NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcranial magnetic stimulation for severe depression

Depression is associated with feelings of sadness, despair, helplessness, hopelessness and lack of interest in life. People with severe depression may be unable to eat or sleep or to take part in social activities, and may become completely withdrawn. Transcranial magnetic stimulation is a possible treatment for severe depression that uses a powerful electromagnet placed on the scalp to induce electric currents in the brain.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making 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 overview was prepared in November 2006.

Procedure name

- Transcranial magnetic stimulation
- Repetitive transcranial magnetic stimulation

Specialty societies

- British Psychological Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Psychiatrists

Description

Indications

Severe depression

Depression refers to a wide range of mental health problems characterised by loss of interest and enjoyment, low mood and a range of associated emotional, cognitive, physical and behavioural symptoms. Behavioural and physical symptoms typically include tearfulness, irritability, social withdrawal, reduced sleep, decreased appetite, lack of libido, fatigue and diminished activity. Low self-esteem and loss of confidence are common, as are feelings of guilt and worthlessness. People with severe depression may also develop psychotic symptoms (hallucinations and/or delusions). Depression is associated with risk of suicide attempt and risk of suicide. The more severe the episode of depression, the less likely it is that remission will occur spontaneously.

It can be difficult to distinguish the mood changes of depression from those that occur 'normally'; diagnosis is usually based on persistence and severity of mood changes, the presence of other symptoms and the degree of functional and social impairment. Different diagnostic criteria and methods of classification of depressive illnesses are in use. The International Classification of Diseases (ICD-10) system uses a list of 10 symptoms associated with depression: severe depression is defined as 7 or more of those symptoms being present for at least 2 weeks. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is another widely used classification system that defines major depressive disorder as either depressed mood or anhedonia, in conjunction with five of a list of other symptoms over a two week period.

There are several scales used to measure depression severity. The Hamilton Depression Rating Scale (HDRS) uses a semi-structured interview to assess a number of variables (including depressed mood, insomnia, agitation, anxiety and weight loss) measured on five-point or three-point scales, with low values indicating less depression. Another clinician rated scale is the Montgomery-Asberg Depression Rating Scale (MADRS) that measures 10 items (including apparent sadness, reported sadness, suicidal thoughts) on a scale of 0 to 6 with low values indicating less depression. The Beck Depression Inventory (BDI) is a self-completed questionnaire composed of items relating to depression symptoms, cognition and physical symptoms; each item is scored from 0 to 3 with low values indicating less depression.

Current treatment and alternatives

Conventional treatment for depression includes antidepressant medication, psychological therapy or a combination of both. Electroconvulsive therapy (ECT) is also sometimes used to treat severe depression and may be used in conjunction with other treatments. ECT involves the application of electric current through the brain under general anaesthesia, while muscle relaxants

are used to minimise muscular contraction. Although ECT has been used for many years, there is still uncertainty about its mechanism of action.

What the procedure involves

Transcranial magnetic stimulation (TMS) does not require anaesthesia and can be performed on an outpatient basis. The patient is usually seated while a purpose-made electromagnet coil is held against the scalp over specific regions of the skull and magnetic fields induce electric currents in the cerebral cortex. Ear plugs are usually worn to diminish the noise from the discharging coil. Imaging may be used to facilitate more precise targeting of selected brain regions. Repetitive TMS (rTMS) uses repeated pulses in a rhythmic and repetitive form rather than one single pulse; it may be high frequency (stimulation occurs faster than once per second, 1 Hz) or low frequency (speed of stimulation 1Hz or less). Low frequency rTMS is considered to inhibit certain areas of the brain, while high frequency activates certain areas. The intensity of rTMS is usually set as a percentage of the patient's motor threshold (MT. This is the minimum stimulus strength required to evoke involuntary muscle movements (usually in hand muscles) 5 times out of 10 when TMS is given over the primary motor cortex. Different dosing protocols in relation to MT parameters can be used, sometime employing dosing intensity at 100% of MT or greater. Depending on intensity parameters, the patient may experience involuntary spasms of scalp muscles. The intended / targeted area for stimulation could be unilateral (most commonly left), or bilateral, depending on treatment protocols. Treatment with rTMS usually involves daily sessions lasting about 30 minutes for 2-4 weeks and possibly longer.

Efficacy

Specialist advisers stated that the main outcome measure of benefit was depression response, as measured by a depression rating scale such as HDRS, MADRS or BDI.

A systematic review of 16 studies, including 394 patients, reported that there was a statistically significant improvement in depression according to HDRS after 2 weeks of treatment with high-frequency rTMS over the left dorsolateral prefrontal cortex compared with sham treatment (11 studies, n = 197, $p = 0.03$). In three studies that reported results after a 2-week follow-up, the difference was no longer statistically significant. The review reported that the difference between active and sham rTMS was not significant when BDI was used as an outcome measure (7 studies, n = 145).[1]

A more recent meta-analysis of 33 studies, including 877 patients, reported that reduction in depressive symptoms ranged from -10.4% to 59.4% for active rTMS and from 15% to 54% for sham rTMS at the end of treatment.[28]

An RCT of 301 patients (not included in the meta-analysis) reported that 18% of patients in the active TMS group achieved response at 4 weeks (MADRS scale) compared with 11% of patients in the sham TMS group ($p < 0.05$). There were no significant differences in the remission rates at 4 weeks (7% in

the active TMS group versus 6% in the sham TMS group, p > 0.10).[53] An RCT of 130 patients reported that overall 51% (66/130) patients achieved response and 27% (35/130) achieved remission at the end of treatment. There was no significant difference in response rates between 1 and 2-Hz rTMS. An RCT of 54 patients reported that 61% (11/18) of patients receiving rTMS at 100% MT and 28% (5/16) of patients receiving rTMS at 80% MT responded to treatment, compared with 6% (1/16) of patients in the sham group (p = 0.0008 for 100% MT versus sham, p = 0.1 for 80% MT versus sham, p = 0.044 for 100% versus 80% MT).[3]

An RCT of 46 patients, comparing rTMS with ECT, reported that significantly more patients responded to ECT than rTMS (59% [13/22] compared with 17% [4/24], p = 0.006). A second RCT of 35 patients reported that 50% (10/20) of patients treated with rTMS responded to treatment and 10% (2/20) achieved remission, compared with 40% (6/15) and 20% (3/15) respectively, of patients treated with ECT (p = 0.6 for both results). An RCT of 41 patients who initially responded to either ECT or rTMS, reported similar rates of relapse during 6 months' follow-up (20% [4/20] for ECT versus 19% [4/21] for rTMS) (p value not stated).[8]

Safety

Specialist advisers stated that potential adverse events included induction of seizure, local scalp discomfort, headache, migraine, nausea, neck stiffness, hearing loss (avoided by wearing ear plugs) and induction of mania.

Headache

Two RCTs reported headache in 10% (6/60) and 11% (2/18 at 100% MT and 2/19 at 80% MT) of patients receiving active rTMS.[5,3] In a case series of 249 patients, headache was reported in 5% (9/187) of patients who had high-frequency rTMS over the left dorsolateral prefrontal cortex, 26% (5/19) of patients who had high-frequency rTMS over the right dorsolateral prefrontal cortex, 45% (5/11) of patients who had low-frequency rTMS over the left dorsolateral prefrontal cortex and 44% (14/32) patients who had low-frequency rTMS over the right dorsolateral prefrontal cortex.[9]

Discomfort or pain at site of stimulation

Four RCTs reported site discomfort or pain in 0% (0/19) to 41% (14/35) of patients.[3,4,5, 53]

Neck pain

In a case series of 249 patients, neck pain was reported in 3% (5/187) of patients who had high-frequency rTMS over the left dorsolateral prefrontal cortex, 11% (2/19) of patients who had high-frequency rTMS over the right dorsolateral prefrontal cortex, 18% (2/11) of patients who had low-frequency rTMS over the left dorsolateral prefrontal cortex and 19% (6/32) patients who had low-frequency rTMS over the right dorsolateral prefrontal cortex.[9]

Transient hearing loss

In a RCT, 1 out of 9 patients receiving active rTMS and 1 out of 9 patients receiving sham rTMS had increases in auditory threshold. One patient was tested again a month later and hearing had returned to baseline levels.

Dental pain

An RCT reported that toothache occurred in 7% (12/165) of patients receiving active TMS.[53]

Induction of mania

In an RCT of 130 patients, one patient developed a hypomanic episode soon after completion of initial phase of treatment.[49] Two case reports were identified that described a total of three patients with either mixed depressive episode or induction of manic symptoms associated with TMS treatment.[56,58]

Induction of seizure

One case report was identified of a patient suffering from a self-limiting complex partial seizure after high frequency rTMS treatment.[57]

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to TMS. Searches were conducted via the following databases, covering the period from 1995 to 11 October 2006: 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.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these 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, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patients	Patients with severe depression
Intervention/test	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 overview

This overview is based on one Cochrane Review (including 16 RCTs), seven additional RCTs (one of which relates to a study that was included in the above mentioned Cochrane review, but presents longer follow-up), and one case series study.[1-9]

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

Existing reviews on this procedure

A Cochrane Review on TMS for treatment of depression was published in 2001 (search date June 2001).[1] The review included 16 RCTs, 14 of which contributed to a meta-analysis. No difference was seen between rTMS and sham TMS using the Beck Depression Inventory or the Hamilton Depression Rating Scale, except at 2 weeks follow-up for left dorsolateral prefrontal cortex and high-frequency rTMS; and also for right dorsolateral prefrontal cortex and low-frequency rTMS, both in favour of rTMS and both using the Hamilton scale. The review concluded that there is no strong evidence for a possible efficacy of TMS for the treatment of depression, although the possibility of benefit could not be excluded.

There are several other reviews on TMS. A recent report identified more than 25 published sham-controlled rTMS studies in depression, including seven meta-analyses published between 2001 and 2005.[10] The report stated that there was clear statistical proof of superiority over placebo effects but not large clinical effects. The authors concluded that the results suggested that a longer course of treatment (four to six weeks) is necessary for optimal outcomes.

Suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 1996, were published in 1998.[11] The report states that there had been seven known seizure episodes caused by rTMS, one of which was in a patient with depression.

Related NICE guidance

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

Interventional procedures

None

Technology appraisals

Guidance on the use of electroconvulsive therapy (ECT). *NICE Technology Appraisal Guidance* No.59 (2003). Available from: www.nice.org.uk/TA059.

Clinical guidelines

Depression: management of depression in primary and secondary care. *NICE Clinical Guideline* No. 23 (2004).

