</td></tr>
<tr><td>2 Hz</td><td>16 (10/63)</td><td>32 (20/63)</td></tr>
</table>
• No significant difference in remission rates were observed between groups

Remission rates (%) of patients who completed each follow-up assessments
<table>
<tr><td></td><td colspan="2">Follow-up</td></tr>
<tr><td>Group</td><td>2 weeks</td><td>4 weeks</td></tr>
<tr><td>1 Hz</td><td>7 (5/67)</td><td>42 (13/31)</td></tr>
<tr><td>2 Hz</td><td>16 (10/63)</td><td>54 (20/37)</td></tr>
</table>
• No significant difference in remission rates were observed between groups

HDRS scores (mean±SD) for patients who completed each follow-up assessment
<table>
<tr><td>Group</td><td>Baseline</td><td>2 weeks</td><td>4 weeks</td></tr>
<tr><td>1 Hz</td><td>24.13±4.87</td><td>17.76±7.76</td><td>8.84±6.62</td></tr>
<tr><td>2 Hz</td><td>22.62±5.07</td><td>15.52±8.59</td><td>7.59±4.78</td></tr>
</table>
• Significant differences were observed between baseline and follow-up HDRS scores, within groups.
• No significant differences were observed between groups at each follow-up period.
</td><td>
• Authors report that patient developed a hypomanic episode soon after completion of therapy. The exact timing of occurrence was not reported
</td></tr>
<tr><td colspan="2">Abbreviations used: DLPFC, dorso-lateral prefrontal cortex; HDRS, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation</td></tr>
</table>

Study 7 Janicak PG (2010)

Details

Study type	**Case series (authors describe the study as a durability study)**
Country	United states
Recruitment period	Not reported
Study population and number	Patients with major depressive disorder **n=120**
Age and sex	Mean age: 49.1 years Sex: 53.5% female
Patient selection criteria	Inclusion criteria: Patients with non-psychotic major depressive disorder who had a partial response (more than a 25% reduction in HDRS-17 scores) within 6 weeks of receiving rTMS during a randomised sham-controlled trial were included (n=99). Patients from the sham stimulation group (n=21) of the randomised controlled trial who subsequently received and responded to active rTMS, were also included. Exclusion criteria: Not reported
Technique	Stimulation was performed at a frequency of 10Hz by applying 3000 pulses to the left DLPFC. Stimulation was delivered at 120% of the motor threshold. Stimulation trains were cycled at 4 seconds on, followed by 26 seconds off. After 6 weeks of receiving rTMS, patients commenced antidepressant monotherapy while being tapered off rTMS during a 3 week transition phase. Patients continued antidepressant monotherapy for 24 weeks. During this period, relapse rates were assessed. If patients exhibited worsening symptoms (an increase in Clinical Global Impressions - Severity of Illness scores by at least 1 point, observed over 2 consecutive weeks) they were offered an additional 6–week course of rTMS.
Follow-up	**6 months after completion of therapy.**
Conflict of interest/source of funding	One of the authors was a Consultant/Advisor for a manufacturer of antidepressants

Analysis

Follow-up issues: None identified

Study design issue: The aim of the study was to assess relapse rates in patients who had a partial response to rTMS. After 6 weeks of receiving rTMS, patients commenced antidepressant monotherapy while being tapered off rTMS for 3 weeks. The type of antidepressant was determined by a review of prior treatments, the patient's subjective experience and any information from the referring clinician. The main antidepressant medications included duloxetine (26%), venlafaxine (17%), bupropion (19%) and escitalopram. The study design precluded any statistical comparisons between patients who initially received active rTMS and those who initially received sham stimulation

Study population issues: 99 patients were originally in the active rTMS group of a sham-controlled randomised controlled trial and 21 patients initially received sham stimulation and subsequently received active rTMS. Authors state that the 'mean number of antidepressant treatment attempts' was 5.5. The mean duration of the current depressive episode was 12.7 months. 16% of patients had a current depressive episode that lasted more than 2 years. 29% of patients were also diagnosed with anxiety disorder

Other issues:

- Relapse was the primary outcome measure; defined as, a recurrence of full Diagnostic and Statistical Manual of Mental Disorders (4th Edition) criteria for major depression for 2 consecutive weeks, or failure to achieve symptomatic improvement despite a 6-week reintroduction course of rTMS.
- The CGI-S scale commonly been used to describe the severity of mental illness in patients. Scores range from 1 to 7, with 1 indicating normal and 7 indicating extremely ill.
- A full response was defined as more than a 50% improvement in pre-treatment HDRS scores.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **n=120 patients (99 patients who were initially treated by active rTMS and 21 patients who initially received sham stimulation)**

Persistence of benefit during long-term follow-up in patients who were originally in the active rTMS group (n=99)

- A full response was reported in 78% (77/99) of patients at the point of entry into the durability study.
- The mean HDRS score was 9.1±6.2 points, at the end of rTMS therapy, and 9.0±7.1 at 6 month-follow-up (p=0.537), indicating a maintained treatment effect. No pre-treatment scores were reported.
- The mean CGI-S score was 2.1±1.1 points, at the end of rTMS therapy, and 1.8±1.1 at 6 month-follow-up (p=0.340), indicating a maintained treatment effect. No pre-treatment scores were reported.
- The relapse rate (Kaplan-Meier estimate) was 12.9% at 6 month follow-up (no p value reported).
- The mean time to relapse was 164±4 days after completion of rTMS therapy.
- A course of repeat rTMS was needed in 38.4% (38/99) of patients: of which, 84.2% (32/38) of patients had improvements in depression.
- The mean time to reintroduction of rTMS was 109±5 days.
- A second or third relapse in depression was reported in 20% (20/99) of patients.

Persistence of benefit during long-term follow-up in patients who initially received sham stimulation and subsequently received active rTMS (n=21)

- The relapse rate (Kaplan-Meier estimate) was 16% at 6 month follow-up.
- A course of repeat rTMS was needed in 52.4% (11/21) of patients: of which, 45% (5/11) of patients had improvements in depression.
- The mean time to reintroduction of rTMS was 116±13.2 days.

