Depression causes low mood or sadness that can last for weeks or months. People with depression often feel hopeless and lose interest in things they used to enjoy. Other symptoms include sleeping badly, and having no appetite or sex drive. Transcranial magnetic stimulation is a possible treatment for depression that uses a powerful electromagnet, placed on the scalp, to produce electric currents in the brain.

The National Institute for Health and Care Excellence (NICE) is examining repetitive transcranial magnetic stimulation for depression and will publish guidance on its safety and efficacy to the NHS. NICE’s Interventional Procedures Advisory Committee has considered the available evidence and the views of specialist advisers, who are consultants with knowledge of the procedure. The Advisory Committee has made provisional recommendations about repetitive transcranial magnetic stimulation for depression.

This document summarises the procedure and sets out the provisional recommendations made by the Advisory Committee. It has been prepared for public consultation. The Advisory Committee particularly welcomes:

- comments on the provisional recommendations
- the identification of factual inaccuracies
- additional relevant evidence, with bibliographic references where possible.

**Note that this document is not NICE’s formal guidance on this procedure. The recommendations are provisional and may change after consultation.**

The process that NICE will follow after the consultation period ends is as follows.

- The Advisory Committee will meet again to consider the original evidence and its provisional recommendations in the light of the comments received during consultation.
The Advisory Committee will then prepare draft guidance which will be the basis for NICE’s guidance on the use of the procedure in the NHS.

For further details, see the Interventional Procedures Programme process guide, which is available from the NICE website.

Through its guidance NICE is committed to promoting race and disability equality, equality between men and women, and to eliminating all forms of discrimination. One of the ways we do this is by trying to involve as wide a range of people and interest groups as possible in the development of our interventional procedures guidance. In particular, we aim to encourage people and organisations from groups who might not normally comment on our guidance to do so.

In order to help us promote equality through our guidance, we should be grateful if you would consider the following question:

Are there any issues that require special attention in light of NICE’s duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations between people with a characteristic protected by the equalities legislation and others?

Please note that NICE reserves the right to summarise and edit comments received during consultations or not to publish them at all where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would otherwise be inappropriate.

Closing date for comments: 23 July 2015

Target date for publication of guidance: November 2015

1 Provisional recommendations

1.1 The evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns. The evidence on its efficacy in the short term is adequate, although the clinical response is variable and some patients may not benefit. Repetitive transcranial magnetic stimulation for depression may be used with normal arrangements for clinical governance and audit, provided that patients are informed, during the consent process, about the other treatment options available and they understand the
possibility that they may derive little or no benefit from the procedure.

1.2 NICE encourages publication of further evidence on patient selection, the use of maintenance treatment and long-term outcomes.

2 Indications and current treatments

2.1 Depression is a common disorder. It is characterised by persistent sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep, appetite and libido, tiredness and poor concentration. It is also often accompanied by feelings of hopelessness and suicidal thoughts. Depression can last from weeks to years, and can be recurrent. It can substantially impair an individual’s ability to function at work or cope with daily life. Treatments for depression include a range of psychological therapies and antidepressant medications. In severe depression, electroconvulsive therapy or transcranial direct current stimulation are sometimes used.

3 The procedure

3.1 Repetitive transcranial magnetic stimulation (rTMS) does not need anaesthesia and can be done on an outpatient basis. A purpose-made electromagnetic coil is held against the scalp with the intention of inducing electric currents in the cerebral cortex. Imaging may be used to help target specific areas of the brain. Treatment is usually considered for patients with depression that has not responded to antidepressant medication.
3.2 In rTMS, repetitive pulses of electromagnetic energy are delivered at various frequencies or stimulus intensities. Conventional rTMS uses continuous pulses of electromagnetic energy whereas theta-burst rTMS uses intermittent pulses. Stimulation can either be delivered unilaterally, over the left or right dorso-lateral prefrontal cortex, or bilaterally over both cortices. Bilateral stimulation may be done sequentially or simultaneously. Treatment with rTMS usually comprises daily sessions lasting about 30 minutes, typically for 2 to 6 weeks.