Depression in children and young people: identification and management in primary, community and secondary care. *NICE Clinical Guideline* No. 28 (2005)

Public health

None

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

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Martin JLR (2001)[1] Systematic review (Cochrane) **Search date: June 2001** **n = 16 randomised controlled trials assessing the therapeutic efficacy and safety of TMS for depression:** Avery DH (1999)[12], n = 6, 10 Hz at 80% MT, follow-up = 2 weeks Berman RM (2000)[13], n = 20 Conca A (1996)[14], n = 24 (not included in meta-analysis) Eschweiler WG (2000)[15], n = 12, 10 Hz at 90% MT Garcia-Toro M (2001a)[16], n = 40, follow-up = 2 weeks, 20 Hz at 90% MT Garcia-Toro M (2001b)[17], n = 28, follow-up = 2 weeks, 20 Hz at 90% MT George MS (1997)[18], n = 12, 20 Hz at 80% MT George MS (2000)[19], n = 32, 5–20 Hz at 100% MT Grunhaus L (2000)[20], n = 40, 10 Hz at 90% MT, 4-week treatment Haag C (1997)[21], n = 18, 10 Hz at 90% MT, 1-week treatment Kimbrell TA (1999a)[22], n = 13, 20 Hz at 80% MT, 4-week treatment Klein E (1999)[23], n = 70, 1 Hz at 110% MT Kolbinger HM (1995)[24], n = 15 Loo C (1999)[25], n = 18, 4-week treatment, 10 Hz at 110% MT	**rTMS (left dorsolateral prefrontal cortex and high frequency) versus sham TMS** ***HDRS (11 studies, n = 197)*** After 2 weeks' treatment, SMD = –0.35 (95% CI –0.66 to –0.04; p = 0.03, n = 9 studies), showing a difference in favour of rTMS. After 2 weeks' post-treatment follow-up, SMD = –0.33 (95% CI –0.84 to 0.17, p = 0.2, n = 3). ***Beck Depression Inventory (7 studies, n = 145)*** After 2 weeks' treatment, SMD = –0.24 (95% CI –0.58 to 0.11, p = 0.18, n = 6 studies). After 2 weeks' post-treatment follow-up, SMD = –0.06 (95% CI –0.56 to 0.43, p = 0.8, n = 3 studies). ***Clinical global impression (1 study, n = 30)*** After 2 weeks' treatment, WMD = –0.70 (95% CI –1.77 to 0.37, p = 0.2). **rTMS (right dorsolateral prefrontal cortex and low frequency) versus sham TMS (1 study, n = 67)** ***HDRS*** After 1 week of treatment, WMD = –4.20 (95% CI –8.44 to 0.04, p = 0.05). After 2 weeks treatment, WMD = –6.00 (95% CI –10.69 to –1.31, p = 0.01) in favour of rTMS. ***Clinical global impression*** After 1 week of treatment, WMD = –5.00 (95% CI –1.11 to 0.11, p = 0.11). After 2 weeks' treatment, WMD = –7.00 (95% CI –0.40 to 0.00, p = 0.05).	'It does not seem that the use of this technique, with its usual safety measures, produces significant adverse effects in the short-term (from 1 to 3 or 4 weeks), apart from in some cases a moderate headache which is easily treated.'	Although the Mosimann article was described as being in press, the journal was not named; the article was not identified in the search for this overview. Clinical global impression is an instrument of evaluation for the severity of illness. Low values indicate a decrease in the severity and/or significant recuperation. The review states that the principal deficiency in methodology is the small sample size of the studies. None of the included studies described the method of concealment allocation. There is heterogeneity of the pathology and evaluation methods.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Martin JLR (2001) *continued.* Mosimann (in press)[26], n = 24, 20 Hz at 100% MT Pridmore S (2000)[27], n = 22 (not included in meta-analysis), 20 Hz at 100% MT All studies had major depression or depressive episode as inclusion criteria. Participants did not have risk of convulsions. 8 studies stated that they included medication resistant patients and 1 study included medication resistant and/or psychotic major depressive disorder. All studies used 2-week treatments unless otherwise stated. There was no follow-up described unless otherwise stated. 45 studies were excluded from quantitative analysis of review. Conflict of interest: one of the authors is involved in an ongoing study included in the review.	**rTMS (left dorsolateral prefrontal cortex and low frequency) versus sham TMS** ***HDRS (2 studies, n = 20)*** After 1 week of treatment, WMD = –2.00 (95% CI –13.49 to 9.49, p = 0.7, n = 1 study). After 2 weeks' treatment, WMD = 2.53 (95% CI –13.53 to 18.59, p = 0.8, n = 1 study). **High- versus low-frequency rTMS (left dorsolateral prefrontal cortex)** ***HDRS (2 studies, n = 22)*** After 1 week of treatment, WMD = –2.60 (95% CI –10.76 to 5.56, p = 0.5, n = 1 study). After 2 weeks' treatment, WMD = –0.40 (95% CI –13.84 to 13.04, p = 0.1, n = 1 study). **rTMS (left dorsolateral prefrontal cortex and high frequency) versus ECT** ***HDRS (1 study, n = 40)*** After 2 weeks' treatment, WMD for all patients = 1.70 (95% CI –3.27 to 6.67, p = 0.5). After 4 weeks, WMD = 4.20 (95% CI –0.74 to 9.14, p = 0.10). For non-psychotic patients, WMD after 2 weeks = –3.90 (95% CI –10.90 to 3.10, p = 0.3). After 4 weeks, WMD = –2.90 (95% CI –10.26 to 4.46, p = 0.4). For psychotic patients, WMD after 2 weeks = 7.90 (95% CI 1.98 to 13.82, p = 0.009) in favour of ECT. After 4 weeks, WMD = 12.40 (95% CI 7.77 to 17.03, p < 0.00001) in favour of ECT. Relative risk of patient withdrawal during study, for rTMS versus sham TMS, for all patients = 0.81 (95% CI 0.36 to 1.83, p = 0.6).		

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Rossini D (2005a)[2]

Randomised controlled trial

Italy

Study period: 2004–2005

n = 99

Population: right-handed patients with major depressive episode using DSM-IV criteria.
• 50% (50/99) active rTMS, 22% (11/50) male
• 50% (49/99) sham rTMS, 18% (9/49) male

Indications: Exclusion criteria: concomitant DSM Axis I diagnosis (all mental health conditions except personality disorders and mental retardation), manic or hypomanic episodes or psychotic features; somatic or neurologic illnesses impairing psychiatric evaluation; age < 18 or > 75 years; left-handed; 21-item HDRS score < 21. No patient had failed to respond to more than one antidepressant treatment for the current episode.

Technique: active treatment was preceded by 7-day washout period; each group was subdivided according to antidepressant medication that was randomly assigned (escitalopram, sertraline or venlafaxine). rTMS and antidepressant were administered for first 2 weeks and pharmacologic treatment only for the following 3 weeks. rTMS over left dorsolateral prefrontal cortex for 10 consecutive working days, 100% MT, 15 Hz; in sham group, coil was held at an angle to give similar sound effect but no cortical stimulation.
Follow-up: 5 weeks (including treatment period)
Conflict of interest: none</td>
<td>Response was defined as ≥ 50% decrease in HDRS total score from baseline; remission was defined as HDRS score ≤ 8 for at least 3 consecutive weeks.

Mean change from baseline in HDRS score (standard error)
<table>
<tr><th>Week</th><th>n</th><th>Active rTMS</th><th>Sham rTMS</th></tr>
<tr><td>1</td><td>99</td><td>7.0 (0.70)</td><td>4.6 (0.71)</td></tr>
<tr><td>2</td><td>96</td><td>12.9 (1.03)</td><td>8.3 (1.06)</td></tr>
<tr><td>3</td><td>96</td><td>15.5 (1.07)</td><td>11.1 (1.09)</td></tr>
<tr><td>4</td><td>93</td><td>17.9 (1.02)</td><td>14.0 (1.01)</td></tr>
<tr><td>5</td><td>89</td><td>19.1 (1.12)</td><td>16.2 (1.14)</td></tr>
</table>
Difference between groups in mean HDRS scores (sham – active)
<table>
<tr><th>week</th><th>estimate</th><th>95% CI</th><th>P value</th></tr>
<tr><td>1</td><td>–2.4</td><td>–4.4 to –0.5</td><td>0.017</td></tr>
<tr><td>2</td><td>–4.6</td><td>–7.6 to –1.7</td><td>0.002</td></tr>
<tr><td>3</td><td>–4.4</td><td>–7.4 to –1.3</td><td>0.005</td></tr>
<tr><td>4</td><td>–3.9</td><td>–6.8 to –1.1</td><td>0.007</td></tr>
<tr><td>5</td><td>–2.9</td><td>–6.1 to 0.2</td><td>0.068</td></tr>
</table>
Response rates at end of second week:
• Active rTMS = 51% (25/49)
• Sham = 21.3% (10/47), p = 0.02
Remission rates at end of second week:
• Active rTMS = 36.7% (18/49)
• Sham = 10.6% (5/47), p = 0.003
Response rates at end of fifth week:
• Active rTMS = 80.0% (36/45)
• Sham = 72.7% (32/44), p = 0.419
Remission rates at end of fifth week:
• Active rTMS = 73.3% (33/45)
• Sham = 54.5% (24/44), p = 0.064</td>
<td>One patient receiving active rTMS and venlafaxine dropped out because of headache and cervical pain.

There were no switches into mania.

No patient developed psychotic symptoms during the trial.</td>
<td>Consecutive patients were allocated to sham group or active group and one of three anti-depressants according to a computer-generated random list.

Assessments were done by two psychiatrists who had good inter-rater reliability and were unaware of treatment allocations.

Patients were blinded to treatment allocation with regards to rTMS and antidepressant.

There were no statistically significant differences at baseline between active and sham rTMS groups.

Intent-to-treat analysis.

The study was powered to detect a medium effect size, corresponding to a difference of about 3.5 points on the HDRS at the end of the rTMS period.