Safety

Adverse events in patients who were originally in the active rTMS group (n=99)

Adverse Events	Overall % (n)	Device related % (n)
Gastrointestinal disorder		
Dry Mouth	8.1 (8)	1 (1)
Nausea	8.1 (8)	0
Constipation	6.1 (6)	1 (1)
Diarrhea	6.1 (6)	0
General Disorders		
Fatigue	11.1 (11)	0
Application site pain	6.1 (6)	6.1 (6)
Infections and Infestations		
URTI	11.1 (11)	0
Nasopharyngeal	5.1 (5)	0
Musculoskeletal & Tissues		
Arthralgia	18.2 (18)	1 (1)
Back pain	10.1 (10)	0
Twitching	8.1 (8)	7.1 (7)
Myalgia	7.1 (7)	0
Pain (extremity)	5.1 (5)	0
Nervous system disorders		
Headache	33.3 (33)	4.0
Dizziness	7.1 (7)	0
Psychiatric disorders		
Insomnia	35.4 (35)	1 (1)
Anxiety	14.1 (14)	0
Libido reduced	8.1 (8)	0
Depression	6.1 (6)	0
Irritability	5.1 (5)	0

Abbreviations used: CGI-S, Clinical Global Impressions-Severity; DLPFC, dorso-lateral prefrontal cortex; HDRS, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation

Study 8 Conca A (2000)

Details

Study type	**Case report**
Country	Austria
Study population	**A 36 year old woman with treatment resistant depression**
Technique	RTMS was initially performed by delivering 20Hz over the left DLPFC at 110% of the motor threshold (5 seconds on, 45 seconds off) while 1Hz was applied over the right DLPFC at 110% of the motor threshold (1 train lasting 300 seconds). After 5 consecutive days of treatment, clinicians altered the treatment protocol so that 10 second trains of 20Hz rTMS were delivered, unilaterally, over the left DLPFC at 110% of the motor threshold. 10 trains were applied with an inter-train interval of 60 seconds.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported
Summary	A 36 year old woman with a history of treatment resistant depression, which had previously responded to combined trazodone and electroconvulsive therapy, consented to receive rTMS as augmentation therapy during her current depressive episode. The patient had been taking trazodone (500mg/day), citalopram (30mg/day), lorazepam (3mg/day) and thyroxin (100µg/day) for more than 2 weeks but showed no signs of psychological improvement before commencement of rTMS. The patient suffered a complex partial seizure during the first session of unilateral rTMS. The seizure neuroanatomically appeared to be localised in the dorsolateral prefrontal cortex. Treating clinicians observed oral automatism but no twitching of limb muscles, focal or generalised motor activities, or eye deviations were observed. The epileptic seizure was self-limiting, lasting 8 seconds; after which, the patient was alert with no postictal confusion. She had no memory of what happened. The patient felt euphoric for approximately18 hours after the seizure occurrence but then became depressed. No subsequent physical sequelae were reported. The authors concluded that increasing the rTMS train duration contributed to the occurrence of the seizure.
Abbreviations: DLPFC, dorso-lateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation	

Efficacy

Changes in depression rating scale scores

In a systematic review of 40 randomised controlled trials including 1592 patients with depression (type unspecified) treated by repetitive transcranial magnetic stimulation (rTMS; n=751) or sham stimulation (n=632), meta-analysis of mean changes in unspecified depression rating scales showed a significant effect in favour of rTMS (Hedges' g value of 0.55, p<0.001)[1].

In a non-randomised comparative study of 185 patients with treatment resistant depression treated by conventional rTMS (n=98) or theta-burst rTMS (n=87), HDRS scores (lower scores indicate less depression) decreased from 22.1±6.9 to 12.3±8.9 and from 21.1±5.1 to 12.7±7.9 respectively, at 1-month follow-up (p value within groups <0.001, p value between groups not significant). In the same study, Beck Depressive Inventory scores (scores range from 0 to 63 with lower scores indicating less depression) decreased from 35.4±10.8 to 22.4±15.5 in the conventional rTMS group and from 35.9±9.9 to 20.2±13.3 in the theta-burst rTMS group at 1-month follow-up (p value within groups <0.001, p value between groups not significant)[5].

Conversion to Clinical Global Impressions-Improvement (CGI-I) scale scores

In a systematic review of 63 studies including 3236 patients treated by rTMS (n=2330), sham stimulation (n=806) or electroconvulsive therapy (ECT; n=100), percentage changes in HDRS scores (lower scores indicate less depression) were pooled and converted to CGI-I scale scores. CGI-I scores range from 1 to 7: a score of 4 means no change, scores less than 4 indicate improvements in depression and scores more than 4 indicate worsening depression. For patients with any type of depression, the mean percentage reduction in HDRS scores was 37% (CGI-I 2.8) in the rTMS group and 22% (CGI-I 3.4) in the sham stimulation group (p<0.05). For patients with treatment resistant depression, the mean percentage reduction in HDRS scores was 48% (CGI-I 2.4) in the rTMS group and 23% (CGI-I 3.4) in the sham stimulation group (p<0.05). When rTMS was compared against ECT in patients with any type of depression, the mean percentage reduction in HDRS scores was 34% (CGI-I equivalent not reported) in the rTMS group and 46% (CGI-I 2.45) in the ECT group (p<0.05)[2].

Response rates

In a systematic review of 10 randomised controlled trials including 634 patients with treatment resistant depression treated by bilateral rTMS, unilateral rTMS or sham stimulation, clinical response data (defined as more than a 50% improvement in HDRS or MADRS scores) were compared between groups. A meta-analysis of clinical response rates in patients treated by bilateral rTMS or sham stimulation revealed a risk ratio of 3.29 in favour of bilateral rTMS (95% confidence interval [CI] 1.69 to 6.38; p=0.0004). A meta-analysis of clinical response rates in patients treated by bilateral rTMS or unilateral rTMS revealed

no significant difference between groups (risk ratio of 1.01; 95% CI 0.81 to 1.26; p=0.93)[3].

In a systematic review of 10 randomised controlled trials including 429 patients with a primary major depressive episode treated by rTMS (n=217) or ECT (n=212), a meta-analysis of clinical response data (defined as more than a 50% improvement in HDRS scores) revealed a risk ratio of 1.52 in favour of ECT (95% CI 1.18 to 1.95; p=0.001)[4].

In the non-randomised comparative study of 185 patients with treatment resistant depression treated by conventional rTMS (n=98) or theta-burst rTMS (n=87), a clinical response (defined as more than a 50% improvement in HDRS scores) was reported in 51% (42/83) and 49% (32/66) of patients respectively at 1-month follow-up (p=0.869)[5].