4 Efficacy

This section describes efficacy outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

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

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

4.3 In a systematic review of 63 studies including 3236 patients treated by rTMS (n=2330), sham stimulation (n=806) or electroconvulsive therapy (ECT; n=100), percentage changes in HDRS scores (lower scores indicate less depression) were pooled and converted to Clinical Global Impression - Improvement scale (CGI-I) scores (scores range from 1 to 7, with lower scores indicating greater improvements in a patient’s mental illness). For patients with any type of depression, the mean percentage reduction in HDRS scores was 37% (CGI-I equivalent, 2.8) in the rTMS group and 22% (CGI-I 3.4) in the sham stimulation group (p<0.05). For patients with treatment-resistant depression, the mean percentage reduction in HDRS scores was 48% (CGI-I 2.4) in the rTMS group and 23% (CGI-I 3.4) in the sham stimulation group (p<0.05). When rTMS was compared against ECT in patients with any type of depression, the mean percentage reduction in HDRS scores was 34% (CGI-I equivalent not reported) in the rTMS group and 46% (CGI-I 2.45) in the ECT group (p<0.05).

4.4 In a systematic review of 10 randomised controlled trials including 634 patients with treatment-resistant depression treated by bilateral rTMS, unilateral rTMS or sham simulation, clinical response (defined as more than a 50% improvement in HDRS or Montgomery–Åsberg Depression Rating Scale scores) was compared between groups. Meta-analysis of clinical response rates in patients treated by bilateral rTMS or sham stimulation revealed a
risk ratio of 3.29 in favour of bilateral rTMS (95% confidence interval [CI] 1.69 to 6.38, \( p=0.0004 \)). In the same study, meta-analysis of remission (classified according to predefined criteria in each included study) revealed no significant difference between patients treated by bilateral rTMS or sham stimulation (risk ratio 0.5; 95% CI 0.19 to 1.31, \( p=0.16 \)).

4.5 In a systematic review of 10 randomised controlled trials including 429 patients with a primary major depressive episode treated by rTMS (n=217) or ECT (n=212), meta-analysis of clinical response (defined as more than a 50% improvement in HDRS scores) revealed a risk ratio of 1.52, in favour of ECT (95% CI 1.18 to 1.95, \( p=0.001 \)). Meta-analysis of remission (classified according to predefined criteria in each included study) revealed a risk ratio of 1.42 in favour of ECT (95% CI 1.16 to 1.75, \( p=0.0007 \)).

4.6 A case series evaluated 120 patients who had at least a partial response (that is, at least a 25% improvement in HDRS scores); 99 patients were recruited from the active rTMS arm of a randomised sham-controlled trial, while 21 patients initially had sham stimulation and subsequently received active rTMS. For patients originally in the active rTMS arm of the trial, the mean HDRS score was 9.1±6.2 at the end of rTMS therapy and 9.0±7.1 at 6-month follow-up (\( p=0.537 \)), indicating a maintained treatment effect. No pre-treatment scores were reported. No mean HDRS scores were reported for patients who initially had sham stimulation and subsequently received active rTMS. In the same study, the relapse rate (Kaplan-Meier estimate) at 6-month follow-up was 13% in patients who were originally in the active rTMS arm of the trial and 16% in patients who initially had sham stimulation and subsequently received active rTMS (No \( p \) value reported).
4.7 Specialist advisers listed improvements in depressive symptoms, and health-related quality of life as efficacy outcomes.

5 Safety

This section describes safety outcomes from the published literature that the Committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the interventional procedure overview.

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

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

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

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

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

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

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

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

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

5.10 Increasingly hostile thoughts were reported in no patients in the conventional rTMS group (n=98) and 1 patient in the theta-burst
rTMS group (n=85) in the non-randomised comparative study of 185 patients with treatment-resistant depression. The timing of occurrence was not reported.

5.11 Device-related insomnia was reported in 1 patient in the case series of 120 patients with major depressive disorder treated by rTMS.

5.12 Device-related arthralgia was reported in 1 patient in the case series of 120 patients with major depressive disorder treated by rTMS.

5.13 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers listed the following anecdotal adverse events: discomfort, unpleasant twitching, worsening psychomotor agitation in patients with mixed affective disorder, transient confusion, transient problems with concentration and/or working memory, and transient hearing loss. They did not suggest any theoretical adverse events.

6 Committee comments

6.1 The Committee recognised the difficulties in conducting research on repetitive transcranial magnetic stimulation (rTMS) for depression, in the context of the variable natural history of depression, the challenges of providing sham treatment, and a variable and often small response. Despite large numbers of patients in the published studies there were difficulties in assessing the effect size. Nevertheless, the Committee noted consistently...
positive outcomes in many studies and a good safety profile. These considerations underpinned the recommendation for use with normal arrangements, provided that patients are properly informed about alternative treatment options, about the risk that they may derive little or no benefit from rTMS and about the possible need for repeated treatments.

6.2 The Committee noted that commentary from patients was positive and described significant benefits to their quality of life, including the advantages, for some patients, of being able to stop the use of oral antidepressant medications.