Three patients (1 in the active treatment group, 2 in the sham treatment group) dropped out within 12 days of treatment because of unpleasant side effects. A further 7 patients (4 active and 3 sham) dropped out for the following reasons: 2 lacked improvement, 2 went on holiday, 2 did not attend planned visit, 1 withdrew consent.</td>
</tr>
</table>

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Rossini D (2005b)[3] **Randomised controlled trial** Italy Study period: not stated **n = 54** Population: right-handed patients with severe and drug-resistant major depressive episode without psychotic features. • 33% (18/54) 100% MT, 33% (6/18) male • 35% (19/54) 80% MT, 21% (4/19) male • Sham = 32% (17/54), 35% (6/17) male Mean age (years): • 100% MT = 57.4 • 80% MT = 54.0 • Sham = 56.3, p = 0.63 Indications: Inclusion criteria: HDRS ≥ 26; lack of improvement to at least two different antidepressants at adequate dosage and duration, administered during current episode. Exclusion criteria: age < 18 years or > 75 years; history of seizures or neurological illnesses; severe medical conditions that could interfere with clinical evaluation; pregnancy; mental retardation; Edinburgh Handedness Inventory laterality score below +70. Technique: all patients underwent 10 sessions over 2 weeks; rTMS over left dorsolateral prefrontal cortex, frequency 15 Hz; in sham group, coil was held at an angle to give similar sound effect but no cortical stimulation. **Follow-up: 5 weeks (including treatment period)** Conflict of interest: none stated	Response was defined as ≥ 50% decrease in HDRS total score from baseline; remission was defined as HDRS score ≤ 8 for at least 3 consecutive weeks. Response rate: • 100% MT = 61% (11/18) • 80% MT = 28% (5/18) • Sham = 6% (1/16) p = 0.0008 for 100% MT versus sham p = 0.10 for 80% MT versus sham p = 0.044 for 100% versus 80% MT Complete remission: • 100% MT = 50% (9/18) • 80% MT = 28% (5/18) • Sham = 0% (0/16) HDRS scores decreased in all three groups, and there was a statistically significant advantage favouring 100% MT group over the sham group (p = 0.042). The significance increased over time. The Clinical Global Impression severity subscale showed an improvement over time similar to that observed on the HDRS.	Mild headache: • 100% MT = 11% (2/18) • 80% MT = 11% (2/19) • Sham = 0% (0/17) Transient mild discomfort at site of stimulation: • 100% MT = 17% (3/18) • 80% MT = 0% (0/19) • Sham = 0% (0/17)	Consecutive patients were allocated to sham group or one of two intervention groups according to a computer-generated random list. Two patients dropped out (one in the sham group [withdrew consent] and one in the 80% MT group [because of worsening clinical condition during the first week of treatment]). There were no significant differences between the groups with respect to baseline HDRS and Clinical Global Impression. Resting MT was determined, only in the active groups, as the lowest intensity needed to induce 5 times out of 10, an involuntary movement in the abductor pollicis brevis (APB) muscle. A similar procedure was carried out in the sham group but the coil was held at an angle so no real movement was induced. Assessments were done by two psychiatrists who had good inter-rater reliability and were unaware of treatment allocations. Sample size was not large enough to detect small to medium differences between the groups by chi-squared test.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Avery DH (2006)[4] **Randomised controlled trial** USA Study period: 2001–2004 **n = 68** Population: patients with current major depressive disorder • 52% (35/68) active rTMS, 40% male (14/35), mean age = 44.3 years • 48% (33/68) sham rTMS, 52% male (17/33), mean age = 44.2 years Indications: inclusion criteria: aged 21–65 years; DSM-IV criteria for current major depressive disorder; failure to respond to, or unable to tolerate, at least two previous adequate antidepressant trials; 17-item HDRS score of ≥17 at both screening and treatment day 1 and a decrease of ≤ 20% between the two visits (at least 2 weeks). Exclusion criteria: previous TMS; bipolar disorder; previous failure of ≥ 9 bitemporal ECT treatments; current major depressive episode > 5 years; history of substance abuse or dependence within past 2 years; antisocial or borderline personality disorder; active suicidal ideation; psychosis; history of seizure disorder; history of closed head injury with loss of consciousness; previous brain surgery; any other major psychiatric or medical comorbidity. Patients were encouraged, although not required, to discontinue current antidepressant medication, sedatives or benzodiazepines.	Response was defined as ≥ 50% decrease in HDRS total score from baseline to end of study that persisted for 1 week; remission was defined as HDRS score < 8 at end of study that persisted for 1 week . Response rates: • Active rTMS = 30.6% (11/35) • Sham = 6.1% (2/33), p = 0.008 Remission rates: • Active rTMS = 20.0% (7/35) • Sham = 3.0% (1/33), p = 0.033 Logistic regression analysis, adjusting for stratification variables, showed TMS had significantly greater odds of response: adjusted odds ratio = 21.08, 95% CI 2.07 to 214.16) Adjusted odds ratio for remission = 25.49, 95% CI 1.09 to 595.75 Of the 11 responders to TMS, 5 (45%) did not relapse during 6-month follow-up period.	No seizures were reported. Pain experienced at first session: • Active = 40% (14/35) • Sham = 0% (0/33) Pain experienced at 15th session: • Active = 33% (11/33) • Sham = 3% (1/30) Pain decreased in TMS group over subsequent treatment sessions. One patient with history of benign positional vertigo experienced vertigo and nausea after each TMS session. There was no evidence of any cognitive compromise or adverse effects on neuropsychological functioning with TMS compared with sham.	91 patients were initially screened: 20 did not meet entry criteria, 2 chose not to participate and there was 1 protocol violation. Randomisation process is described in the paper. There were no significant differences between subjects randomised to receive active rTMS or sham treatment. Three patients in sham group dropped out: 1for lack of response, 1 for unknown reasons and 1 for protocol violation. Two patients in the active group dropped out, both because of inconvenience of the study. Patients and assessors were blinded to treatment allocation throughout the study period. The authors state that the response and remission rates were clinically as well as statistically significant. Responders were given continuation medication 2 weeks after last TMS session because of ethical concerns about leaving them untreated.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Avery DH (2006) *continued.* Technique: 15 rTMS treatment sessions over a 4-week period (left dorsolateral prefrontal cortex, 10 Hz, 110% estimated prefrontal threshold). Patients who met response criteria were followed with continuation pharmacotherapy for 6 months after last TMS session. **Follow-up: 2 week post-treatment assessment period (patients who met response criteria were followed up for 6 months).** Conflict of interest: several authors have been consultants for or received research support from several pharmaceutical companies (original paper gives full list of disclosures).			

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Fitzgerald PB (2003)[5]

Randomised controlled trial

Australia

Study period: 2000–2002

n = 60

Population: patients with treatment-resistant depression (54 with major depressive episode, 6 with bipolar disorder, depressive episode)
• 33% (20/60) high-frequency left-sided rTMS, 60% male (12/20), mean age = 42.2 years
• 33% (20/60) low-frequency right-sided rTMS, 65% male (13/20), mean age = 45.6 years
• 33% (20/60) sham, 45% male (9/20), mean age = 49.2 years

Indications: all patients scored > 20 on MADRS and had had a minimum of two courses of antidepressant medication for at least 6 weeks that had failed; 46 patients were taking medication during the trial. Exclusion criteria: significant medical illnesses, neurological disorders or other Axis I psychiatric disorders.

Technique: low-frequency left-sided rTMS applied at 1 Hz and 100% MT; high-frequency right-sided rTMS at 10 Hz and 100% MT. Sham therapy entailed holding the coil at an angle.

Follow-up: 4-week treatment period
Conflict of interest: none stated</td>
<td>Mean MADRS scores :
<table>
<tr><th></th><th>baseline</th><th>At 2 weeks</th></tr>
<tr><td>High-frequency rTMS</td><td>36.1</td><td>30.8</td></tr>
<tr><td>Low-frequency rTMS</td><td>37.7</td><td>32.2</td></tr>
<tr><td>Sham</td><td>35.7</td><td>35.4</td></tr>
</table>
p < 0.005 for high and low frequency versus sham
p = 0.91 for high versus low frequency rTMS

Mean BDI scores :
<table>
<tr><th></th><th>baseline</th><th>At 2 weeks</th></tr>
<tr><td>High-frequency rTMS</td><td>33.1</td><td>26.7</td></tr>
<tr><td>Low-frequency rTMS</td><td>35.0</td><td>27.2</td></tr>
<tr><td>Sham</td><td>32.3</td><td>29.0</td></tr>
</table>
p = 0.08 for low frequency versus sham
p = 0.16 for high frequency versus sham

Mean Global Assessment of Functioning scores:
<table>
<tr><th></th><th>baseline</th><th>At 2 weeks</th></tr>
<tr><td>High-frequency rTMS</td><td>43.0</td><td>45.2</td></tr>
<tr><td>Low-frequency rTMS</td><td>43.5</td><td>46.3</td></tr>
<tr><td>Sham</td><td>42.7</td><td>42.5</td></tr>
</table>
p = 0.03 for low frequency versus sham
p = 0.09 for high frequency versus sham

Response rate (> 20% reduction in MADRS score by 2 weeks):
• High-frequency rTMS = 40% (8/20)
• Low-frequency rTMS = 35% (7/20)
• Sham = 10% (2/20), p = 0.07

Mean change in MADRS score from week 2 to week 4:
• High-frequency rTMS = 14.1%
• Low-frequency rTMS = 38.8%, p = 0.05</td>
<td>11% (7/60) of patients reported site discomfort or pain
10% (6/60) of patients reported headache

One patient in each of the active rTMS groups reported transient dizziness for a short time after treatment.

No deterioration in performance was found in any cognitive measures.</td>
<td>Randomisation described.

Patients and assessors were blinded to treatment.

There were no differences between the 3 groups in age, sex or clinical variables.

The Global Assessment of Functioning scale is a numeric scale (0 to 100) that rates the social, occupation and psychological functioning of adults. A higher score denotes superior functioning.

After 10 sessions of treatment, patients but not assessors were informed of treatment group. All patients who met the initial response criteria continued to receive single-blind treatment for another 2 weeks. Patients who did not achieve response were offered the option of crossing over to the other active treatment. Patients initially randomised to the sham group were randomised to 1 of the 2 active treatments.