Remission rates

In the systematic review of 10 randomised controlled trials including 634 patients with treatment resistant depression treated by bilateral rTMS, unilateral rTMS or sham stimulation, remission data (classified according to predefined criteria in each included study) were compared between groups. A meta-analysis of remission rates in patients treated by bilateral rTMS or sham stimulation revealed no significant difference between groups (risk ratio of 0.5; 95% CI 0.19 to 1.31; p=0.16). A meta-analysis of remission rates in patients treated by bilateral rTMS or unilateral rTMS revealed no significant difference between groups (risk ratio of 0.77; 95% CI 0.52 to 1.16; p=0.22)[3].

In the systematic review of 10 randomised controlled trials including 429 patients with a primary major depressive episode treated by rTMS (n=217) or ECT (n=212), a meta-analysis of remission data (classified according to predefined criteria in each included study) revealed a risk ratio of 1.42 in favour of ECT (95% CI 1.16 to 1.75; p=0.0007)[4].

In the non-randomised comparative study of 185 patients with treatment resistant depression treated by treated by conventional rTMS (n=98) or theta-burst rTMS (n=87), remission (defined as a post-treatment HDRS score≤7 or Beck Depression Inventory score≤12) was reported in 39% (37/96) and 28% (24/86) of patients respectively at 1-month follow-up (p value not significant)[5].

Durability of treatment effect and relapse

A case series evaluated 120 patients who had at least a partial response (at least a 25% improvement in HDRS scores); 99 patients were recruited from the active rTMS group of a randomised sham-controlled trial, while 21 patients initially had sham stimulation and subsequently received active rTMS. For patients originally in the active rTMS group of the trial, the mean HDRS score was 9.1±6.2 at the end of rTMS therapy and 9.0±7.1 at 6-month follow-up (p value not significant); indicating a maintained treatment effect. No pre-treatment scores were reported. No mean HDRS scores were reported for patients who initially had sham

stimulation and subsequently received active rTMS. In the same study, the relapse rate (Kaplan–Meier estimate) at 6-month follow-up was 13% in patients who were originally in the active rTMS group of the trial and 16% in patients who initially had sham stimulation and subsequently received active rTMS[7].

Safety

Seizure

A self-limiting complex partial seizure was reported in 1 patient who received unilateral rTMS at a frequency of 20 Hz and at 110% of the motor threshold. The patient was awake after 8 seconds; she was alert with no postictal confusion and had no memory of what happened. No subsequent physical sequelae were reported[8].

Mood changes

Increasingly hostile thoughts were reported in no patients in the conventional rTMS group (n=98) and 1 patient in the theta-burst rTMS group (n=87) in the non-randomised comparative study of 185 patients with treatment resistant depression. The timing of occurrence was not reported [5].

A hypomanic episode was reported in 1 patient, soon after completion of therapy, in a randomised controlled trial of 130 patients treated by 1 Hz or 2 Hz rTMS. The exact timing of occurrence was not reported[6].

Headache

Headache was reported in 10% (46/472) of patients treated by high-frequency rTMS, 4% (4/109) treated by low-frequency rTMS and 3% (12/461) given sham stimulation in a systematic review of 40 randomised controlled trials that included 1592 patients with depression (type unspecified)[1].

Intolerable headache was reported in 1% (1/98) of patients in the conventional rTMS group and 5% (4/87) of patients in the theta-burst rTMS group in a non-randomised comparative study of 185 patients with treatment resistant depression[5].

Scalp discomfort

Scalp discomfort was reported in 9% (45/472) of patients treated by high-frequency rTMS, 2% (2/109) treated by low-frequency rTMS and 2% (9/461) given sham stimulation in the systematic review of 40 randomised controlled trials that included 1592 patients with depression (type unspecified)[1].

Pain

Pain at the rTMS application site was reported in 6% (6/99) of patients in a case series of 120 patients with major depressive disorder treated by rTMS[7].

Facial twitching

Facial twitching was reported in 2% (9/472) of patients treated by high-frequency rTMS, none treated by low-frequency rTMS (n=109) and none given sham stimulation (n=461) in the systematic review of 40 randomised controlled trials that included 1592 patients with depression (type unspecified)[1].

Eye watering

Eye watering was reported in 2% (7/472) of patients treated by high-frequency rTMS, none treated by low-frequency rTMS (n=109) and none given sham stimulation (n=461) in the systematic review of 40 randomised controlled trials that included 1592 patients with depression (type unspecified)[1].

Local erythema

Local erythema was reported in 1% (6/472) of patients treated by high-frequency rTMS, none treated by low-frequency rTMS (n=109) and none given sham stimulation (n=461) in the systematic review of 40 randomised controlled trials that included 1592 patients with depression (type unspecified)[1].

Drowsiness

Drowsiness was reported in 3% (12/472) of patients treated by high-frequency rTMS, none treated by low-frequency rTMS (n=109) and none given sham stimulation (n=461) in the systematic review of 40 randomised controlled trials that included 1592 patients with depression (type unspecified)[1].

Vertigo

Vertigo was reported in no patients in the conventional rTMS (n=98) group and 1 patient in the theta-burst rTMS group (n=87) in a non-randomised comparative study of 185 patients with treatment resistant depression[5]

Insomnia

Device-related insomnia was reported in 1 patient in a case series of 120 patients with major depressive disorder treated by rTMS[7].

Arthralgia

Device-related arthralgia was reported in 1 patient in a case series of 120 patients with major depressive disorder treated by rTMS[7].

Validity and generalisability of the studies

- The literature search identified a large number of systematic reviews, randomised controlled trials, non-randomised comparative studies and case series that were published after NICE's initial evaluation of rTMS in 2007.
- There were a number of variations in stimulation parameters between studies; these were principally in relation to rTMS frequencies (between 1 Hz and

20 Hz), motor thresholds (between 80% and 120%) and treatment sites (unilateral or bilateral).

- Included studies evaluated rTMS rather than single-pulse TMS.
- Two systematic reviews explicitly stated that studies that evaluated depression in adolescents or children were excluded[2,3].
- Most studies used HDRS scores as the primary outcome measure.
- Studies mainly assessed patients with major depressive disorder and/or treatment resistant depression.
- The longest follow-up period was 6 months[6].