The authors state that treatment for at least 4 weeks is necessary for clinically meaningful benefits to be achieved.</td>
</tr>
</table>

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
McDonald W (2006)[6] **Randomised controlled trial** USA Study period: not stated **n = 62** Population: patients with severe major depression and intolerant and/or resistant to antidepressant medication • 19% (12/62) sham: 58% (7/12) male, mean age = 54 years • 40% (25/62) fast left followed by slow right rTMS: 28% (7/25) male, mean age = 49 years • 40% (25/62) slow right followed by fast left rTMS: 64% (16/25) male, mean age = 49 years Indications: inclusion criteria: age between 18 and 70 years; severity of symptoms specificed by American Psychiatric Association criteria for an acute course of ECT; treatment resistance to at least three antidepressant medications during current episode. Exclusion criteria: evidence of dementia on neuropsychological testing; organic brain syndrome; organic mood disorder; substance dependence within last 6 months; significant central neurological disorder; previous course of TMS. Technique: 10 sessions of fast left (10 Hz) rTMS followed by slow right (1 Hz) or slow right followed by fast left, 110% MT. **Follow-up: 3 months** Conflict of interest: none stated	Response rate (50% decline in HDRS): • fast left rTMS = 28% (7/25) • slow right rTMS = 12% (3/25) • sham = 8% (1/12) p = not significant Remission rate (HDRS ≤ 7): • fast left rTMS = 12% (3/25) • slow right rTMS = 0% (0/25) • sham = 0% (0/12) Mean HDRS scores declined in all three arms from baseline to day 10. Mean HDRS scores after 10th treatment: • fast left rTMS = 16.2 • slow right rTMS = 22.3 • sham = 19.8 Mean difference between slow right and fast left = 6.1, p = 0.007. Mean Beck Depression Inventory scores after 10th treatment: • fast left rTMS = 15.3 • slow right rTMS = 22.8 • sham = 22.8 Mean difference between sham and fast left = 7.5, p = 0.07. Percentage decline from baseline in HDRS after 10th treatment: • fast left rTMS = 37.4% • slow right rTMS = 19.4% • sham = 29.4% p = 0.014 for fast left versus slow right	No safety outcomes were reported.	Patients and assessors were blind to treatment allocation. Intention-to-treat analysis. There were significant differences in the number of medication trials subjects received before TMS (6.5 in sham, 7 in fast left group and 10 in slow right group, p = 0.003).

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Koerselman F (2004)[7]

Randomised controlled trial

The Netherlands

Study period: 1997–2001

n = 52

Population: patients with a moderate or severe DSM-IV major depressive episode completing a 2-week stimulation period
• 50% (26/52) rTMS: 54% (14/26) male
• 50% (26/52) sham: 35% (9/26) male
Mean age (years):
• rTMS = 51
• sham = 52, p = not significant
Indications: inclusion criteria: age > 16 years; DSM-IV criteria for major depressive episode; score ≥ 20 on HDRS.
Exclusion criteria: history of epilepsy; any other medical disorder that precluded the administration of rTMS. Patients taking psychotropic medication were accepted if the dosage had not been changed for 6 weeks (antidepressants) or 2 weeks (hypnotics and anxiolytics) before study inclusion.

Technique: rTMS over the left dorsolateral prefrontal cortex was delivered daily, five sessions per week for 2 weeks (20 Hz, 80% MT). Sham treatment was performed by holding the coil at an angle.

Follow-up: 12 weeks

Conflict of interest: none</td>
<td>Mean HDRS score decrease by week (weeks 1 and 2 are treatment weeks)
<table>
<tr><td></td><td colspan="2">rTMS</td><td colspan="2">Sham</td><td></td></tr>
<tr><td>week</td><td>n</td><td>HDRS</td><td>n</td><td>HDRS</td><td>P value</td></tr>
<tr><td>0</td><td>26</td><td>25.9</td><td>26</td><td>25.9</td><td>0.99</td></tr>
<tr><td>1</td><td>26</td><td>22.1</td><td>26</td><td>23.8</td><td>0.36</td></tr>
<tr><td>2</td><td>25</td><td>21.1</td><td>24</td><td>21.9</td><td>0.71</td></tr>
<tr><td>4</td><td>23</td><td>20.6</td><td>23</td><td>20.2</td><td>0.88</td></tr>
<tr><td>8</td><td>19</td><td>15.5</td><td>19</td><td>21.2</td><td>0.06</td></tr>
<tr><td>14</td><td>12</td><td>14.7</td><td>15</td><td>18.7</td><td>0.21</td></tr>
</table>
Drop out rate and reasons during 12-week follow-up after completion of stimulation sessions
<table>
<tr><td></td><td>rTMS</td><td>Sham</td></tr>
<tr><td>Increase of symptoms</td><td>19% (5/26)</td><td>12% (3/26)</td></tr>
<tr><td>Strong increase of symptoms</td><td>0% (0/26)</td><td>4% (1/26)</td></tr>
<tr><td>Decrease of symptoms</td><td>19% (5/26)</td><td>12% (3/26)</td></tr>
<tr><td>Strong decrease of symptoms</td><td>4% (1/26)</td><td>4% (1/26)</td></tr>
<tr><td>Other*</td><td>12% (3/26)</td><td>12% (3/26)</td></tr>
<tr><td>Total</td><td>54% (14/26)</td><td>42% (11/26)</td></tr>
</table>
*Other = ECT, holiday, no-show, or moved to other treatments

Random-effects model showed that final HDRS score was significantly different between the groups, in favour of the rTMS group over the sham group (p = 0.06)</td>
<td>Not reported.</td>
<td>Patients and assessors were blinded to treatment modality.

An additional three patients were initially recruited to the study; two dropped out after one rTMS session (one had emergency ECT because of suicidal ideation and one complained of extreme dizziness); the 3rd patient dropped out after five sessions because extra medication was needed. These patients were excluded from this study as they had not completed the stimulation.

Randomisation process was not described.

The authors state that the stimulation parameters used for this study may be insufficient according to current knowledge.</td>
</tr>
</table>

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Dannon PN (2002)[8]

Randomised controlled trial

Israel

Study period: not stated

n = 41

Population: patients with major depressive disorder with or without psychotic features referred for ECT, who initially responded to a course of either ECT or rTMS.
• 49% (20/41) ECT
• 51% (21/41) rTMS

Indications: inclusion criteria: age > 18 years; DSM-IV diagnosis of major depressive disorder (17-item HDRS ≥ 18); no personal or first-degree family history of seizure; no major medical, neurological or neurosurgical disorder. Patients who responded to an initial course of ECT or rTMS were followed up (response was defined as HDRS ≤ 10 or 60% in HDRS).

Technique: rTMS over left dorsolateral prefrontal cortex daily for 20 days (90% MT, 10 Hz) using Magstim Rapid instrument. Antidepressant medications at adequate doses were prescribed at the end of the TMS and ECT treatment.

Follow-up: 6 months

Conflict of interest: none stated</td>
<td>Relapse was defined as a return of depressive symptoms meeting DSM-IV criteria for major depressive disorder with HDRS ≥ 16.

Rates of relapse over 6-month follow-up:
• ECT = 20% (4/20)
• rTMS = 19% (4/21), p = not significant
(Three of the four patients in the rTMS group were treated again with rTMS and responded to the second course.)

Clinical variables at 3 months' follow-up
<table>
<tr><th></th><th>ECT group (n = 20)</th><th>rTMS group (n = 21)</th></tr>
<tr><td>HDRS</td><td>7.71 ± 5.03</td><td>6.40 ± 4.91</td></tr>
<tr><td>Global Assessment of Functioning Scale</td><td>75.52 ± 13.81</td><td>79.75 ± 12.92</td></tr>
<tr><td>Michigan Adequacy of Treatment scale</td><td>1.92 ± 1.04</td><td>2.28 ± 1.07</td></tr>
</table>
All p values were reported as 'not significant'.

Clinical variables at 6 month follow-up
<table>
<tr><th></th><th>ECT group (n = 20)</th><th>rTMS group (n = 21)</th></tr>
<tr><td>HDRS</td><td>8.40 ± 5.60</td><td>7.90 ± 7.14</td></tr>
<tr><td>Global Assessment of Functioning Scale</td><td>72.80 ± 11.94</td><td>77.75 ± 17.13</td></tr>
<tr><td>Michigan Adequacy of Treatment scale</td><td>1.82 ± 0.98</td><td>2.44 ± 1.03</td></tr>
</table>
All p values were reported as 'not significant'.</td>
<td>No safety outcomes were reported.</td>
<td>An earlier report from the same study was included in the Cochrane Review (Grunhaus, 2000).

The total number of patients treated with ECT or rTMS is not reported. The study only includes those patients who responded to either treatment.

An additional two patients responded to treatment with rTMS but dropped out from the study (reasons not given in the paper).

The paper does not describe the Michigan Adequacy of Treatment Scale.</td>
</tr>
</table>

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Machii K (2006)[9] **Case series** USA Study period: 1997–2003 **n = 249** Population: patients with major unipolar depression, participating in randomised controlled trials at study centre Indications: inclusion criteria: unipolar major depression according to DSM-IV criteria; without psychotic features or other co-morbid Axis I disorders; right-handedness; aged 21–80 years; naïve to TMS. Technique: ≥ 10 daily sessions over 2 weeks, high-frequency (10 or 20 Hz) or low-frequency (1 Hz) rTMS to left or right dorsolateral prefrontal cortex, 110% MT. **Follow-up: not stated** Conflict of interest: none stated	No efficacy outcomes were reported.	*High-frequency rTMS, left dorsolateral prefrontal cortex (n = 187)* • Headache = 4.8% (9/187) • Neck pain = 2.7% (5/187) • Tinnitus = 1.1% (2/187) • Acute mood change = 0.5% (1/187) *High-frequency rTMS, right dorsolateral prefrontal cortex (n = 19)* • Headache = 26.3% (5/19) • Neck pain = 10.5% (2/19) *Low-frequency rTMS, left dorsolateral prefrontal cortex (n = 11)* • Headache = 45.4% (5/11) • Neck pain = 18.2% (2/11) *Low-frequency rTMS, right dorsolateral prefrontal cortex (n = 32)* • Headache = 43.8% (14/32) • Neck pain = 18.8% (6/32) There were no seizures in any of the patients.	The paper also includes a review of adverse effects reported in the literature between 1998 and 2003. Reviewed studies used TMS for a range of indications, including in healthy volunteers. The data presented in this table are collated by the authors from a number of randomised controlled trials taking place at their study centre.

Table 2 Summary of key efficacy and safety findings on transcranial magnetic stimulation for severe depression (studies identified after consultation)

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Herrmann LL (2006)[28] **Meta-analysis** Search date: not stated **n = 33 studies** • **Active rTMS = 475 patients** • **Sham rTMS = 402 patients** Pascual-Leone et al (1996)[29] George et al (1997)[18] Avery et al (1999)[12] Kimbrell et al (1999)[22] Klein et al (1999)[23] Loo et al (1999)[25] Padberg et al (1999)[30] Stikhina et al (1999)[31] Berman et al (2000)[13] Eschweiler et al (2000)[15] George et al (2000)[19] Garcia-Toro et al (2001)[17] Lisanby et al (2001)[32] Manes et al (2001)[33] Boutros et al (2002)[34] Padberg et al (2002)[35] Loo et al (2003)[36] Nahas et al (2003)[37] Herwig et al (2003)[38] Hoppner et al (2003)[39] Fitzgerald et al (2003)[5] Hausmann et al (2004)[40] Jorge et al (2004)[41] Holtzheimer et al (2004)[42] Kauffmann et al (2004)[43] Mosimann et al (2004)[26] Poulet et al (2004)[44]	For the active rTMS group, reductions in depressive symptoms (as indicated by reductions in scores on the HDRS and MADRS) ranged from -10.4% to 59.4%, with a mean of 33.6%. For the sham rTMS group, reductions ranged from -15% to 54%, with a mean of 17.4%. Pooled estimate of effect size = 0.65 (95% CI 0.51 to 0.79), indicating a clinically significant effect of rTMS. However, the test for heterogeneity was highly significant, indicating that the variability in outcome measures between the studies exceeded that expected by chance. 'Studies enrolling participants taking unstable medication and studies using stimulation intensities of less than 90% MT may result in smaller levels of rTMS efficacy.' No treatment parameters that systematically predicted efficacy of rTMS were identified.	No safety data were presented.	A paired-samples t test indicated that there was no significant difference between sham and active treatment groups in terms of baseline depression scores. The authors note that there was great variability in the results of individual trials. Strict double-blinding often cannot be guaranteed because of sham conditions that may be detected by patients. The authors state that the absence of strong predictors of treatment response and the emergence of weak predictors that either are independent of the experimental treatment (confounding medication) or related to the ease of discriminating active and sham treatment (stimulus strength) are consistent with a placebo mechanism for the TMS antidepressant effect. The authors conclude that either study sizes and numbers and designs are insufficient to afford the power necessary to detect predictors of study effect or TMS has a non-specific effect on depression that is not influenced by study parameters.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Herrmann LL (2006) continued. Koerselman et al (2004)[7] Rumi et al (2005)[45] Miniussi et al (2005)[46] Rossini et al (2005)[2] Avery et al (2006)[4] Januel et al (2006)[47] Inclusion criteria: studies had to be of randomised parallel or crossover design with sham control with both patients and investigators unaware of whether patients were receiving real or sham rTMS. Patients were required to have a diagnosis of depression (major depressive disorder or bipolar disorder). Studies included were required to report their findings using either the HDRS or the MADRS. Stimulation intensity: • 80% = 7 studies • 90% = 7 studies • 100% = 5 studies • > 100% = 10 studies Random effects meta-analysis. Efficacy was only examined immediately after treatment and not at follow-up. Conflict of interest: one author has received reimbursement of travel expenses from MAGSTIM Co. and a free loan of stimulators from Dantec Ltd.			

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Rosa MA (2006)[48]

Randomised controlled trial

Brazil

Study period: not stated

n = 35

Population: patients with refractory unipolar non-psychotic depression
• ECT = 43% (15/35), 53% (8/15) male
• rTMS = 57% (20/35), 40% (8/20) male
Mean age:
• ECT = 46.0 years
• rTMS = 41.8 years, p = 0.252
Mean HDRS score:
• ECT = 32.1
• rTMS = 30.1, p =0.926
Indications: inclusion criteria were age between 18 and 65 years, unipolar depressive disorder according to DSM-IV criteria, with no psychotic symptoms and a HDRS score ≥ 22. Refractoriness was defined as a lack of response to at least two antidepressants of different classes, with augmentation. Patients were excluded if they had a past history of epilepsy, past neurosurgery with presence of metal clips, any other neurological or psychiatric diseases, presence of cardiac pacemakers, or pregnancy.
Technique: Dantec Magpro (Medtronic Inc.) magnetic stimulator was used to apply rTMS to left dorsolateral prefrontal cortex, 10 Hz at 100% MT, 20 sessions (over 4 weeks).
Follow-up: none
Conflict of interest: none</td>
<td>Response rate (≥ 50% decline in HDRS):
• ECT = 40% (6/15)
• rTMS = 50% (10/20)
p = 0.557

Remission rate (HDRS ≤ 7):
• ECT = 20% (3/15)
• rTMS = 10% (2/20)
p = 0.631

Intention to treat analysis
Response rate (≥ 50% decline in HDRS):
• ECT = 30% (6/20)
• rTMS = 45% (10/22)
p = 0.35

Remission rate (HDRS ≤ 7):
• ECT = 15% (3/20)
• rTMS = 9% (2/22)
p = 0.65

Clinical Global Impression scores (± standard deviation)
<table>
<tr><th>Time of evaluation</th><th>ECT</th><th>rTMS</th></tr>
<tr><td>Baseline</td><td>4.7 (0.8)</td><td>4.3 (0.8)</td></tr>
<tr><td>2 weeks</td><td>4.0 (1.0)</td><td>3.1 (1.1)</td></tr>
<tr><td>4 weeks (end of treatment)</td><td>3.2 (1.5)</td><td>3.1 (1.3)</td></tr>
</table>
</td>
<td>There was no significant difference between the two groups in neuropsychological tests performance after 2 weeks and 4 weeks of treatment. However, patients in the ECT group had a trend of worsening in neuropsychological performance whereas patients in the rTMS group showed no change or a slight improvement after treatment.

‘No patients showed any signs of partial or generalised seizure’.

‘Patients in the ECT group had a higher frequency of headache and confusion after ECT treatment compared to rTMS treatment’.</td>
<td>An additional seven patients were entered into the study but did not complete it. Five patients in the ECT group were excluded (three did not complete 2 weeks of treatment and the other two did not attend follow-up evaluation due to personal problems). Two patients in rTMS group were excluded: one developed a dissociative state after the first session of rTMS, which lasted about 5 minutes, with no further complications and the other patient developed hypomanic symptoms after 5 days of rTMS.

Patients referred for ECT were invited to enter the study and randomised according to a computer-generated list.

There were no statistically significant differences in demographic or clinical characteristics between the two groups.</td>
</tr>
</table>