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

In 2011, the United States Federal Drugs Agency published guidance for manufacturers on producing appropriate descriptions, labels and instructions for use of rTMS devices. The document did not evaluate the safety or efficacy of the rTMS but did recommend safe treatment parameters for avoiding seizures:

Freq (Hz)	INTENSITY (% of Motor Threshold)													
	80-100	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**
1	>1800	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Vagus nerve stimulation for treatment-resistant depression. NICE interventional procedure guidance 330 (2009). Available from http://www.nice.org.uk/guidance/IPG330

Technology appraisals

- Computerised cognitive behaviour therapy for depression and anxiety: review of technology appraisal 51. NICE technology appraisal 97 (2006). Available from http://www.nice.org.uk/guidance/TA97
- Guidance on the use of electroconvulsive therapy. NICE technology appraisal 59 (2003). Available from http://www.nice.org.uk/guidance/TA59

NICE guidelines

- Antenatal and postnatal mental health: clinical management and service guidance. NICE clinical guideline 192 (2014). Available from: http://www.nice.org.uk/guidance/cg192
- Common mental health disorders: identification and pathways to care. NICE clinical guideline 123 (2011). Available from http://www.nice.org.uk/guidance/CG123
- Depression in adults with a chronic physical health problem: treatment and management. NICE clinical guideline 91 (2009). Available from http://www.nice.org.uk/guidance/CG91
- Depression in adults: the treatment and management of depression in adults. NICE clinical guideline 90 (2009). Available from http://www.nice.org.uk/guidance/CG90
- Depression in children and young people: identification and management in primary, community and secondary care. NICE clinical guideline 28 (2005). Available from http://www.nice.org.uk/guidance/CG28

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The

advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for repetitive transcranial magnetic stimulation for depression were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent 50 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 23 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Issues for consideration by IPAC

Ongoing trials:

- NCT01516931: Efficacy of Repetitive Transcranial Magnetic Stimulation in the Prevention of Relapse of Depression; study type: randomised controlled trial; location: China; estimated enrolment: 540; estimated study completion date: February 2015; however, the clinical trials website states that the study is currently recruiting patients.
- NCT01191333: The Effectiveness of rTMS in Depressed VA Patients; study type: randomised controlled trial; location: United States; estimated enrolment: 360; estimated study completion date: January 2017.
- NCT01583023: Using Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Bipolar Depression; study type: randomised controlled trial; location: United States; estimated enrolment: 45; estimated study completion date: April 2015.
- NCT01566591: Safety and Efficacy Study of Deep Transcranial Magnetic Stimulation in Bipolar Depression; study type: randomised controlled trial;

location: United States; estimated enrolment: 120; estimated study completion date: December 2015.

- NCT01515215: Repetitive Transcranial Magnetic Stimulation (rTMS) for Treatment Resistant Depressive Disorder; study type: randomised controlled trial; location: Canada; estimated enrolment: 120; estimated study completion date: September 2014; however, the clinical trials website states that the study is ongoing but not recruiting patients.
- NCT01701284: Repetitive Transcranial Magnetic Stimulation in Cancer Patients With Depression and Anxiety (rTMSinCP); study type: randomised controlled trial; location: United States; estimated enrolment: 30; estimated study completion date: August 2017.
- NCT01842542: Efficacy and Safety Study of NeuroStar TMS Therapy in Patients With Major Depressive Disorder With Postpartum Onset; study type: case series; location: United States; estimated enrolment: 25; estimated study completion date: December 2017; however, the clinical trials websites states that the study is currently recruiting patients.
- NCT02213016: Effectiveness of Repetitive Transcranial Magnetic Stimulation in Depressed Patients; study type: randomised controlled trial; location: Mexico; estimated enrolment: 80; estimated study completion date: September 2016.
- NCT01860157: Deep rTMS for Treatment-Resistant Late-life Depression; study type: randomised controlled trial; location: Canada; estimated enrolment: 80; estimated study completion date: October 2017.
- NCT02016456: TMS Treatment for Depression in the National Health Service (TDEP): randomised controlled trial; location: United Kingdom; estimated enrolment: 124; estimated study completion date: July 2019.

References

1. Slotema CW, Blom JD, Hoek HW, Sommer IE (2010) 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. J Clin Psychiatry. 71(7):873-84. doi: 10.4088/JCP.08m04872gre.
2. Lepping P, Schönfeldt-Lecuona C, Sambhi RS, et al. (2014) A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. Acta Psychiatr Scand. 130(5):326-41. doi: 10.1111/acps.12276.
3. Zhang YQ, Zhu D, Zhou XY, et al. (2015) Bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials. Braz J Med Biol Res. 48(3):198-206. doi: 10.1590/1414-431X20144270.
4. Ren J, Li H, Palaniyappan L, et al. (2014) Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 51:181-9. doi: 10.1016/j.pnpbp.2014.02.004.
5. Bakker N, Shahab S, Giacobbe P, et al. (2015) rTMS of the dorsomedial prefrontal cortex for major depression: safety, tolerability, effectiveness, and outcome predictors for 10 Hz versus intermittent theta-burst stimulation. Brain Stimul. 8(2):208-15. doi: 10.1016/j.brs.2014.11.002.
6. Fitzgerald PB, Huntsman S, Gunewardene R, et al. (2006) A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. Int J Neuropsychopharmacol 9: 655–66.
7. Janicak PG, Nahas Z, Lisanby SH, et al. (2010) Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. Brain Stimul. 3(4):187-99. doi: 10.1016/j.brs.2010.07.003.
8. Conca A, König P, Hausmann A. (2000) Transcranial magnetic stimulation induces 'pseudoabsence seizure'. Acta Psychiatr Scand. 101(3):246-8.

Appendix A: Additional papers on repetitive transcranial magnetic stimulation for depression

The literature search identified a large number of systematic reviews, randomised controlled trials, non-randomised comparative studies and case series. The following table outlines some of the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Dell'Osso B (2011). Meta-Review of Metanalytic Studies with Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Major Depression. Clin Pract Epidemiol Ment Health 7, 167–177	Review	The publication summarised results of recently published systematic reviews that assessed the efficacy of rTMS.	The publication is a large narrative review that did not perform any primary data collection or meta-analysis of clinical trials.
Hovington CL, McGirr A, Lepage M et al. (2013) Repetitive transcranial magnetic stimulation (rTMS) for treating major depression and schizophrenia: a systematic review of recent meta-analyses. Ann Med. 45(4), 308-21	Review	The publication summarised results of recently published systematic reviews that assessed the efficacy of rTMS.	The publication is a large narrative review that did not perform any primary data collection or meta-analysis of clinical trials.
Lam RW, Chan P, Wilkins-Ho M, Yatham LN. (2008) Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. Canadian Journal of psychiatry. 53(9):621-31.	Systematic review n=1092 patients with treatment resistant depression treated by active rTMS or sham stimulation. Follow-up: treatment periods ranged from 1 week to 4 weeks.	Meta-analysis of clinical response revealed a pooled response rate of 25% in the active rTMS group and 9% in the sham stimulation group ($p<0.05$). Meta-analysis of remission revealed a pooled remission rate of 17% in the active rTMS group and 6% in the sham stimulation group ($p<0.05$).	Table 2 already includes large, high-quality systematic reviews which reported similar efficacy outcome measures.
Kedzior KK, Reitz SK (2014) Short-term efficacy of repetitive transcranial magnetic stimulation (rTMS) in depression- reanalysis of data from meta-analyses up to 2010. BMC Psychology 2 (1): 39. doi: 10.1186/s40359-014-0039-y. eCollection 2014.	Systematic review n=40 RCTs including 1583 patients (844 rTMS vs 739 sham) FU=Up to 20 treatment sessions	Meta-anaysis of mean changes in Hamilton Depression Rating Scale (HDRS) scores revealed a standardised mean difference of -0.54, in favour of rTMS (95% CI: -0.68 to -0.41; $p<0.001$). Meta-analysis of mean changes in Montgomery–Åsberg Depression Rating Scale (MADRS) scores revealed a standardised mean difference of -0.44, in favour of rTMS (95% CI: -	Larger systematic reviews that reported similar outcome measures are already in table 2.

		0.69 to -0.20; p<0.001).). Meta-analysis of mean changes in Beck Depression Inventory scores revealed a standardised mean difference of -0.42, in favour of rTMS (95% CI: -0.58 to -0.26; p<0.001).	
Schutter DJ (2009) Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychological medicine. 39(1):65-75.	Systematic review n=1164 patients with a major depressive episode treated by active rTMS or sham stimulation. Follow-up: not reported	Meta-analysis of changes in depressive rating scales revealed a Hedges' g value of 0.39 in favour of active rTMS (p<0.0001). Authors state that medication resistance and intensity of rTMS did not play a role in the effect size.	Table 2 already includes large, high-quality systematic reviews which reported similar efficacy outcome measures.
Gaynes BN, Lloyd SW, Lux L, Gartlehner G, et al. (2014) Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. Journal of clinical psychiatry 75(5):477-89; doi: 10.4088/JCP.13r08815.	Systematic review n=1164 patients with a treatment resistant depression treated by active rTMS or sham stimulation. Follow-up: up to 6 weeks	Meta-analysis of changes in HDRS scores revealed a mean difference of -4.53, in favour of active rTMS (p<0.05). Meta-analysis of response rates revealed a risk ratio of 3.38 in favour of rTMS (p<0.05)	Table 2 already includes large, high-quality systematic reviews which reported similar efficacy outcome measures.
Kedzior KK, Reitz SK, Azorina V, Loo C (2015) Durability OF the antidepressant effect of the high-frequency repetitive transcranial magnetic stimulation (rTMS) In the absence of maintenance treatment in major depression: a systematic review and meta-analysis of 16 double-blind, randomized, sham-controlled trials. Depression & Anxiety 32 (3) 193-203.2015.	Systematic review n=16 RCTs including 495 patients (253 rTMS vs 242 sham) FU=Up to 16 weeks	Meta-analysis of mean changes in MADRS and HDRS scores revealed a standardised mean difference of -0.48, in favour of rTMS (95% CI: -0.70 to -0.25, p<0.001).	Larger systematic reviews that reported similar outcome measures are already in table 2.
Gross M, Nakamura L, Pascual-Leone A, et al. (2007) Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatrica Scandinavica 116: 165–73.	Systematic review n=274 patients with a treatment resistant depression treated by active rTMS or sham stimulation. Follow-up: not reported	Meta-analysis of changes in HDRS, BDI and MADRS scores revealed a mean standardised mean difference of -0.76, in favour of active rTMS (95% CI -1.01 to -0.51).	Table 2 already includes large, high-quality systematic reviews which reported similar efficacy outcome measures.
Micallef-Trigona, B. (2014) Comparing the effects of	Systematic review	The pooled mean reduction of HDRS scores was 9.3 in	Table 2 already includes large, high-

repetitive transcranial magnetic stimulation and electroconvulsive therapy in the treatment of depression: a systematic review and meta-analysis. Depression Research and Treatment. Online publication: doi: 10.1155/2014/135049	n=384 patients with major depressive disorder treated by rTMS or ECT. Follow-up: not reported	the rTMS group and 15.42 in the ECT group (p=0.011). The mean effect size for rTMS was 1.33 whilst that for ECT was 2.14.	quality systematic reviews which reported similar efficacy outcome measures.
Berlim MT, van den Eynde F, Daskalakis Z J. (2013) Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. Depression & Anxiety 30 (7) 614-623.2013.	Systematic review n=294 patients with major depressive disorder treated by high-frequency rTMS or ECT Follow-up: not reported	Meta-analysis of changes in depression rating scales revealed a Hedges' g value of -0.93, in favour of ECT (p= 0.007). Authors state that the associated number needed to treat for remission was 6, in favour of ECT. No differences on dropout rates for HF-rTMS and ECT groups were found.	Table 2 already includes large, high-quality systematic reviews which reported similar efficacy outcome measures.
Martin JLR, Barbanoj MJ, Schlaepfer TE, et al. (2001) Transcranial magnetic stimulation for treating depression. Cochrane Database of Systematic Reviews, Issue 4: CD003493.	Systematic review (included in previous guidance) n=197 patients with different types of depression treated by active rTMS or sham stimulation Follow-up: not reported	Meta-analyses of changes in HDRS scores, in patients treated by left rTMS or sham revealed a standardised mean difference of -0.35, in favour of rTMS (p=0.03). Meta-analyses changes in HDRS scores, in patients treated by right rTMS or sham revealed a standardised mean difference of -4.20, in favour of rTMS (p=0.05).	Table 2 already includes large, high-quality systematic reviews which reported similar efficacy outcome measures.
Herrmann LL, Ebmeier KP. (2006) Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. Journal of Clinical Psychiatry 67: 1870–6	Systematic review (included in previous guidance) n=877 patients with different types of depression treated by active rTMS or sham stimulation Follow-up: not reported	The pooled estimate of effect size was 0.65 (95% CI 0.51 to 0.79), indicating a clinically significant effect in favour of rTMS. The mean reduction in HDRS and MADRS scores was 33.6% (range: 10.4% to 59.4%) in the active rTMS group and 17.4% (range: 15% to 54%) in the sham stimulation group.	Table 2 already includes large, high-quality systematic reviews which reported similar efficacy outcome measures.
O'Reardon JP, Solvason HB, Janicak PG, et al. (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biological Psychiatry doi:10.1016/j.biopsych.2007.01.018	Randomised controlled trial (included in previous guidance) n=301 patients with major depressive disorder treated by rTMS or sham stimulation	HDRS scores improved from 22.6 to 17.1 in the active rTMS group and from 22.9 to 19.4 in the sham stimulation group at 6 week follow-up (p value between groups=0.006). The response rate (using HDRS scores) was 20.6% in the active rTMS group and 11.6% in the sham stimulation group at 4 week follow-up (p<0.05). The	Study was included in one of the systematic reviews in table 2. Furthermore, larger studies that reported similar outcome measures were available.