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Fitzgerald PB (2006)[49] **Randomised controlled trial** Australia Study period: not stated **n = 130** Population: patients with treatment-resistant depression • 1 Hz rTMS = 52% (67/130), male = 33% (22/67), mean age = 50.5 years • 2 Hz rTMS = 48% (63/130), male = 40% (25/63), mean age = 48.1 years Mean HDRS score: • 1 Hz rTMS = 24.13 • 2 Hz rTMS = 22.62, p =0.08 117 patients were taking antidepressant medication during the study. Indications: patients were included if they were experiencing moderate to severe depression (> 16 on 17-item HDRS). All patients had failed to respond to a minimum of two courses of antidepressant medication for at least 6 weeks in the current episode. Patients were excluded with significant currently active medical illness, current neurological disease or a contraindication to rTMS. Patients with a current DSM-IV diagnosis of alcohol or substance dependence were excluded. Technique: Medtronic Magpro30 magnetic stimulator, 110% MT for right-sided rTMS, 100% MT for left-sided TMS. **Follow-up: none** Conflict of interest: two authors have received support for research conducted with Neuronetics Inc.	Response rate at week 2 (> 50% decline in HDRS) for all patients: • 1 Hz rTMS = 27% (18/67) • 2 Hz rTMS = 32% (20/63) Remission rate at week 2 (HDRS < 8) for all patients: • 1 Hz rTMS = 7% (5/67) • 2 Hz rTMS = 16% (10/63) Response rate at week 4 (> 50% decline in HDRS) for all patients: • 1 Hz rTMS = 42% (28/67) • 2 Hz rTMS = 52% (33/63) Remission rate at week 4 (HDRS < 8) for all patients: • 1 Hz rTMS = 19% (13/67) • 2 Hz rTMS = 32% (20/63) Response rate at week 2 (> 50% decline in HDRS) for patients completing 2 week assessment: • 1 Hz rTMS = 27% (18/67) • 2 Hz rTMS = 32% (20/63) Remission rate at week 2 (HDRS < 8) for patients completing 2 week assessment: • 1 Hz rTMS = 7% (5/67) • 2 Hz rTMS = 16% (10/63) Response rate at week 4 (> 50% decline in HDRS) for patients completing 4 week assessment: • 1 Hz rTMS = 77% (24/31) • 2 Hz rTMS = 81% (30/37) Remission rate at week 4 (HDRS < 8) for patients completing 4 week assessment: • 1 Hz rTMS = 42% (13/31) • 2 Hz rTMS = 54% (20/37) 'There appeared to be no difference in response rates between 1 and 2-Hz right prefrontal cortex rTMS.' Overall, 51% (66/130) patients achieved response and 27% (35/130) achieved remission.	One patient developed a hypomanic episode soon after completion of phase 1 treatment.	Patients were sequentially randomised using a computer-generated random number sequence. Patients and raters were blind to treatment. Patients classified as 'initial responders' were offered a further two weeks of rTMS. Patients who failed to respond by two weeks were offered treatment with left-sided rTMS. The study was reported to be powered to show a five-point difference in the study end-point variable between the groups. There were no significant baseline differences between the groups. 1.5% (2/130) patients failed to complete initial 2 week treatment, both withdrew consent. 86 patients met criteria to continue treatment for a further 2 weeks and 68 chose to do so (31 in 1-Hz group and 37 in 2-Hz group). Results for 'all' patients uses the last observation carried forward method. Not all patients who responded at 2 weeks continued further in the study.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Eranti S (2007)[50] **Randomised controlled trial** UK Study period: 2002–2004 **n = 46** Population: patients with major depression referred for ECT • ECT = 48% (22/46), 27% (6/22) male • rTMS = 52% (24/46), 33% (8/24) male Mean age: • ECT = 68.3 years • rTMS = 63.6 years Mean HDRS score: • ECT = 24.8 • rTMS = 23.9 Indications: right-handed patients ≥ 18 years old referred for ECT to treat a major depressive episode. Exclusion criteria were inability to have rTMS because of metallic implants or foreign bodies, history of seizures, substance misuse in previous 6 months, being medically unfit for general anaesthesia or ECT, rTMS or ECT in previous 6 months, dementia or other axis I diagnosis, and inability or refusal to provide informed consent. Patients continued their usual medical care and psychotropic medications. Technique: Magstim Super Rapid stimulator (Magstim Co., UK) was used to give rTMS at 110% MT to left dorsolateral prefrontal cortex for a total of 15 daily sessions. Follow-up: 6 months Conflict of interest: none	Primary outcome measure = HDRS End of treatment HDRS scores were significantly lower in the ECT group than the rTMS group (95% CI for difference 3.40 to 14.05, p = 0.002) At 6-month follow-up, the HDRS score did not differ between groups (95% CI -6.92 to 6.33, p = 0.93). Response rate at end of treatment (50% reduction in baseline HDRS)): • ECT = 59% (13/22) • rTMS = 17% (4/24), p = 0.006 Remission rate at end of treatment (HDRS score ≤ 8): • ECT = 59% (13/22) • rTMS = 17% (4/24), p = 0.006 Mean percentage reduction in HDRS from baseline at end of treatment : • ECT = 58% • rTMS = 22% Absolute difference in percentage reduction from baseline = 36% (95% CI 14% to 58%) (predefined equivalence range = up to 18.1 percentage points) Beck Depression Inventory showed significantly lower scores for ECT than for rTMS (95% CI for difference 2.27 to 15.58, p = 0.01) Visual analogue mood scales showed significantly lower scores for ECT than for rTMS (95% CI for difference 106.54 to 302.78, p < 0.001) Brief Psychiatric Rating Scale showed significantly lower scores for ECT than for rTMS (95% CI for difference 0.47 to 11.69, p = 0.03)	Patients in ECT group were estimated to have overall significantly lower scores for subjective side effect symptoms after treatment (95% CI for difference = 0.51 to 5.33, p = 0.02). (Measured using Columbia ECT subjective side effects schedule). No significant differences were found on self- and observer-rated cognitive measures.	107 patients were eligible for entry to the study, but only 46 consented to enter. Patients were randomly allocated to ECT or rTMS by an independent third party using a computer database containing a randomisation list. The randomisation was stratified by the patient's health trust. Raters were blind to treatment allocation but patients were not. Rater treatment guesses were available for 38 patients, 5 of whom had inadvertently informed the raters. Of the remaining 33, raters guessed correctly for 30 (91%). The main reason given for the correct guess was extent of response. Outcomes were analysed on an intention-to-treat basis. 20% (9/46) patients were lost to follow-up. 6 patients in rTMS group discontinued treatment before course was complete.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Loo C (2001)[51] Randomised controlled trial Australia Study period: not stated n = 18 Population: patients with major depression • active rTMS = 50% (9/18) • sham rTMS = 50% (9/18) Male = 50% (9/18) Mean age = 48 years (range 33–78) Indications: DSM-IV major depressive episode, antidepressant medications were either withdrawn 5 days before rTMS (n = 5) or failed treatments were maintained at steady doses throughout the study. Technique: rTMS was delivered daily on consecutive weekdays (5 sessions per week), 10 Hz at 110% MT. After initial 2 weeks of treatment, all patients were given the choice of continuing openly with active rTMS to a maximum of 4 weeks of active rTMS. In 4 patients, the position of stimulation was later checked at MRI scanning. Follow-up: none Conflict of interest: none stated	Efficacy data were not reported.	During 2-week period of randomised treatment, there was no significant mean deterioration in any neuro-psychological test score. Results were not significantly different between active and sham groups. Audiology results did not differ between active and sham treatments. No significant changes were detected after the first 4 weeks of rTMS. In 5 patients exposed to 6 weeks rTMS (2 weeks sham, 4 weeks active), mean auditory threshold for right ear at the 1 kHz frequency rose from 9.0 decibels to 14.0 decibels. There were no subjective complaints of hearing loss. Small bilateral increases in threshold were noted in one patient in the 6- to 8-kHz range after 4 weeks of rTMS (15 decibel increase) and in another patient in the 3- to 4-kHz range after 6 weeks of rTMS (20 decibel increase). The latter patient was retested and hearing had returned to baseline levels a month later. Two patients developed left temporal EEG abnormalities (one received sham rTMS) that were not considered to be clinically significant.	Patients were randomly allocated to receive 2 weeks of real or sham rTMS on a blinded basis.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Ropohl A (2004)[52] Case report Study period: not stated n = 1 Population: patient with a 2-year history of major depressive disorder presenting with moderate depressive episode. In addition to psychopharmacotherapy, rTMS treatment of left dorsolateral prefrontal cortex was applied. Technique: not reported Follow-up: not reported Conflict of interest: none stated	Not reported.	The patient reported a pulsating, local dental twinge in the upper left jaw correlated with rTMS treatment. During the inter train interval the dental pain disappeared, but emerged again during the next train of stimuli. The intensity of pain gradually diminished during the course of treatment. The pain was found to be dependent on the stimulus intensity.	Reported in letter to the editor. The authors consider that local irritation of the trigeminal nerve by the pulsating magnetic fields seems to be the most likely explanation.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
O'Reardon JP (2007)[53] Randomised controlled trial (multisite) United States, Australia and Canada Study period: 2004–2005 n = 301 Population: medication-free patients who had not benefited from prior treatment • active TMS = 51.5% (155/301) • sham TMS = 48.5% (146/301) Indications: inclusion criteria were antidepressant medication-free outpatients, aged 18–70, with a DSM-IV diagnosis of major depressive disorder, single episode or recurrent, with a current episode duration of 3 years or less. The episode had a Clinical Global Impressions Severity of Illness score of at least 4 and a total score of at least 20 on the 17-item HDRS. Symptom stability was required during a 1-week no-treatment lead-in period. Patients were required to have failed at least one but no more than four adequate antidepressant treatments in this or the most recent episode. Alternatively, patients were eligible if they had marked intolerance to antidepressants (four failed attempts to tolerate adequate medication trial).	Primary efficacy outcome = MADRS at 4 weeks Secondary outcome measures = MADRS at 6 weeks, HDRS at 4 and 6 weeks. Response was defined as at least 50% reduction from baseline score. Remission was defined by an absolute scale-specific score. Beyond the primary efficacy time point, 48% (74) patients in active TMS group and 63% (92) patients in sham TMS group elected to enter open-label extension study. Symptom scores at week 4 (Standard deviation) The symptom score for MADRS became statistically significant (p = 0.038) after a post-hoc correction for inequality of symptom severity at baseline (six patients with baseline scores in the 'mild' range were excluded). Symptom scores at week 6 (Standard deviation) Response rates at week 4	Discontinuation because of adverse events: • Active = 4.5% • Sham = 3.4% (the paper states that this was most commonly due to scalp discomfort) Suicidality: • Active = 0.6% • Sham = 1.9% There was a single suspected suicide gesture in the sham group. Exacerbation of depression: • Active = 0.6% • Sham = 1.9% **Adverse events occurring in the active treatment group at a rate of 5% or more and at least twice the rate of sham:** Eye pain: • Active = 6.1% (10/165) • Sham = 1.9% (3/158) Toothache: • Active = 7.3% (12/165) • Sham = 0.6% (1/158) Application site discomfort: • Active = 10.9% (18/165) • Sham = 1.3% (2/158) Application site pain: • Active = 35.8% (59/165) • Sham = 3.8% (6/158)	Patients were randomised to receive either active TMS or sham TMS and were blinded to treatment allocation. An additional 24 patients were randomised (10 active and 14 sham) but did not have at least one post-baseline assessment and were not included in further analysis. All treatment personnel were blinded to treatment allocation. All efficacy outcome measures were assessed by blinded raters. If patients failed to show a meaningful clinical benefit after 4 weeks of participation in the acute treatment phase, they could crossover to an open-label, acute treatment extension study. Therefore, complete randomisation was only present up to 4-week period. Baseline symptom severity at randomisation differed between groups on the primary outcome measure (MADRS), but not on any of the other symptom scales. Intent to treat analysis. 92% (277/301) patients continued to week 4 of study. All analyses were conducted in a last-observation carried forward manner. Adequacy of blinding for patients and raters was not formally assessed.

	Active TMS	Sham TMS	p value
Female	55.5%	50.7%	0.421
Mean age (years)	47.9	48.7	0.509
MADRS baseline score	32.8	33.9	0.036
HDRS-17 baseline score	22.6	22.9	0.508
HDRS-24 baseline score	30.1	30.5	0.568

	Active TMS (n = 155)	Sham TMS (n = 146)	p value
MADRS	27 (11.1)	29.8 (10.1)	0.057
HDRS-17	17.4 (6.5)	19.4 (6.5)	0.006
HDRS-24	23.4 (8.9)	25.9 (8.8)	0.012

	Active TMS (n = 155)	Sham TMS (n = 146)	p value
MADRS	26.8 (12.8)	30 (10.8)	0.058
HDRS-17	17.1 (7.7)	19.6 (7.0)	0.005
HDRS-24	23.2 (10.6)	26 (9.4)	0.015

	Active TMS (n = 155)	Sham TMS (n = 146)	p value
MADRS	18.1%	11.0%	<0.05
HDRS-17	20.6%	11.6%	<0.05
HDRS-24	19.4%	11.6%	<0.05

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>O'Reardon JP (2007) continued.

Exclusion criteria included lifetime history of psychosis, bipolar disorder, or obsessive-compulsive disorder; posttraumatic stress disorder and eating disorders (in past year); lack of response to an adequate trial of ECT; prior treatment with TMS or vagus nerve stimulator implant; pregnancy; a personal or close family history of seizure disorder; neurologic disorder or medication therapy known to alter seizure threshold; presence of ferromagnetic material in or in close proximity to the head.

Technique: The study had a lead-in phase (1 week, no treatment), a 6-week acute treatment period and a taper phase (3 weeks reduced frequency, start of antidepressant). During acute treatment phase, TMS sessions were delivered daily on 5 consecutive days for a maximum of 30 sessions (6 weeks), 120% MT. The left dorsolateral prefrontal cortex was the treatment location and TMS was delivered using the Neuronetics Model 2100 Therapy System investigational device (Neuronetics Inc, Malvern, Pennsylvania). The sham coil had an embedded magnetic shield and had a similar appearance, placement and acoustic properties to the active coil.