		remission rate (using HDRS scores) was 7.1% in the active rTMS group and 6.2% in the sham stimulation group at 4 week follow-up (not significant).	
Leuchter AF, Cook IA, Feifel D et al. (2015) Efficacy and Safety of Low-field Synchronized Transcranial Magnetic Stimulation (sTMS) for Treatment of Major Depression. 8(4):787-94. doi: 10.1016/j.brs.2015.05.005.	Randomised controlled trial n=202 patients (103 rTMS vs sham) FU=6 weeks	Mean HDRS scores improved from 21.78 to 12.78 in the rTMS group and from 21.23 to 14.57 in the sham stimulation group at 6 week follow-up (p=0.033). The response rate (defined as more than a 50% reduction in HDRS scores) was 33.9% in the rTMS group and 29.5% in the sham stimulation group at 6 week follow-up (not significant). The remission rate (defined as an HDRS score less than 7) was 15.3% in the rTMS group and 16.4% in the sham stimulation group (not significant).	Larger studies that reported similar outcome measures are already in table 2.
Brunelin J, Jalenques I, Trojak B et al, (2014) The efficacy and safety of low frequency repetitive transcranial magnetic stimulation for treatment-resistant depression: the results from a large multicenter French RCT. Brain Stimul. 7(6):855-63. doi: 10.1016/j.brs.2014.07.040.	Randomised controlled trial (included in previous guidance) n=170 patients with treatment resistant depression treated by active rTMS+placebo, active rTMS + venlafaxine or, sham stimulation + venlafaxine. Follow-up: 6 weeks	HDRS scores improved from 25.8 to 14.0 in the active rTMS + placebo group, 26.1 to 15.4 in the active rTMS + venlafaxine group, and from 25.8 to 14.3 in the sham stimulation + venlafaxine group. The remission rate was 40.7% in the active rTMS + placebo group, 28.0% in the active rTMS + venlafaxine group, and 43.1% in the sham stimulation + venlafaxine group.	Large systematic reviews and comparative studies are included in table 2.
Rossini D, Magri L, Lucca A, et al. (2005) Does rTMS hasten the response to escitalopram, sertraline or venlafaxine in patients with major depressive disorder? A double-blind randomized, sham-controlled trial. Journal of Clinical Psychiatry 66: 1569–75.	Randomised controlled trial (included in previous guidance) n=99 patients with major depressive disorder treated by rTMS or sham stimulation Follow-up: 5 weeks	The mean reduction in HDRS scores was 19.1 in the active rTMS group and 16.2 in the sham stimulation group at 5 week follow-up. The response rate was 80% in the active rTMS group and 73% in the sham stimulation group at 5 week follow-up (p=0.419). The remission rate was 73% in the active rTMS group and 55% in the sham stimulation group at 5 week follow-up (p=0.064).	Study was included in one of the systematic reviews in table 2. Furthermore, larger studies that reported similar outcome measures were available.
Avery DH, Holtzheimer PE,	Randomised	The response rate was	Study was included

Fawaz W, et al. (2006) A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biological Psychiatry 59: 187–94.	controlled trial (included in previous guidance) n=68 patients with major depressive disorder treated by rTMS or sham stimulation Follow-up: 2 weeks after treatment. Patients who met response criteria were followed-up for 6 months.	31% in the active rTMS group and 6% in the sham stimulation group at follow-up (p=0.008). The remission rate was 20% in the active rTMS group and 3% in the sham stimulation group at follow-up (p=0.033). Logistic regression analysis, adjusting for stratification variables, showed TMS had significantly greater odds of response: adjusted odds ratio was 21.08, 95% CI 2.07 to 214.16)	in one of the systematic reviews in table 2. Furthermore, larger studies that reported similar outcome measures were available.
Li CT, Chen MH, Juan CH (2014) Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain.137(7): 2088-98. doi: 10.1093/brain/awu109.	Randomised controlled trial n=60 patients with treatment resistant depression treated by A) continuous theta-burst stimulation, B) intermittent theta-burst stimulation, C) a combination of continuous and intermittent theta-burst stimulation or D) sham theta-burst stimulation Follow-up: 12 weeks after treatment.	Authors state: "After 2 weeks of theta-burst stimulation treatment, depression improved in all groups. Groups B and C had better antidepressant responses (as reflected by % decreases in depression score) than Groups A and D (P = 0.001, post hoc analysis: B > A, B > D, C > A, and C > D), even after controlling for age and refractoriness scores. The mean antidepressant effect was highest in Group C and followed by that in Group B. Additionally, a significant placebo effect was found in patients with low refractoriness; this disappeared in patients with moderate-to-high refractoriness."	Large systematic reviews and comparative studies are included in table 2.
Fitzgerald PB, Brown TL, Marston NAU, et al. (2003) Transcranial magnetic stimulation in the treatment of depression. Archives of General Psychiatry 60: 1002–8.	Randomised controlled trial (included in previous guidance) n=60 patients with treatment resistant depression treated by high-frequency rTMS, low-frequency rTMS or sham stimulation. Follow-up: 2 weeks after treatment. Patients who met response criteria were followed-up for	Mean HDRS scores changed from 36.1 to 30.8, 37.7 to 32.2 and 35.7 to 35.4 in the high-frequency rTMS, low-frequency rTMS and sham stimulation groups, respectively, at 2 week follow-up. Significant differences were observed when high-frequency and low-frequency rTMS were compared against sham stimulation. No significant difference was observed high-frequency and low-frequency rTMS	Study was included in one of the systematic reviews in table 2. Furthermore, larger studies that reported similar outcome measures were available.

	6 months.		
George MS, Lisanby SH, Avery D, et al. (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry; 67(5):507-16. doi: 10.1001/archgenpsychiatry.2010.46.	Randomised controlled trial n=90 patients with major depressive disorder treated by active rTMS or sham Follow-up: 6 weeks	HDRS scores improved from 26.26 to 21.61 in the active rTMS group and from 26.51 to 23.38 in the sham stimulation group (p value between groups=0.06). CGI-S scores improved from 4.62 to 3.96 in the active rTMS group and 4.63 to 4.30 in the sham stimulation group (p value between groups=0.001)	Study was included in one of the systematic reviews in table 2. Furthermore, larger studies that reported similar outcome measures were available.
Plewnia C, Pasqualetti P, Große S (2014) Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. J Affect Disord. 156:219-23. doi: 10.1016/j.jad.2013.12.025.	Randomised controlled trial n=32 patients treated by theta-burst rTMS plus conventional rTMS or sham stimulation Follow-up: 6 weeks	Only 20 patients (9 in the theta-burst rTMS group and 11 in the sham stimulation group) completed the 6 week assessment period. Mean MADRS scores decreased from 26.8 to 16.6 in the theta-burst rTMS group and from 26.6 to 19.6 in the sham stimulation group. Six patients treated by theta-burst rTMS and 1 patient who received sham stimulation reached remission criterion	Large systematic reviews and comparative studies are included in table 2.
Carpenter LL, Janicak PG, Aaronson ST et al (2012) Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 29(7), 587–596	Case series n=307 patients with major depressive disorder Follow-up: 6 weeks	There was a significant improvement in CGI-S scores from baseline to end of treatment (-1.9 ± 1.4, p< 0.0001). The clinician-assessed response rate (CGI-S) was 58.0%. The remission rate was 37.1%. Patient-reported response rate ranged from 56.4% to 41.5% and remission rate ranged from 28.7% to 26.5%	Large systematic reviews and comparative studies are included in table 2.
Connolly RK, Helmer A, Cristancho MA et al (2012) Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. J Clin Psychiatry 73(4), 567–573	Case series n=100 patients with major depressive disorder Follow-up: Unclear	The CGI-I response rate was 50.6% at 6 week follow-up. The remission rate was 24.7% at 6 week follow-up. The mean change in HDRS scores was -7.8 points. The HDRS response and remission rates were 41.2% and 35.3%, respectively.	Large systematic reviews and comparative studies are included in table 2.
Euba R, Panihhidina I, Zamar A (2015) Treatment-resistant depression: experience of the first repetitive transcranial magnetic stimulation clinic in	Case series n=62 patients with treatment resistant depression	Mean BDI-II scores decreased by a mean of 17.9 points (from 31.6) at mean follow-up of 4.3 weeks. Mean Beck Anxiety Inventory scores decreased	Large systematic reviews and comparative studies are included in table 2.

the UK. Future neurology. 10, No. 3, Pages 211-215, DOI 10.2217/fnl.15.8	Follow-up: mean of 4.3 weeks	by a mean of 11 points (from 19) at mean follow-up of 4.3 weeks. Remission was reported in 66% (41/62) of patients.	

Appendix B: Related NICE guidance for repetitive transcranial magnetic stimulation for depression

Guidance	Recommendations
Interventional procedures	**Vagus nerve stimulation for treatment-resistant depression. NICE interventional procedure guidance 330 (2009)** 1.1 Current evidence on the safety and efficacy of vagus nerve stimulation (VNS) for treatment-resistant depression is inadequate in quantity and quality. Therefore this procedure should be used only with special arrangements for clinical governance, consent and audit or research. It should be used only in patients with treatment-resistant depression. 1.2 Clinicians wishing to undertake VNS for treatment-resistant depression should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and/or their parents/carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having VNS for treatment-resistant depression (see section 3.1). 1.3 Patient selection and management should be carried out by a multidisciplinary team including a psychiatrist and a surgeon (usually a neurosurgeon), with other relevant specialists (for example, a clinical psychologist and an appropriately trained technician). 1.4 NICE encourages further research into VNS for treatment-resistant depression. Research outcomes should include depression rating scales, objective measures of depressive symptoms and patient-reported quality of life. NICE may review the procedure on publication of further evidence.
Technology appraisals	**Computerised cognitive behaviour therapy for depression and anxiety: Review of Technology Appraisal 51. NICE technology appraisal 97 (2006)** This review concerns five specific packages for the delivery of computerised cognitive behaviour therapy (CCBT) accessed via a referral from a general practitioner (GP): three for

	depression (Beating the Blues, COPE and Overcoming Depression), one for panic/phobia (FearFighter) and one for obsessive-compulsive disorder (OCD) (OCFighter, previously known as BTSteps). This guidance should be read in the context of the Clinical Guidelines on depression, anxiety and OCD). 1.1 This recommendation has been replaced by recommendations in the two depression clinical guidelines (CG90 and CG91) published in October 2009. 1.2 This recommendation has been replaced by recommendations in the two depression clinical guidelines (CG90 and CG91) published in October 2009. 1.3 This recommendation has been replaced by the generalised anxiety disorder and panic disorder guideline (CG113), published in January 2011, and by the social anxiety disorder guideline (CG159), published in May 2013. 1.4 OCFighter (previously known as BTSteps) is not recommended as an option for delivering CBT in the management of OCD. 1.5 People currently using OCFighter, whether as routine therapy or as part of a clinical trial, should have the option to continue on therapy until the person, or the GP and/or specialist, consider it appropriate to stop. **Guidance on the use of electroconvulsive therapy. NICE technology appraisal 59 (2003)** The recommendations in this technology appraisal relating to the treatment of depression have been replaced by recommendations in 'Depression in adults (update)' (NICE clinical guideline 90) published in October 2009). Note that the recommendations in this technology appraisal relating to the treatment of catatonia-prolonged or severe manic episodes and schizophrenia have not changed. The recommendations relating to depression have been removed from this web viewer version. 1.1 It is recommended that electroconvulsive therapy (ECT) is used only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is