Follow-up: none (results were reported at 4-week and 6-week end points)

Potential conflict of interest: The trial was supported by a grant from Neuronetics Inc and one of the authors is an employee of Neuronetics. The paper lists a number of potential conflicts of interest from the authors.</td>
<td>Remission rates at week 4
<table><tr><th></th><th>Active TMS (n = 155)</th><th>Sham TMS (n = 146)</th><th>p value</th></tr><tr><td>MADRS</td><td>7.1%</td><td>6.2%</td><td>>0.10</td></tr><tr><td>HDRS-17</td><td>7.1%</td><td>6.2%</td><td>>0.10</td></tr><tr><td>HDRS-24</td><td>9.0%</td><td>8.2%</td><td>>0.10</td></tr></table>
Response rates at week 6
<table><tr><th></th><th>Active TMS (n = 155)</th><th>Sham TMS (n = 146)</th><th>p value</th></tr><tr><td>MADRS</td><td>23.9%</td><td>12.3%</td><td><0.01</td></tr><tr><td>HDRS-17</td><td>24.5%</td><td>13.7%</td><td><0.05</td></tr><tr><td>HDRS-24</td><td>23.9%</td><td>15.1%</td><td><0.05</td></tr></table>
Remission rates at week 6
<table><tr><th></th><th>Active TMS (n = 155)</th><th>Sham TMS (n = 146)</th><th>p value</th></tr><tr><td>MADRS</td><td>14.2%</td><td>5.5%</td><td><0.05</td></tr><tr><td>HDRS-17</td><td>15.5%</td><td>8.9%</td><td>0.065</td></tr><tr><td>HDRS-24</td><td>17.4%</td><td>8.2%</td><td><0.05</td></tr></table></td>
<td>Facial pain:
• Active = 6.7% (11/165)
• Sham = 3.2% (5/158)
Muscle twitching:
• Active = 20.6% (34/165)
• Sham = 3.2% (5/158)
Skin pain:
• Active = 8.5% (14/165)
• Sham = 0.6% (1/158)

No seizures were observed.</td>
<td></td>
</tr>
</table>

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Gross M (2007)[54] Systematic review and meta-analysis Brazil, USA Literature search for articles published from December 2005 to November 2006. **n = 5 studies, 274 patients** Mean age of patients = 44.7 years 66.8% female Mean baseline HDRS score = 23.5 Januel D et al (2006)[47], 90% MT Avery DH et al (2006)[4], 110% MT Rossini D et al (2005)[2], 100% MT Fitzgerald PB (2006)[49], 105% MT Garcia-Toro M et al (2006)[55], 110% MT Inclusion criteria: English language; use of rTMS at any frequency and any location; mood effects assessed by a continuous mood scale such as HDRS, Beck Depression Inventory or MADRS; randomised, double-blind studies with sham rTMS group; mean and standard deviation of mood scores before and after treatment or other statistical parameters that could be used to deduce these values. Conflict of interest: none stated	Pooled effect size (standardised mean difference between the active and sham rTMS groups) from the random effects model = -0.76 (95% CI -1.01 to -0.51) Test for heterogeneity failed to show a significant heterogeneity.		The study compared results with an earlier meta-analysis already described in table 2 (Martin et al, 2001)[1]. Four of the five studies included in the meta-analysis have been summarised previously in table 2.[2,4,47,49] Parameters of stimulation varied with regard to site and frequency. The authors note that the power of this meta-analysis was reduced as only five studies were included. The quality of studies was described as variable and suggested as a reason to explain the differences between this meta-analysis and the previous one.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Rachid F (2006)[56] Case report Switzerland Study period: not stated n = 1 Population: woman suffering from refractory chronic major depression undergoing rTMS treatment Age = 39 years Technique: rTMS treatment regimen involved 20 Hz rTMS, 90% MT once daily for two consecutive weeks using a Magstim Super Rapid™ device. The coil was applied over the left dorsolateral prefrontal cortex. Conflict of interest: none	After 1 week of treatment, depression had not improved (MADRS score was 36 versus 34 before treatment).	The patient had no history of manic, hypomanic and/or mixed episodes. When the patient started rTMS treatment, she was on medication regimen including serotonergic drugs to treat depression, insomnia, anxiety, opioid dependence and migraine headaches. After 1 week of rTMS treatment, the patient developed dysphoria with increased irritability, a sensation of 'crowded thinking', flight of ideas and word-finding difficulties. She developed heat intolerance, mild sweating, myoclonus over upper extremities, hand tremors, severe headaches and showed mild hyperreflexia on neurological examination. She was diagnosed as having a mild serotonin syndrome. Because of these adverse effects, rTMS was discontinued at the ninth session. She continued to experience depressive mixed symptoms which remitted within a few days after the introduction of valproic acid.	The authors note that there are several possibly contributing factors in this case, making it difficult to ascertain a causal link or rTMS to this specific psychopathology. The authors state that this is the first report of mixed depressive episode during rTMS treatment.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Conca A (2000)[57] Case report n = 1 Population: woman with drug-resistant depression (mixed depressive-anxious state) Age = 36 years The patient was taking medication including a combined noradrenaline and serotonin reuptake inhibitor. Technique: Initial treatment was bilateral rTMS without any change in medication (110% MT, 20 Hz, 5 s duration, 10 trains and intertrain interval lasting 45 s over left side; 110% MT, 1 Hz, 300 s and 1 train over right side). After 5 days, high frequency rTMS was applied over the left dorsolateral prefrontal cortex as an add-on antidepressive strategy (110% MT, 20 Hz, 10 s duration and 10 trains with an intertrain interval of ≥ 60 s).		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. No motor activities were observed. The epileptic seizure was self-limiting (8 s) and the patient did not report any physical sequelae.	The authors report that rTMS in combination with drugs modulating the norepinephrine turnover, may have contributed to the occurrence of complex partial seizure. The authors conclude that the increase of rTMS train duration contributed to the occurrence of the seizure.

Abbreviations used: CI, confidence intervals; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; MT, motor threshold; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; TMS, transcranial magnetic stimulation; WMD, weighted mean difference.

Study details	Key efficacy findings	Key safety findings	Comments
Sakkas P (2003)[58] Case reports n = 2 Population: patients with drug-resistant depression Case 1: 55-year old man with drug-resistant depression (taking selective serotonin reuptake inhibitor medication) Case 2: 46-year old man with bipolar affective disorder and depression for the last year (not taking medication). Technique: Magstim ultra rapid device, rTMS applied over left prefrontal cortex, 110% MT, 20 Hz, 2 s train duration, as many trains as possible (about 40). Two sessions of rTMS were given daily for 5 days a week.	Case 1: patient's depression lifted after 3 weeks of concomitant rTMS and SSRI treatment, but he also manifested hypomanic behaviour. Treatment with rTMS was discontinued and patient was given neuroleptic treatment. After 4 months, the patient became depressed again and was treated with rTMS. After 2 weeks, he responded favourably but also became hypomanic. He was put on mood stabilising treatment and remained well a year later. Case 2: rTMS was initially administered 3 days a week but patient failed to respond after a month of treatment. rTMS was then increased to 5 days a week (twice daily) and after 2 weeks, depression eventually subsided. However, the patient became hypomanic. Frequency of rTMS was reduced to avoid induction of full-scale mania and the patient became normothymic.	Induction of manic symptoms	The authors comment that the treatment regimen they use is more aggressive than usual. The duration of each train (2 s) exceeded the duration suggested by guidelines (1.6 s maximum).[11]

Validity and generalisability of the studies

- Several different outcome scales were used; the systematic review reported a significant difference between rTMS and sham treatment using the Hamilton Depression Rating Scale but the difference was not statistically significant when the Beck Depression Inventory scale was used.
- Studies use different stimulation parameters, including high- & low- frequency over the left or right dorsolateral prefrontal cortex, and varying durations of treatment. All of the studies use rTMS rather than single-pulse TMS.
- All the RCTs are small and may lack power to show a clinically significant difference.
- The inclusion criteria varied between the studies. Five studies excluded patients with psychosis and two studies included only patients who were resistant to medication. Three studies included only right-handed patients.
- No study included patients less than 16 years of age.
- No study reported a long-term follow-up. Two studies reported results after a 6-month follow-up in patients who initially responded to rTMS treatment.

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Dr D McLoughlin, Dr J Pearson, Professor K Matthews.

- The procedure is novel and of uncertain safety and efficacy.
- There are concerns about efficacy of the procedure.
- The potential impact of the procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is moderate to major.

Issues for consideration by IPAC

- There is a lot of literature on TMS, including several systematic reviews, and it is hard to summarise it all in a short overview.

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56. Rachid F, Golaz G, Bondolfi G, et al. (2006) Induction of a mixed depressive episode during rTMS treatment in a patient with refractory major depression. *World Journal of Biological Psychiatry* 7: 261–4.

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Appendix A: Additional papers on transcranial magnetic stimulation for severe depression not included in summary table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table or the Cochrane Review (table 2). It is by no means an exhaustive list of potentially relevant studies.

Abbreviations used: ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; MT, motor threshold; RCT, randomised controlled trial; rMTS, repetitive transcranial magnetic stimulation.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Anderson IM, Delvai NA, Ashim B et al (2007) Adjunctive fast repetitive transcranial magnetic stimulation in depression. *British Journal of Psychiatry* 190: 533-534.	RCT n = 29 (13 active TMS, 16 sham TMS) Follow-up = 12 weeks 110% MT	76% (19/25) patients correctly guessed treatment allocation. One patient in active group was mildly hypomanic at 4 weeks. Four days after his last treatment he had a series of epileptic seizures but a primary cause was not identified. Responders at treatment end-point: • Active = 55% (6/11) • Sham = 7% (1/14) p < 0.05 Responders at 12 weeks: • Active = 33% (3/9) • Sham = 8% (1/13) p = not stated	Small sample size.
Bortolomasi M, Minelli A, Fuggetta G et al (2007) Long-lasting effects of high frequency repetitive transcranial magnetic stimulation in major depressed patients. *Psychiatry Research* 150:181-186.	RCT n = 19 (12 active TMS, 7 sham TMS) Follow-up = 12 weeks 90% MT	A significant difference between groups, with a reduction in baseline depression scores for active rTMS, was seen at 1 and 4 weeks. After 3 months, patients treated with active rTMS reverted to previous depressive mood state.	Small sample size
Brakemeier EL, Luborzewski A, Danke-Hopfe H, et al (2007) Positive predictors for antidepressive response to prefrontal repetitive transcranial magnetic stimulation (rTMS). *Journal of Psychiatric Research* 41 (5): 395–403.	Case series n = 70	Response = 21% (15/70) A high level of sleep disturbances was a significant predictor for treatment response to rTMS.	Small case series.
Chistyakov AV, Kaplan B, Rubichek O, et al (2005) Antidepressant effects of different schedules of repetitive transcranial magnetic stimulation vs. clomipramine in patients with major depression: relationship to changes in cortical excitability. *International Journal of Neuropsychopharmacology* 8: 223–33	59 patients	10 Hz less well tolerated than 3 Hz rTMS. Improvement (> 50% reduction in HDRS): • left active 3 Hz = 55% (6/11) • right active 3 Hz = 17% (2/12) • left active 10 Hz = 17% (1/6) • right active 10 Hz = 33% (2/6) • sham rTMS (with clomipramine) = 13% (2/15)	Small sample sizes and no follow-up. Main focus of study was to measure cortical ex0citability.
Chistyakov AV, Kaplan B, Rubichek O, et al (2005) Effect of electroconvulsive therapy on cortical excitability in patients with major depression: a transcranial magnetic stimulation study. *Clinical Neurophysiology* 116: 386–92	22 patients	rTMS did not add to beneficial effect of ECT.	Small sample size.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Figiel GS, Epstein C, McDonald WM, et al (1998) The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *Journal of Neuropsychiatry and Clinical Neurosciences* 10: 20–25	50 patients	Response rate = 42% (21/50) (56% of young patients and 23% of elderly patients).	Small case series.
Fitzgerald PB, Benitez J, de Castella et al (2006) A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. American Journal of Psychiatry 163: 88–94	50 patients (treatment resistant)	Low-frequency right-side followed by high-frequency left-side rTMS. Response rate: • Active = 44% (11/25) • Sham = 8% (2/25), p < 0.05 Clinical remission: • Active = 36% (9/25) • Sham = 0% (0/25), p = 0.005 Therapeutic response increased over a period of 6 weeks.	Larger RCTs of active versus sham rTMS are included.
Fitzgerald PB, Benitez J, de Castella AR, et al (2006) Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse. *Australian and New Zealand Journal of Psychiatry* 40: 764–8	19 patients	rTMS used to treat episodes of depressive relapse with little reduction in efficacy over time. Approximately 10 months elapsed between treatment episodes.	Small case series.
Fregni F, Marcolin MA, Myczkowski M et al (2006) Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. *International Journal of Neuropsychopharmacology* 9 (6): 641–54.	Meta-analysis (6 trials)	TMS has better outcome in younger and less treatment-resistant patients.	Meta-analysis of more trials is included.
Fregni F, Santos CM, Myczkowski ML, et al (2004) Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 75: 1171–4	42 patients with depression and Parkinson's disease	rTMS had the same antidepressant efficacy as fluoxetine.	Small sample size and focuses on depression in patients with Parkinson's disease.
Fujita K, Koga Y (2005) Clinical application of single-pulse transcranial magnetic stimulation for the treatment of depression. *Psychiatry and Clinical Neurosciences* 59: 425–32	23 patients	Single-pulse TMS has a wide range of antidepressive effects without inducing adverse effects.	Small sample size.
Grunhaus L, Schreiber S, Dolberg OT, et al (2003) A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biological Psychiatry* 53: 324–31	40 patients	Response rate: • rTMS = 55% (11/20) • ECT = 60% (12/20), p = not significant	Small sample size.
Hausmann A, Kemmler G, Walpoth M et al (2004) No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single-centre randomised, double-blind, sham controlled "add on" trial. *Journal of Neurology, Neurosurgery and Psychiatry* 75: 320–2	41 patients. Follow-up = 28 days.	rTMS, applied as 'add-on' therapy in a unilateral and bilateral stimulation paradigm did not exert an additional antidepressant effect.	Small sample size.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Janicak PG, Dowd SM, Martis B, et al (2002) Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomised trial. Biological Psychiatry 51: 659–67	25 patients	No significant difference between rTMS and ECT.	Small sample size.
Loo CK, Mitchell PB, McFarquhar TF, et al (2007) A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychological Medicine 37 (3): 341–9.	RCT (active versus sham rTMS) n = 38	rTMS given twice daily rather than once daily. Difference in improvement for active and sham groups reached significance for MADRS but not HDRS and self-rating scores.	RCTs with larger sample sizes are included.
Luborzewski A, Schubert F, Seifert F, et al. (2007) Metabolic alterations in the dorsolateral prefrontal cortex after treatment with high-frequency repetitive transcranial magnetic stimulation in patients with unipolar major depression. *Journal of Psychiatric Research* 41 (7): 606-615.	Case series n = 17 100% MT	35% (6/17) patients were responders (50% reduction of Hamilton depression rating scale). Baseline concentrations of glutamate increased after successful rTMS.	Small sample size.
Mosimann UP, Schmitt W, Greenberg BD, et al (2004) Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Research* 126: 123–33	24 patients (mean age 62 years)	Significant antidepressant effects within 2 weeks in both sham and active rTMS groups - there were no between-group differences.	Small sample size.
O'Connor M, Brenninkmeyer C, Morgan A, et al (2003) Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: a neurocognitive risk-benefit analysis. *Cognitive and Behavioral Neurology* 16: 118–27	28 patients. Follow-up = 2 weeks.	ECT had a more positive effect on mood than rTMS but also had transient negative cognitive side effects that were not seen with rTMS.	Small sample size.
O'Reardon JP, Blumner KH, Peshek AD, et al. (2005) Long-term maintenance therapy for major depressive disorder with rTMS. *Journal of Clinical Psychiatry* 66: 1524–8.	10 patients	Long-term maintenance therapy. rTMS given for periods ranging from 6 months to 6 years. 7 out of 10 patients experienced either marked or moderate benefit, which was sustained without the addition of concomitant antidepressant medication in 3 patients.	Small sample size.
Pridmore S, Bruno R, Turnier-Shea Y, et al (2000) Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *International Journal of Neuropsychopharmacology* 3: 129–134	32 patients	rTMS produced results comparable to those with ECT on some of the measures used.	Small sample size.
Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, et al (2005) Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *British Journal of Psychiatry* 186: 410–6	30 patients (treatment-refractory)	Treatment response was comparable, but rTMS had no adverse effects on memory unlike ECT.	Small sample size.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Stern WM, Tormos JM, Press DZ et al. (2007) Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. *Journal of Neuropsychiatry & Clinical Neurosciences* 19: 179–186.	n = 45 (10 high frequency left-sided TMS, 10 low frequency left-sided TMS, 10 low frequency right-sided TMS, 15 sham TMS) Follow-up = 2 weeks after end of treatment 110% MT	Authors believe 10 days of stimulation to be sub-optimal. Both high-frequency left-sided rTMS and low-frequency right-sided rTMS led to a clinically significant antidepressant effect in 60% of patients.	Small sample size
Su TP, Huang CC, Wei IH (2005) Add-on rTMS for medication-resistant depression: a randomised, double-blind, sham-controlled trial in Chinese patients. *Journal of Clinical Psychiatry* 66: 930 – 7	30 patients (medication-resistant)	Response rate = 60% for active rTMS and 10% for sham treatment. Mania was induced in one patient.	Small sample size.
Walter G, Martin J, Kirkby K, et al (2001) Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. *Australian and New Zealand Journal of Psychiatry 35*: 58–61	48 patients	Almost 75% of patients believed TMS had been helpful. The vast majority rated TMS as more acceptable than having, or the prospect of having, ECT.	Small case series.

Appendix B: Related published NICE guidance for transcranial magnetic stimulation for severe depression

Guidance programme	Recommendation
Interventional procedures	None applicable
Public health	None applicable
Technology appraisals	*Guidance on the use of electroconvulsive therapy (ECT). NICE Technology Appraisal Guidance No.59 (2003)* 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: • severe depressive illness • 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 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

Guidance programme	Recommendation
	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 severe depressive illness, 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 As the longer-term benefits and risks of ECT have not been clearly established, it is not recommended as a maintenance therapy in depressive illness. 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.

Guidance programme	Recommendation
Clinical guidelines	*Depression: management of depression in primary and secondary care. NICE Clinical Guideline No. 23 (2004)* TMS was not within the scope of this guideline. Key priorities for implementation included: **Initial presentation of severe depression** When patients present initially with severe depression, a combination of antidepressants and individual cognitive behavioural therapy (CBT) should be considered as the combination is more cost-effective than either treatment on its own. **Maintenance treatment with antidepressants** Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for 2 years. **Combined treatment for treatment-resistant depression** For patients whose depression is treatment resistant, the combination of antidepressant medication with CBT should be considered. **CBT for recurrent depression** CBT should be considered for patients with recurrent depression who have relapsed despite antidepressant treatment, or who express a preference for psychological interventions. With regards to ECT, the guideline states: • Electroconvulsive therapy (ECT) should only be used to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatments has proven ineffective, and/or when the condition is considered to be potentially life-threatening, in a severe depressive illness. • When considering ECT, review risks and potential benefits to the individual, including: the risks associated with the anaesthetic; current comorbidities; anticipated adverse events, particularly cognitive impairment; and the risks of not having treatment. • Particular care is needed when considering ECT treatment during pregnancy, in older people, and in children and young people, because the risks may be increased. • 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 and about the risks and potential benefits specific to that individual. • Advance directives should be taken fully into account and the individual's advocate and/or carer should be consulted.

Guidance programme	Recommendation
	• Clinical status should be assessed after 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. • A repeat course of ECT should be considered under the circumstances indicated above only for individuals who have severe depressive illness, 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. • As the longer-term benefits and risks of ECT have not been clearly established, it is not recommended as a maintenance therapy in depressive illness. *Depression in children and young people: identification and management in primary, community and secondary care. NICE Clinical Guideline No. 28 (2005)* TMS was not within the scope of this guideline. Key priorities for implementation included: • Children and young people with moderate to severe depression should be offered, as a first-line treatment, a specific psychological therapy (individual cognitive behavioural therapy [CBT], interpersonal therapy or shorter-term family therapy; it is suggested that this should be of at least 3 months' duration). • Antidepressant medication should not be offered to a child or young person with moderate to severe depression except in combination with a concurrent psychological therapy. Specific arrangements must be made for careful monitoring of adverse drug reactions, as well as for reviewing mental state and general progress. Regarding ECT, the guideline states: • Only consider ECT for young people (12–18 years) with very severe depression and either life-threatening symptoms (such as suicidal behaviour) or intractable and severe symptoms that have not responded to other treatments. • Use ECT extremely rarely in young people (12–18 years) and only after careful assessment by a practitioner experienced in its use, and in a specialised environment in accordance with NICE recommendations. • Do not use ECT in the treatment of depression in children (5–11 years).

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

Database	Date searched	Version searched
Cochrane Library	11/10/06	Issue 3, 2006
CRD databases (DARE & HTA)	11/10/06	Issue 3, 2006
Embase	11/10/06	1980 to 2006 Week 40
Medline	11/10/06	1966 to September Week 4 2006
Premedline	11/10/06	October 10, 2006
CINAHL	11/10/06	1982 to October Week 1 2006
British Library Inside Conferences	-	-
NRR	11/10/06	Issue 3, 2006
Controlled Trials Registry	11/10/06	_

Search strategy used in Medline

The search strategy was adapted for use in the databases above

1	Transcranial Magnetic Stimulation/	1373
2	((transcranial or trans-cranial) adj3 magnetic adj3 (stimulation or activation)).tw.	3475
3	(tms or rtms).tw.	3824
4	or/1-3	5356
5	Depression/	41643
6	Depression, Postpartum/	1354
7	Depressive Disorder/	42765
8	Depressive Disorder, Major/	6488
9	Seasonal Affective Disorder/	856
10	Bipolar Disorder/	19932
11	Mood Disorders/	6432
12	depress$.tw.	193661
13	((bipolar or bi-polar or seasonal or mood or dysthymic) adj3 (disorder or episode)).tw.	9538
14	or/5-13	234916
15	4 and 14	576
16	animals/	4119854
17	humans/	9821616
18	16 not (16 and 17)	3118706
19	15 not 18	533
20	limit 19 to english language	487
21	limit 20 to yr="1995 - 2006"	476