	considered to be potentially life-threatening, in individuals with: • catatonia • a prolonged or severe manic episode. 1.2 The decision as to whether ECT is clinically indicated should be based on a documented assessment of the risks and potential benefits to the individual, including: the risks associated with the anaesthetic; current co-morbidities; anticipated adverse events, particularly cognitive impairment; and the risks of not having treatment. 1.3 The risks associated with ECT may be enhanced during pregnancy, in older people, and in children and young people, and therefore clinicians should exercise particular caution when considering ECT treatment in these groups. 1.4 Valid consent should be obtained in all cases where the individual has the ability to grant or refuse consent. The decision to use ECT should be made jointly by the individual and the clinician(s) responsible for treatment, on the basis of an informed discussion. This discussion should be enabled by the provision of full and appropriate information about the general risks associated with ECT (see Section 1.9) and about the risks and potential benefits specific to that individual. Consent should be obtained without pressure or coercion, which may occur as a result of the circumstances and clinical setting, and the individual should be reminded of their right to withdraw consent at any point. There should be strict adherence to recognised guidelines about consent and the involvement of patient advocates and/or carers to facilitate informed discussion is strongly encouraged. 1.5 In all situations where informed discussion and consent is not possible advance directives should be taken fully into account and the individual's advocate and/or carer should be consulted. 1.6 Clinical status should be assessed following each ECT session and treatment should be stopped when a response has been achieved, or sooner if there is evidence of adverse effects. Cognitive function should be monitored on an ongoing basis, and at a minimum at the end of each course of treatment. 1.7 It is recommended that a repeat course of ECT should be considered under the circumstances indicated in 1.1 only for individuals who have catatonia or mania and who have

	previously responded well to ECT. In patients who are experiencing an acute episode but have not previously responded, a repeat trial of ECT should be undertaken only after all other options have been considered and following discussion of the risks and benefits with the individual and/or where appropriate their carer/advocate. 1.8 This recommendation has been updated and replaced by NICE clinical guideline 90. 1.9 The current state of the evidence does not allow the general use of ECT in the management of schizophrenia to be recommended. 1.10 National information leaflets should be developed through consultation with appropriate professional and user organisations to enable individuals and their carers/advocates to make an informed decision regarding the appropriateness of ECT for their circumstances. The leaflets should be evidence based, include information about the risks of ECT and availability of alternative treatments, and be produced in formats and languages that make them accessible to a wide range of service users.
NICE guidelines	**Common mental health disorders: Identification and pathways to care. NICE clinical guideline 123 (2011)** 1.1 Improving access to services 1.2 Stepped care 1.3 Step 1: Identification and assessment 1.4 Steps 2 and 3: Treatment and referral for treatment 1.5 Developing local care pathways **Depression in adults with a chronic physical health problem: Treatment and management. NICE clinical guideline 91 (2009)** 1.1 Care of all people with depression 1.2 Stepped care 1.3 Step 1: recognition, assessment and initial management in primary care and general hospital settings 1.4 Step 2: recognised depression in primary care and general hospital settings – persistent subthreshold depressive symptoms or mild to moderate depression 1.5 Step 3: recognised depression in primary care and general hospital settings – persistent subthreshold depressive symptoms or mild to moderate depression with inadequate

	response to initial interventions, and moderate and severe depression 1.6 Step 4: complex and severe depression **Depression in adults: The treatment and management of depression in adults. NICE clinical guideline 90 (2009)** 1.10.4 Electroconvulsive therapy (ECT) 1.10.5 Transcranial magnetic stimulation **Depression in children and young people: Identification and management in primary, community and secondary care. NICE clinical guideline 28 (2005)** Guideline includes recommendations on the use of electroconvulsive therapy (ECT). **Antenatal and postnatal mental health: Clinical management and service guidance. NICE clinical guideline 192 (2014)** Guideline includes recommendations on the use of electroconvulsive therapy (ECT) but does not include TDCS.

Appendix C: Literature search for repetitive transcranial magnetic stimulation for depression

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	28/08/2015	Issue 8 of 12, August 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	28/08/2015	Issue 8 of 12, August 2015
HTA database (Cochrane Library)	28/08/2015	Issue 3 of 4, July 2015
MEDLINE (Ovid)	28/08/2015	1946 to August Week 3 2015
MEDLINE In-Process (Ovid)	28/08/2015	August 27, 2015
EMBASE (Ovid)	28/08/2015	1974 to 2015 week 34
CINAHL (NLH Search 2.0)	28/08/2015	N/A
PubMed	01/09/2015	N/A
JournalTOCS	01/09/2015	N/A

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Transcranial magnetic stimulation/
2	((transcranial or trans-cranial) adj4 magnetic adj4 (stimulation or activation)).tw.
3	(tms or rtms).tw.
4	or/1-3
5	depression/
6	Depression, Postpartum/
7	depressive disorder/
8	depressive disorder, major/
9	seasonal affective disorder/
10	bipolar disorder/
11	mood disorder/
12	depress*.tw.
13	((bipolar or bi-polar or seasonal or mood or dysthymic) adj4 (disorder or episode)).tw.
14	or/5-13

15	4 and 14
16	Randomized Controlled Trial.pt.
17	Controlled Clinical Trial.pt.
18	Clinical Trial.pt.
19	exp Clinical Trials as Topic/
20	Placebos/
21	Random Allocation/
22	Double-Blind Method/
23	Single-Blind Method/
24	Cross-Over Studies/
25	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
26	(random$ adj3 allocat$).tw.
27	placebo$.tw.
28	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
29	(random$ adj3 allocat$).tw.
30	placebo$.tw.
31	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
32	(crossover$ or (cross adj over$)).tw.
33	or/16-32
34	15 and 33
35	animals/ not humans/
36	34 not 35
37	limit 36 to english language
38	limit 37 to ed=20061011-20150228